CROI 2014

Conference on Retroviruses and Opportunistic Infections

Program and Abstracts



IAS–USA
International Antiviral Society–USA

March 3-6, 2014 Boston, Massachusetts

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CROI 2014 PROGRAM COMMITTEE

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San Francisco, CA, United States
Donna M. Jacobsen, Executive Director

COMMERCIAL SUPPORT

In the interest of objective, balanced, and scientifically rigorous activities, the IAS–USA seeks grant support from multiple 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 2014 has received grant support commitments from the following commercial companies:

Platinum

MERCK

ViiV Healthcare

Gold

Bristol-Myers Squibb

janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Silver

abbvie

GILEAD

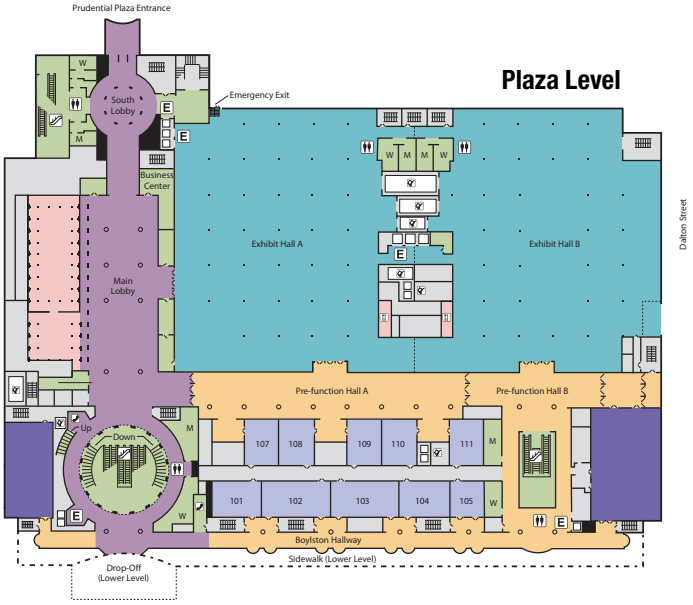
Salix PHARMACEUTICALS, INC.

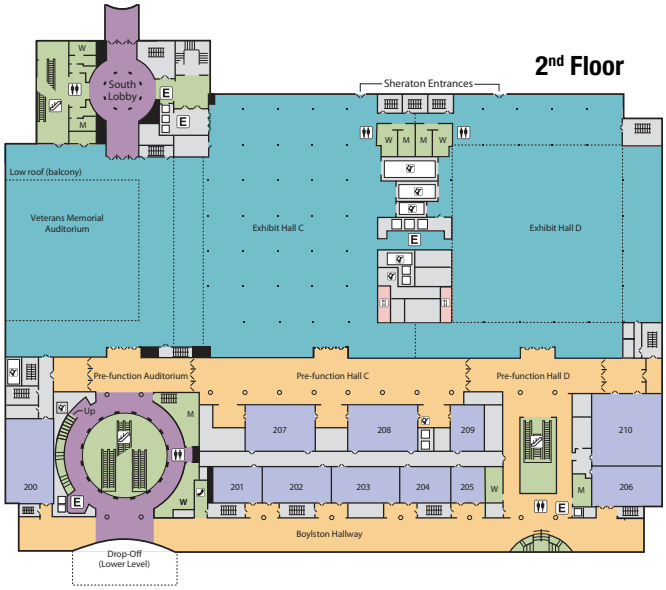
Additional support has been provided by Mylan, Inc

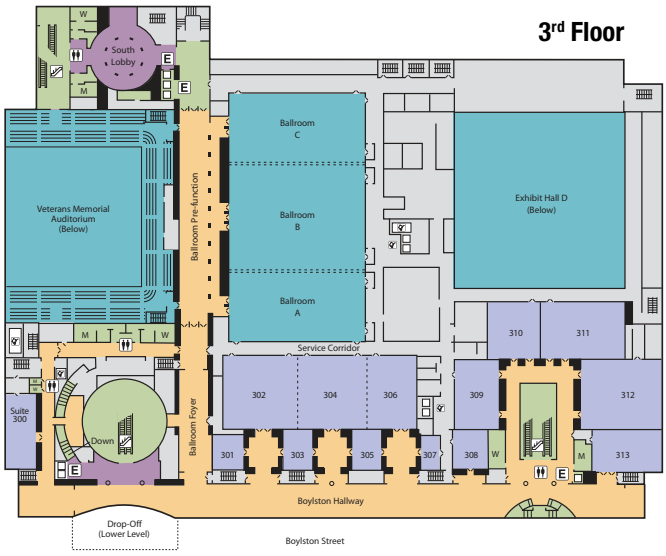
CONFERENCE SCHEDULE OVERVIEW

	Monday, March 3, 2014	Tuesday, March 4, 2014	Wednesday, March 5, 2014	Thursday, March 6, 2014
8:30 AM		**Plenary:** HPV Vaccines: Progress To Date and Future Worldwide Directions **Auditorium**	**Plenary:** B-Cell Responses To HIV Infection: Challenges and Opportunities **Auditorium**	**Plenary:** HIV-1 Infection and Type-1 Interferon **Auditorium**
9:00 AM	**Program Committee Workshop for New Investigators and Trainees** **Ballroom B/C**	**Plenary:** HIV in People Who Use Drugs **Auditorium**	**Plenary:** NeuroHIV in 2014: Beyond Dementia **Auditorium**	**Plenary:** PEPFAR/Global Fund at 10 Years: Past, Present and Future **Auditorium**
9:30 AM				
10:00 AM		**ORAL ABSTRACT CONCURRENT SESSIONS** Hepatitis **Ballroom B/C** NeuroHIV: Developments in Treatment and Pathogenesis **RM 304** Prevention and Epidemiology: Evolving Trends **Ballroom A** Host Factors and HIV/SIV Replication **RM 312**	**ORAL ABSTRACT CONCURRENT SESSIONS** Critical Issues in MTCT: Maternal Health and HIV Treatment in Children **RM 304** HIV/SIV Pathogenesis **RM 312** Randomized Controlled Trials and Antiretroviral Resistance **Ballroom B/C** TB and Other Coinfections **Ballroom A**	**ORAL ABSTRACT CONCURRENT SESSIONS** Interferon and Antibody at the Interface of Innate and Adaptive Immunity To HIV **RM 312** CV and Other Complications **Ballroom B/C** Persistence **Ballroom A** Antiretroviral Scale-Up in Sub-Saharan Africa: Challenges and Opportunities **RM 304**
12:15 PM		**LUNCH**	**LUNCH**	**LUNCH**
1:15 PM				
1:30 PM	**Martin Delaney Panel: Hepatitis C Virus: From Trials and Tribulations To Triumph** **Ballroom B/C**	**THEMED DISCUSSION CONCURRENT SESSIONS** Acute HCV Infection **RM 309** Restriction Factors **Ballroom A** Heart Failure, Cardiac Steatosis, and HIV **RM 304** Response To Early ART Initiation in Infants **RM 312** Treatment Cascade and Loss To Follow-Up **RM 311**	**THEMED DISCUSSION CONCURRENT SESSIONS** Frailty and Functional Impairment **RM 309** Clinical Pharmacology in Patient Care **Ballroom A** How Transmission Networks Drive Epidemics **RM 304** Gut and Immune Activation **RM 312** Reproductive Hormones in Women: Impact On Risk and Barrier Dysfunction **RM 311** Real-World Experiences With Hepatitis C **Ballroom B/C**	**THEMED DISCUSSION CONCURRENT SESSIONS** Kaposi Sarcoma **RM 309** Pulmonary Complications of HIV Infection **Ballroom A** Incidence Assays **RM 304** What We Learn From Bone Marrow Transplants **RM 312** CNS Viral Escape and Neuroinflammation on ART **RM 311**
2:30 PM	**CONCURRENT WORKSHOPS** Clinical Trial Design and Analysis **Ballroom B/C** Frontiers in Laboratory Science Workshop **Ballroom A** Workshop for Clinicians Who Are New To Hepatitis C Management: A Case-Based Interactive Session **RM 304**	**POSTER SESSIONS**	**POSTER SESSIONS**	**POSTER SESSIONS**
4:00 PM		**CONCURRENT SYMPOSIA** Toward a Cure: A Challenging Game of Hide and Seek **Ballroom B/C** HCV and Beyond **Ballroom A** PrEP: Use It or Lose It **RM 304**	**CONCURRENT SYMPOSIA** TB: Looking To the Future: Resistance, Persistence, Monitoring, and Control **Ballroom B/C** Visualizing the Virus **Ballroom A** Know Your Epidemic: From Data To Action **RM 304**	**CONCURRENT SYMPOSIA** Interferon: Whatever Turns You On **RM 304** The Road To Elimination: Preventing and Treating HIV Infection in Infants **RM 311** Intimate Infections: What's Love Got To Do With It? **RM 312**
4:30 PM				
5:00 PM	**Opening Session** **Bernard Fields Lecture:** Making and Breaking Barriers To Cross-Species HIV-1 Transmission **Auditorium** **N'Galy-Mann Lecture:** Application of Scientific Knowledge and Evidence To Limit the Progression of HIV/AIDS and Fight Other Endemic Diseases in West Africa **Auditorium** **Close**		**ORAL ABSTRACT SESSION** Malignancies and Pharmacology **RM 312**	
7:00 PM	**Welcome Reception**			

HYNES FLOOR PLANS







GENERAL INFORMATION

Overview

The 2014 Conference on Retroviruses and Opportunistic Infections (CROI) will be held at the John B. Hynes Veterans Memorial (Hynes) Convention Center from March 3 to 6, 2014. 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/AIDS research leaders internationally. The goal of the conference is to provide a forum for researchers to 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 ultimately accelerating progress in HIV/AIDS research.

Americans with Disabilities Act

CROI 2014 endeavors to fully comply with the legal requirements of the Americans with Disabilities Act (ADA). If you require assistance onsite, please visit the Attendee Services booth on the Plaza level during the conference.

CROI Foundation

The CROI Foundation is a not for profit organization that operates exclusively for the charitable and educational purpose of organizing, promoting, and presenting the Conference on Retroviruses and Opportunistic Infections (CROI). The CROI Foundation appoints the members of the Program Committee, the Committee is responsible for the scientific content of the conference.

The CROI Foundation Board of Directors

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

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

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IAS–USA

The International Antiviral (formerly AIDS) Society–USA (IAS–USA) is a 501(c)(3) not-for-profit professional education organization. The IAS–USA serves as the CROI 2014 Conference Secretariat.

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 who are actively involved in medical care.

Continuing Medical Education (CME)

Accreditation Statement

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

The IAS–USA designates this live activity for a maximum of **27.50** *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 had Accreditation with Commendation, being a member of an elite group of organizations in the United States that have been awarded this prestigious status, which is, in the words of the ACCME, "reserved for programs that are truly exceptional."

Objectives

After participating in CROI 2014, 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 HIV field 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 research investigators working in 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 on different facets of HIV and its complications.

CME Credit Information

Physicians (MD, DO, and international equivalents) are eligible to receive continuing medical education (CME) credit for participation in the 2014 Conference on Retroviruses and Opportunistic Infections (CROI). 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 emailed to all CROI participants, to the account they used to register for the conference. On March 7, 2014, all CROI participants will receive a final email 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 Friday, March 21. 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 symposia (4:00 PM to 6:00 PM), you would have a total of 4 hours to apply towards your credits. At the end of CROI please add together the hours from the entire conference for your certificate. You may claim a maximum of **27.50** *AMA PRA Category 1 Credits™* for this activity.

A CME hour worksheet can be found here
http://croi2014.org/sites/default/files/uploads/croi2014_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, moderators, conveners, 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 our audience aware of author/contributor interests and commitments with commercial companies or other entities so that they may 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.

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.

Welcome Reception

Please join us after the opening session, Monday, March 3, for an attendee welcome reception at the Hynes Convention Center. Light hors d'ouevres and refreshments will be served. The reception will be held March 3 in Hall C.

Meals

Morning coffee breaks and afternoon snack breaks will be available to conference registrants in the Poster Hall. Outtakes Express concession stand on Level 2, will be open from 9 AM to 1:30 PM Tuesday through Thursday. The Outtakes Express stand will have cold items for purchase such items as wraps, sandwiches, salads, snacks, and chips as well as beverages. **Attendees are on their own for lunch during the hours of approximately 12 noon to 1:30 PM 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

Towne Stove and Spirits
The Capital Grille

At the Prudential Center

(next to the South Lobby main entrance of the Convention Center)

5 Napkin Burger
Ben & Jerry's
California Pizza
Cheesecake Factory
Flamers
Gourmet India
Legal Sea Foods
Paradise Bakery
Pizzeria Regina
Qdoba
Teavana
Top of the Hub
Au Bon Pain
Boston Chowda Co
Cheeseboy
Dunkin' Donuts
Godiva
Haru
Panda Express
PF Chang's
Poulet
Sarku Japan
Tossed
Wagamama

At the Sheraton Boston

(next to the South Lobby main entrance of the Convention Center)

SideBar & Grille
Café Apropos
Starbucks

At the Marriott Copley, Copley Place Mall, and Westin Copley Place

(within 1 block of the Convention Center)

Bar 10
The Huntington
The Palm
Starbucks
Champion's Sports Bar
Legal Sea Foods
Turner Fisheries
Osushi

Overflow Accommodations for Session Rooms

Most session rooms will have designated overflow areas. Should any session draw substantially higher attendance than can be accommodated, a nearby space will be available to provide a live audio and video feed.

USB Flash Drive

Each participant was supplied a blank 4Gbyte USB flash drive upon badge pickup. The 2014 Program at a Glance and Agenda and Abstracts Book are available online to be loaded on to 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.CROI2014.org

Webcasts and Podcasts

Plenaries, symposia, scientific overviews, oral abstract sessions, and themed discussions will be webcast and podcast. Attendees who ask questions during these presentations should understand that their questions will be included in the webcast and podcast and as such grant permission. Webcasts are also available as streaming video for the Apple iPad and iPhone.

Visit www.CROI2014.org or www.CROIwebcasts.org to access the CROI 2014 webcasts and podcasts. Webcasts will be available within 24 hours of the end of the session.

WiFi Access at the Conference

Complimentary WiFi access is provided at the Hynes Convention Center. There are 2 network options:

- Hynes Wireless
- Hynes Wireless Fast (only for recent models of smart phones and tablets)

There is no login information required.

Badges

Badge pickup will be available at the registration lobby; please bring 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 OR FORGET TO BRING YOUR BADGE. Payment of an additional registration fee ($730) will be required to replace a lost badge.**

New Mothers/Lactation Room

CROI has provided New Mothers/Lactation Rooms for nursing mothers. These rooms are located on the 3rd floor in rooms 307 and 308.

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.

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 Hynes Convention Center

Services	Location	Hours	Notes
Boston Information	Main Lobby Plaza Level	Sunday 3 PM–5 PM Monday 11 AM–7 PM Tuesday to Thursday 10 AM–6 PM	Local information and reservations assistance
Bag and Coat Check	Plaza Level	Monday 8 AM–9:30 PM Tuesday/Wednesday 7:30 AM–6:30 PM Thursday 7:30 AM–6:30 PM	$3.00 per item
CyberCafe	Hall C 2nd Level	Sunday 3 PM–5 PM Monday to Wednesday 7 AM–7 PM Thursday 7 AM–6 PM	Computers with Internet access available for webcasts, abstract searches, and messages
Media Center	Room 208 2nd Level	Monday 9 AM–7 PM Tuesday to Thursday 8 AM–6:30 PM	There is no onsite press registration. Registered press can pick up press kits and obtain location for press conferences.
Message Center	Main Lobby Plaza Level	Sunday 3 PM–5 PM Monday 7 AM–7 PM Tuesday 7 AM–6 PM Wednesday/Thursday 8 AM–6 PM	Access to voice and text messages in addition to the CyberCafe
Badge Pickup Attendee Services Housing Information Scholarship Badge Pickup Media Badge Pickup	Main Lobby Plaza Level	Sunday 3 PM–6 PM Monday 7 AM–7 PM Tuesday 7 AM–6 PM Wednesday 8 AM–6 PM Thursday 8 AM–12 PM	Location and hours to pick up badges and conference materials, and request special assistance
Speaker Ready Room and Electronic Poster Drop-off	Room 200 2nd Level	Sunday 3 PM–6 PM Monday to Thursday 7:30 AM–6 PM	Oral abstract, invited, and themed discussion session speakers should drop off presentations at least 24 hours before their presentation. Poster presenters should submit an electronic version of their poster for placement on the CROI website before their assigned session.
New Mothers/Lactation Room	3rd Floor Rooms 307 & 308	Monday 9 AM–7 PM Tuesday to Thursday 8 AM–6:00 PM	CROI has provided New Mothers/Lactation Rooms for nursing mothers.

Hotel Information

CROI 2014 hotels are listed below. For more detailed housing information, please visit: www.CROI2014.org/housing.

Omni Parker House
60 School Street
Boston, MA 02108
PH: +1 617 227 8600

The Boston Park Plaza Hotel & Towers
50 Park Plaza at Arlington Street
Boston, MA 02116
PH: +1 617 426 2000

Hyatt Regency Boston
One Avenue de Lafayette
Boston, MA 02111
PH: +1 617 912 1234

Taj Boston
15 Arlington Street
Boston, MA 02116
PH: +1 617 536 5700

Sheraton Boston Hotel
39 Dalton Street
Boston, MA 02199
PH: +1 617 236 2000

Marriott Boston Copley Place
110 Huntington Avenue
Boston, MA 02116
PH: + 1 617 236 5800

The Westin Copley Place Boston
10 Huntington Avenue
Boston, MA 02116
PH: +1 617 262 9600

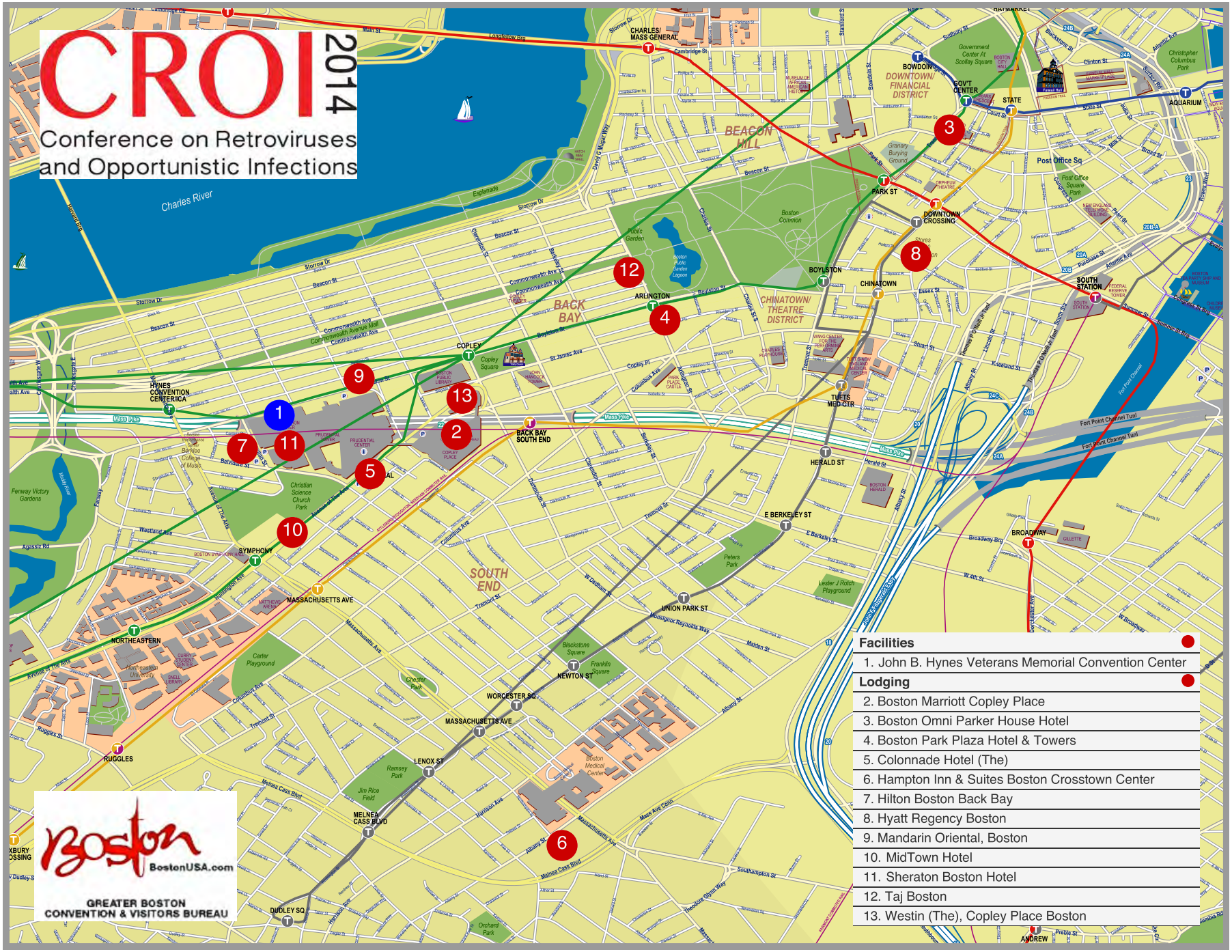
Hilton Boston Back Bay
40 Dalton Street
Boston, MA 02115
PH: +1 617 236 1100

The Colonnade Hotel
120 Huntington Avenue
Boston, MA 02116
PH: +1 617 424 7000

Mandarin Oriental Boston
776 Boylston Street
Boston, MA 02199
PH: +1 617 535 8888

The Midtown Hotel
220 Huntington Avenue
Boston, MA 02115
PH: +1 617 262 1000

Hampton Inn & Suites – Crosstown Center
811 Massachusetts Avenue
Boston, MA 02118
PH: + 1 617 445 6400


CROI 2014
Conference on Retroviruses and Opportunistic Infections
Charles River
Facilities
1. John B. Hynes Veterans Memorial Convention Center
Lodging
2. Boston Marriott Copley Place
3. Boston Omni Parker House Hotel
4. Boston Park Plaza Hotel & Towers
5. Colonnade Hotel (The)
6. Hampton Inn & Suites Boston Crosstown Center
7. Hilton Boston Back Bay
8. Hyatt Regency Boston
9. Mandarin Oriental, Boston
10. MidTown Hotel
11. Sheraton Boston Hotel
12. Taj Boston
13. Westin (The), Copley Place Boston
BostonUSA.com
GREATER BOSTON CONVENTION & VISITORS BUREAU

Scientific Categories

A Virology
B Molecular Epidemiology and HIV/SIV Evolution
C Pathogenesis: Human Studies
D Pathogenesis: Animal Studies
E Host Immune Responses
F HIV Persistence
G Neuropathogenesis
H Clinical Pharmacology
I Antiretroviral Therapy: Preclinical
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
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 Intervention Studies
W Epidemiology
X Health Care Delivery and Health Systems in Low and Middle Income Settings

Abstract Content

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

Abstract Review Process

The Scientific Program Committee and a panel of external reviewers reviewed the more than 1900 submitted abstracts. Each abstract was scored by 4 to 10 reviewers selected for each abstract category based upon their individual expertise.

OC and SC members were instructed to review the abstracts for the quality and originality of the work and to score them numerically. All reviewers were instructed to abstain from scoring any abstract on which they are an author/co-author, have a financial or personal conflict of interest, or do not have the appropriate expertise to evaluate.

Scores for each abstract are averaged and the standard deviation is calculated to assess variability. If variability is high, outlier scores are identified and censored. Abstracts with high variability in scores are 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
- Inappropriate 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)

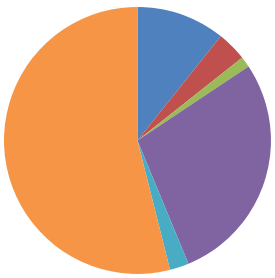
Statistics

Registration and Demographics

4103	Total Registrants
322	Young Investigator Scholarship Awardees
28	Community Educator Scholarship Awardees
34	International Scholarship Awardees
85	Countries represented
47%	Non US Attendees

Abstracts

Total general abstracts submitted:	2137
Total general abstracts accepted:	953
General oral abstracts:	111
General poster abstracts:	842
Total late breaker abstracts submitted:	217
Total late breaker accepted:	74
Late breaker oral abstracts:	20
Late breaker poster abstracts:	54
Total abstracts submitted:	2354
Total abstracts accepted:	1027



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ORAL SESSIONS

MONDAY MARCH 3, 2014

Session W1 Workshop

9:00 AM – 1:15 PM **Ballroom B/C**

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 learners have been conducting active research in the field for less than 3 years.

Objectives: At the completion of the workshop, learners will be able to:

- Recognize 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

Conveners

Judith S. Currier, *University of California Los Angeles, Los Angeles, CA, United States*

John W. Mellors, *University of Pittsburgh School of Medicine, Pittsburgh, PA, United States*




1 HIV Pathogenesis: Current Understanding and Future Research

Dana H. Gabuzda, *Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, United States*



2 HIV Cure Research

John W. Mellors, *University of Pittsburgh, Pittsburgh, PA, United States*



3 HIV Vaccine Immunology: Recent Progress and Continuing Challenges

Richard A. Koup, *Vaccine Research Center, National Institute of Allergy and Infectious Disease, National Institutes of Health, Bethesda, MD, United States*



4 HIV Prevention Research: Progress and Challenges

Sharon L. Hillier, *University of Pittsburgh School of Medicine, Magee-Womens Hospital, Pittsburgh, PA, United States*



5 Pathogenesis and Control of HCV Infection

David L. Thomas, *The Johns Hopkins University School of Medicine, Baltimore, MD, United States*

Session MD Panel

1:30 PM – 2:30 PM **Ballroom B/C**

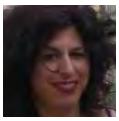
6 Martin Delaney Panel: Hepatitis C Virus: From Trials and Tribulations To Triumph

The Martin Delaney Panel is held annually during the workshops for Young pioneering HIV/AIDS activist Martin Delaney (1945-2009). It recognizes the important contributions of community advocacy and engagement to research.

Panel Leaders

Jeff Taylor, *AIDS Treatment Activists Coalition, Palm Springs, CA, United States*

Tracy Swan, *Treatment Action Group, New York, NY, United States*

Panelists

Isabelle Andrieux-Meyer, *Médecins sans Frontières, Geneva, Switzerland*

Jules Levin, *National AIDS Treatment Advocacy Project (NATAP), New York, NY, United States*

Lynn E. Taylor, *Brown University, Providence, RI, United States*





Session W2 Workshop

2:30 PM – 4:30 PM **Ballroom B/C**

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 learners are familiar with the basic design of randomized and observational clinical studies.

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

- Discuss one or more possible solutions to adherence challenges
- Define factorial designs and discuss their advantages and disadvantages
- Define meta-analyses and discuss their advantages and disadvantages

Conveners

Susan Buchbinder, *San Francisco Department of Public Health, San Francisco, CA, United States*

Richard Chaisson, *The Johns Hopkins University School of Medicine, Baltimore, MD, United States*




7 Adherence: The Achilles Heel for Trial Interventions

David R. Bangsberg, *Massachusetts General Hospital Center for Global Health, Boston, MA, United States*



8 Studying Multiple Interventions: Factorial Designs and Other Approaches

Richard J. Hayes, *London School of Hygiene and Tropical Medicine, London, United Kingdom*



9 So Many Trials, So Little Time: Meta-Analysis Do's and Don'ts

Dean A. Follmann, *National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, United States*



Session W3 Workshop

2:30 PM – 4:30 PM **Ballroom A**

Frontiers in Laboratory Science Workshop

The purpose of this workshop is to present the main technological and conceptual developments in life sciences that are influencing HIV research or hold a significant potential for research. The presentation should educate and engage investigators and clinicians, and spark interest in emerging technologies. The workshop format is designed to provide in-depth views on technologies that define B and T cell development and characterization, progress in the study of host-pathogen interactions at molecular and cellular levels, and new approaches to genetic editing. Applications in HIV research will be discussed.

Conveners

Galit Alter, *Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology, and Harvard, Cambridge, MA, United States*



Amalio Telenti, *Institute of Microbiology, University of Lausanne, Lausanne, Switzerland*



10 Systems Immunology Approaches for Vaccine Profiling and Antibody Discovery

Sai Reddy, *Swiss Federal Institute of Technology Zurich, Basel, Switzerland*



11 3-D Structural Analysis of HIV Using Correlative CryoEM and Live Cell Imaging

Peijun Zhang, *University of Pittsburgh School of Medicine, Pittsburgh, PA, United States*



12 Virus-Host Interactions Revealed Through Proteomics/Phosphoproteomics

Beatrix Ueberheide, *New York University Langone Medical Center, New York, NY, United States*



13 CRISPRs and Other Genome Editing Systems

Paul F. Bates, *University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA, United States*



Session W4 Workshop

2:30 PM – 4:30 PM **Room 304**

Workshop for Clinicians Who Are New To Hepatitis C Management: A Case-Based Interactive Session

Target audience: This session is directed to persons newly engaged in the care of HCV-infected patients

Level of knowledge: It is assumed that learners are familiar with fundamental principles of medicine and antimicrobial therapy

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

- List the practices routinely required for HCV-infected persons with cirrhosis
- Describe patients for whom HCV treatment is not currently advisable
- List the recommended therapies for persons with genotypes 1-4 HCV infection

Conveners

David L. Thomas, *The Johns Hopkins University School of Medicine, Baltimore, MD, United States*



Robert T. Schooley, *University of California San Diego, San Diego, CA, United States*



14 Liver Management

Kenneth E. Sherman, *University of Cincinnati College of Medicine, Cincinnati, OH, United States*



15 Interactive Case Presentations

David L. Wyles, *University of California San Diego, San Diego, CA, United States*



Susanna Naggie, *Duke Clinical Research Institute, Durham, NC, United States*



Opening Session

5:00 PM – 7:00 PM **Auditorium**

Welcome

Session NL1 Lecture

Bernard Fields Lecture

The Bernard Fields Lecture, named in tribute to the exemplary work of the esteemed microbiologist and virologist Bernard Fields, is given during the opening session, to recognize the speaker for their important and relevant contributions to the fields of virology and viral pathogenesis.

17 Making and Breaking Barriers To Cross-Species HIV-1 Transmission

Paul D. Bieniasz, *Aaron Diamond AIDS Research Center, The Rockefeller University, New York, NY, United States*



Session NL2 Lecture

N'Galy-Mann Lecture

The N'Galy-Mann Lecture, named in honor of Drs Bosenge N'Galy and Jonathan Mann for their pioneering work in HIV science in Africa, is given during the opening session and recognizes an HIV/AIDS researcher for his or her important and relevant work in the fields of epidemiology or clinical research.

18 Application of Scientific Knowledge and Evidence To Limit the Progression of HIV/AIDS and Fight Other Endemic Diseases in West Africa

Souleymane Mboup, *Centre Hospitalier Universitaire Aristide le Dantec, Dakar, Senegal*



Welcome Reception

7:00 PM – 9:00 PM **Hall C**

Please join us after the opening session, Monday, March 3, for an attendee welcome reception at the Hynes Convention Center. Light hors d'ouevres and refreshments will be served.

TUESDAY MARCH 4, 2014

Session PL1 Plenary

8:30 AM – 9:00 AM **Auditorium**



19 **HPV Vaccines: Progress To Date and Future Worldwide Directions**

Douglas R. Lowy, *National Cancer Institute, Bethesda, MD, United States*

Session PL2 Plenary

9:00 AM – 9:30 AM **Auditorium**



20 **HIV in People Who Use Drugs**

Adeeba Kamarulzaman, *University of Malaya, Kuala Lumpur, Malaysia*

Session O-1 Oral Abstracts

10:00 AM – 12:15 PM **Ballroom B/C**

Hepatitis

Moderators

Jürgen Rockstroh, *University Hospital Bonn, Bonn, Germany*

Kristen M. Marks, *Weill Cornell Medical College, New York, NY, United States*

21 **Longitudinal Phenotypic Profiling of Early HCV-Specific CD4 T Cells in HIV- and HIV+ Individuals**

Diana Y. Chen[1], Lyndon K. Matsubara[1], Joelle Brown[1], Stephanie S. Kulaga[2], Jasneet Aneja[2], Lia Lewis-Ximenez[3], Eddie James[4], William W. Kwok[4], Arthur Y. Kim[2], Georg M. Lauer[1]

[1]Gastrointestinal Unit, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States, [2]Infectious Disease Division, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States, [3]Laboratorio de Hepatites Virais, Instituto Oswaldo Cruz, Fundacao Oswaldo Cruz, Rio de Janeiro, Brazil, [4]Benaroya Research Institute at Virginia Mason, Seattle, WA, United States

22 **Rapid Peripheral In Vivo Cellular Changes During Interferon-Free Treatment of Hepatitis C**

Eric G. Meissner[1], Brian Santich[1], Yu-Jin Lee[1], Olga Prokunina[1], Anuoluwapo Osinusi[1,2], Anita Kohli[1,2], Henry Masur[3], Susan Moir[1], Shyamasundaran Kottilil[1]

[1]Laboratory of Immunoregulation, NIAID/NIH, Bethesda, MD, United States, [2]SAIC-Frederick, Inc, Frederick, MD, United States, [3]CCMD/NIH, Bethesda, MD, United States

23 **Faldaprevir Plus Pegylated Interferon Alfa-2a/Ribavirin in HIV/HCV Coinfection: STARTVerso4**

Douglas Dieterich[1], Cristina Tural[2], Mark Nelson[3], Keikawus Arastéh[4], Vicente Soriano[5], Josep Guardiola[6], Sanjay Bhagani[7], Jürgen K. Rockstroh[8], Jerry O. Stern[9], Anne-Marie Quinson[9]

[1]Mount Sinai Medical Center, New York, NY, United States, [2]Hospital Universitari Germans Trias i Pujol, Barcelona, Spain, [3]Chelsea and Westminster Hospital, London, United Kingdom, [4]EPIMED/Vivantes Auguste-Viktoria-Klinikum, Berlin, Germany, [5]Hospital Carlos III, Madrid, Spain, [6]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [7]The Royal Free Hospital, London, United Kingdom, [8]Department of Medicine I, University of Bonn, Bonn, Germany, [9]Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, United States

24 **Simeprevir (TMC435) Plus PegIFN/Ribavirin in HCV Genotype-1/HIV-1 Coinfection (Study C212)**

Douglas Dieterich[1], Jürgen K. Rockstroh[2], Chloe Orkin[3], Félix Gutiérrez[4], Marina B. Klein[5], Jacques Reynes[6], Lotke Tambuyzer[7], Monika Peeters[7], Alan Jenkins[8], Wolfgang Jessner[7]

[1]Icahn School of Medicine at Mount Sinai, New York, NY, United States, [2]Medizinische. Universitätsklinik I, Bonn, Germany, [3]Royal London Hospital, London, United Kingdom, [4]Hospital General de Elche and Universidad Miguel Hernández, Alicante, Spain, [5]McGill University Health Centre, Montreal, QC, Canada, [6]Gui De Chauliac University Hospital, Montpellier, France, [7]Janssen Infectious Diseases BVBA, Beerse, Belgium, [8]Janssen Research & Development, Raritan, NJ, United States

25 **All-Oral Combination of Daclatasvir, Asunaprevir, and BMS-791325 for HCV Genotype 1 Infection**

Gregory T. Everson[1], Paul J. Thuluvath[2], Eric Lawitz[3], Tarek Hassanein[4], Maribel Rodriguez-Torres[5], **Trevor Hawkins**[6], Vinod Rustgi[7], Federico Hinestrosa[8], James Levin[9], Karen Sims[10]

[1]University of Colorado Denver, Aurora, CO, United States, [2]Mercy Medical Center, Baltimore, MD, United States, [3]The Texas Liver Institute, University of Texas Health Science Center, San Antonio, TX, United States, [4]Southern California Liver Centers, Coronado, CA, United States, [5]Fundación de Investigación, San Juan, Puerto Rico, [6]Southwest CARE Center, Santa Fe, NM, United States, [7]Metropolitan Research, Arlington, VA, United States, [8]Orlando Immunology Center, Orlando, FL, United States, [9]Dean Foundation for Health, Research and Education, Inc, Madison, WI, United States, [10]Bristol-Myers Squibb, Hopewell, NJ, United States

26 **Sofosbuvir Plus Ribavirin for HCV Genotype 1-3 Infection in HIV Coinfected Patients (PHOTON-1)**

Susanna Naggie[1], Mark Sulkowski[2], Jacob Lalezari[3], W. Jeffrey Fessel[4], Karam Mounzer[5], Margaret Shuhart[6], Anne Luetkemeyer[7], David Asmuth[8], Douglas Dieterich[9], Maribel Rodriguez-Torres[10], and The Gilead PHOTON-1 Study Team

[1]Duke Clinical Research Institute, Durham, NC, United States, [2]The Johns Hopkins University, Baltimore, MD, United States, [3]Quest Clinical Research, San Francisco, CA, United States, [4]Kaiser Permanente, San Francisco, CA, United States, [5]Philadelphia FIGHT, Philadelphia, PA, United States, [6]Harborview Medical Center, Seattle, WA, United States, [7]San Francisco General Hospital, San Francisco, CA, United States, [8]University of California Davis Medical Center, Sacramento, CA, United States, [9]Mount Sinai School of Medicine, New York, NY, United States, [10]Fundacion De Investigacion, San Juan, PR, United States

27LB **Combination Oral, Hepatitis C Antiviral Therapy for 6 or 12 Weeks: Final Results of the SYNERGY Trial**

Anita Kohli[1,2], Zayani Sims[1], Amy Nelson[3], Anu Osinusi[3,4], Geb Tefari[5], Phil Pang[6], William Symonds[6], John McHutchison[6], Henry Masur[1], Shyam Kottilil[3]

[1]Critical Care Medicine Department, National Institutes of Health, Bethesda, MD, United States, [2]Clinical Research Directorate/Clinical Monitoring Research Program, Leidos Biomedical Research, Inc. (formerly SAIC–Frederick, Inc.), Frederick National Laboratory for Cancer Research, Frederick, MD, United States, [3]Laboratory of Immunoregulation, National Institutes of Health, Bethesda, MD, United States, [4]University of Maryland, Baltimore, MD, United States, [5]Unity Health Care, Washington, DC, United States, [6]Gilead Sciences, Foster City, CA, United States

28LB **Daclatasvir in Combination With Simeprevir ± Ribavirin for Hepatitis C Virus Genotype 1 Infection**

Stefan Zeuzem[1], **Christophe Hezode**[2], Jean-Pierre P. Bronowicki[3], Veronique Loustad-Ratti[4], Francisco Gea[5], Maria Buti[6], Maria Beumont-Mauviel[7], Navdeep Boparai[8], Gaston Picchio[9], Stephanie Noviello[8], on behalf of the LEAGUE-1 Study Team

[1]JW Goethe University Hospital, Frankfurt a.m., Germany, [2]Hôpital Henri Mondor, Paris, France, [3]Centre Hospital Universitaire de Nancy, Vandoeuvre Les Nancy, France, [4]Université Limoges, Limoges, France, [5]University Hospital La Paz, Madrid, Spain, [6]Hospital Vall Hebron, Barcelona, Spain, [7]Janssen Infectious Disease BVBA, Beerse, Belgium, [8]Bristol-Myers Squibb, Princeton, NJ, United States, [9]Janssen Research and Development, Titusville, NJ, United States

29LB **PEARL III: SVR ≥99% After 12 Wks of ABT-450/r/267 + ABT-333 ± RBV in Treatment Naïve HCV GT1b Infection**

Peter Ferenci[1], Anders Nyberg[2], David Bernstein[3], Yaacov Baruch[4], Vladimir Chulanov[5], Wangang Xie[6], Daniel Cohen[6], Thomas Podsadecki[6], **K Rajender Reddy**[7], on behalf of the PEARL-III Study Group

[1]Universitaetsklinik fuer Innere Medizin III, Vienna, Austria, [2]Kaiser Permanente, San Diego, CA, United States, [3]North Shore University Hospital, Manhasset, NY, United States, [4]Rambam Health Care Campus, Haifa, Israel, [5]Federal Budget Institute of Science, Moscow, Russian Federation, [6]AbbVie Inc., North Chicago, IL, United States, [7]University of Pennsylvania, Philadelphia, PA, United States

Session O-2 Oral Abstracts

10:00 AM – 12:00 PM Room 304

NeuroHIV: Developments in Treatment and Pathogenesis

Moderators

Edwina J. Wright, *The Alfred Hospital, Monash University, Melbourne, Australia*

Victor G. Valcour, *University of California San Francisco, San Francisco, CA, United States*

30 **Early Antiretroviral Therapy Appears To Normalize Intrathecal Markers of Immune Activation**

Julia Peterson[1], Evelyn Lee[1], Dietmar Fuchs[2], Richard W. Price[1], Serena Spudich[3]

[1]Neurology, University of California San Francisco, San Francisco, CA, United States, [2]Innsbruck Medical University, Innsbruck, Austria, [3]Neurology, Yale University, New Haven, CT, United States

31 **Immediate Antiretroviral Therapy Mitigates the Development of Neuronal Injury in Acute HIV**

Michael J. Peluso[1], Victor Valcour[2], Jintanat Ananworanich[3, 4], Pasiri Sithinamsuwan[5], Thep Chalermchai[4], Nitiya Chomchey[4], Bonnie Slike[6], Magnus Gisslen[7], Henrik Zetterberg[7], Serena Spudich[8], on behalf of the RV254/SEARCH 010 and 011 Study Teams

[1]Department of Medicine, Brigham and Women's Hospital, Boston, MA, United States, [2]Memory and Aging Center, University of California San Francisco, San Francisco, CA, United States, [3]Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, [4]SEARCH, The Thai Red Cross AIDS Research Center, Bangkok, Thailand, [5]Phramongkutklao Hospital, Bangkok, Thailand, [6]US Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD, United States, [7]University of Gothenburg, Gothenburg, Sweden, [8]Yale University School of Medicine, New Haven, CT, United States

32 **Replication of HIV-1 in the Central Nervous System of Adults Early After Infection**

Christa Buckheit Sturdevant[1], Gretja Schnell[1], Richard W. Price[2], Serena Spudich[3], Ronald Swanstrom[1]

[1]UNC Chapel Hill, Chapel Hill, NC, United States, [2]University of California San Francisco, San Francisco, CA, United States, [3]Yale University, New Haven, CT, United States

33 **Persistent CSF, But Not Plasma HIV RNA Is Associated With Increased Risk of New-Onset Depression**

Edward R. Hammond[1], Rosa M. Crum[1], Glenn J. Treisman[1], Shruti H. Mehta[1], Ronald J. Ellis[2], Igor Grant[2], Scott L. Letendre[2], Christina M. Marra[3], Susan Morgello[4], Justin C. McArthur[1]

[1]The Johns Hopkins University, Baltimore, MD, United States, [2]University of California San Diego, San Diego, CA, United States, [3]University of Washington, Seattle, WA, United States, [4]Icahn School of Medicine at Mount Sinai, New York, NY, United States

34 **CSF Metabolomics Reveals Altered Waste Clearance and Accelerated Aging in HIV Patients With HAND**

Edana Cassol[1], Vikas Misra[1], Anupriya Dutta[1], Susan Morgello[2], Dana Gabuzda[1]

[1]Cancer Immunology and AIDS, Dana-Farber Cancer Institute, Boston, MA, United States, [2]The Mount Sinai Medical Center, New York, NY, United States

35 **Cerebral Small Vessel Disease and HAND in ARV-Treated Subjects**

Virawudh Soontornniyomkij, Anya Umlauf, Benchawanna Soontornniyomkij, Ben Gouaux, Will Toperoff, David J. Moore, Eliezer Masliah, Igor Grant, **Cristian L. Achim**

UC San Diego, San Diego, CA, United States

Session O-3 Oral Abstracts

10:00 AM – 12:30 PM Ballroom A

Prevention and Epidemiology: Evolving Trends

Moderators

Rochelle P. Walensky, *Harvard Medical School, Massachusetts General Hospital, Boston, MA, United States*

Ian M. McGowan, *University of Pittsburgh, Pittsburgh, PA, United States*

36 **Temporal Trends in Prognostic Markers of HIV-1 Virulence and Transmissibility**

Nikos Pantazis[1], Kholoud Porter[2], Dominique Costagliola[3], Andrea De Luca[4], Jade Ghosn[5], Marguerite Guiguet[3], Anthony D. Kelleher[6], Charles Morrison[7], Rodolphe Thiebaut[8], Giota Touloumi[1], on behalf of the CASCADE Collaboration in EuroCoord

[1]Hygiene, Epidemiology & Medical Statistics, Athens University Medical School, Athens, Greece, [2]MRC Clinical Trials Unit at University College London, London, United Kingdom, [3]INSERM U943, Université Pierre et Marie Curie - Paris 6, UMR S 943, Paris, France, [4]Institute of Clinical Infectious Diseases, Università Cattolica del Sacro Cuore, Roma, Italy, [5]Internal Medicine and Infectious Diseases, Bicetre University Hospital, Kremlin Bicetre, Paris, France, [6]Kirby Institute, University of New South Wales, Sidney, Australia, [7]FHI 360, Durham, NC, United States, [8]INSERM U897 Centre of Epidemiology and Biostatistics, ISPED Bordeaux School of Public Health, University Bordeaux Segalen, Bordeaux, France

37 **Transmission Clusters, Recent Infection and STIs Among New HIV Cases: Implications for Prevention**

Hong-Ha M. Truong[1, 2], Sharon Pipkin[3], Kara O'Keefe[3], Brian Louie[3], Teri Liegler[1], Willi McFarland[1, 3], Robert M. Grant[1, 2], Mark Pandori[3], Kyle Bernstein[3], Susan Scheer[3]

[1]University of California San Francisco, San Francisco, CA, United States, [2]Gladstone Institute of Virology and Immunology, San Francisco, CA, United States, [3]Department of Public Health, San Francisco, CA, United States

38 **Race and Age Disparities in HIV Incidence and Prevalence Among MSM in Atlanta, GA**

Eli S. Rosenberg[1], Patrick S. Sullivan[1], Colleen F. Kelley[2], Travis H. Sanchez[1], Nicole Luisi[1], Carlos del Rio[3], Laura F. Salazar[4], Paula F. Frew[5], John L. Peterson[6]

[1]Epidemiology, Emory University Rollins School of Public Health, Atlanta, GA, United States, [2]Infectious Diseases, Emory University School of Medicine, Atlanta, GA, United States, [3]Hubert Department of Global Health, Emory University Rollins School of Public Health, Atlanta, GA, United States, [4]Institute of Public Health, Georgia State University, Atlanta, GA, United States, [5]Medicine, Emory University School of Medicine, Atlanta, GA, United States, [6]Psychology, Georgia State University, Atlanta, GA, United States

39 **Correlating GSK1265744 Plasma Levels To Prevention of Rectal SHIV Transmission in Macaques**

Chasity D. Andrews[1], William Spreen[2], Yun Lan Yueh[2], Agegnehu Gettie[1], Kasi Russell-Lodrigue[3], Hiroshi Mohri[1], Cecilia Cheng-Mayer[1], Zhi Hong[2], Martin Markowitz[1], David D. Ho[1]

[1]Aaron Diamond AIDS Research Center, The Rockefeller University, New York, NY, United States, [2]GlaxoSmithKline, Research Triangle Park, NC, United States, [3]Tulane National Primate Research Center, Covington, LA, United States

40LB **Monthly GSK744 Long-Acting Injections Protect Macaques Against Repeated Vaginal SHIV Exposures**

Jessica Radzio[1], William Spreen[2], Yun Lan Yueh[2], James Mitchell[1], Leecresia Jenkins[1], **J. Gerardo Garcia-Lerma**[1], Walid Heneine[1]

[1]Division of HIV/AIDS Prevention, CDC, Atlanta, GA, United States, [2]GlaxoSmithKline, Research Triangle Park, NC, United States

41 **Safety and Pharmacokinetics/Pharmacodynamics of Dapivirine and Maraviroc Vaginal Rings**

Beatrice A. Chen[1], Lori Panther[2], Craig Hoesley[3], Craig Hendrix[4], Ariane van der Straten[5], Marla Husnik[6], Lydia E. Soto-Torres[7], Annalene Nel[8], Sherri Johnson[9], Charlene S. Dezzutti[10]

[1]University of Pittsburgh, Pittsburgh, PA, United States, [2]The Fenway Institute, Boston, MA, United States, [3]University of Alabama at Birmingham, Birmingham, AL, United States, [4]The Johns Hopkins University, Baltimore, MD, United States, [5]RTI International, San Francisco, CA, United States, [6]Statistical Center for HIV/AIDS Research & Prevention, Fred Hutchinson Cancer Research Center, Seattle, WA, United States, [7]NIAID/DAIDS, Bethesda, MD, United States, [8]International Partnership for Microbicides, Silver Spring, MD, United States, [9]FHI 360, Research Triangle Park, NC, United States, [10]Magee-Women's Research Institute, Pittsburgh, PA, United States

42LB **FAME-02: A Phase I Trial To Assess Safety, PK, and PD of Gel and Film Formulations of Dapivirine**

Katherine E. Bunge[1], Charlene S. Dezzutti[2], Ingrid Macio[1], Craig W. Hendrix[3], Lisa C. Rohan[2], Mark A. Marzinke[3], Brid Devlin[4], Leslie A. Meyn[2], Hans M. L. Spiegel[5], Sharon L. Hillier[2]

[1]Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh, Pittsburgh, PA, United States, [2]Magee-Womens Research Institute, Pittsburgh, PA, United States, [3]Department of Medicine, The Johns Hopkins University, Baltimore, MD, United States, [4]International Partnership for Microbicides, Silver Spring, MD, United States, [5]Division of AIDS, National Institutes of Health, Bethesda, MD, United States

43 **Single-Agent TDF Versus Combination FTC/TDF PrEP Among Heterosexual Men and Women**

Jared Baeten[1, 2], Deborah Donnell[1, 2], Patrick Ndase[1], Nelly Mugo[1, 3], Connie Celum[1], Partners PrEP Study Team

[1]University of Washington, Seattle, WA, United States, [2]Fred Hutchinson Cancer Research Center, Seattle, WA, United States, [3]Kenya Medical Research Institute, Nairobi, Kenya

44 **Divergent Adherence Estimates With Pharmacokinetic and Behavioral Measures in VOICE (MTN003)**

Ariane van der Straten[1, 2], Elizabeth R. Brown[3], Jeanne M. Marrazzo[4], Zvavahera M. Chirenje[5], Kailazarid Gomez[6], Jeanna M. Piper[7], Craig W. Hendrix[8]

[1]Women's Global Health Imperative, RTI International, San Francisco, CA, United States, [2]Department of Medicine, Center for AIDS Prevention Studies (CAPS), University of California San Francisco, San Francisco, CA, United States, [3]Statistical Center for HIV/AIDS Research & Prevention (SCHARP), Fred Hutchinson Cancer Research Center, Seattle, WA, United States, [4]Department of Medicine, Division of Infectious Diseases, University of Washington, Seattle, WA, United States, [5]Department of Obstetrics and Gynecology, University of Zimbabwe, Harare, Zimbabwe, [6]FHI 360, Research Triangle Park, NC, United States, [7]Division of AIDS, National Institute of Allergy and Infectious Diseases, Bethesda, MD, United States, [8]Department of Medicine, The Johns Hopkins University, Baltimore, MD, United States

153LB **HIV Transmission Risk Through Condomless Sex If HIV+ Partner On Suppressive ART: PARTNER Study**

Alison Rodger[1], Tina Bruun[2], Valentina Cambiano[1], Pietro Vernazza[3], Vicente Estrada[4], Jan Van Lunzen[5], Simon Collins[6], Anna Maria Geretti[7], Andrew Phillips[1], Jens Lundgren[8], for the PARTNER Study Group

[1]Research Department of Infection & Population Health, University College London, London, United Kingdom, [2]Copenhagen HIV Programme, University of Copenhagen, Copenhagen, Denmark, [3]Infectious Diseases, Cantonal Hospital, St. Gallen, Switzerland, [4]Department of Infectious Diseases, Hospital Clínico San Carlos, Madrid, Spain, [5]Department of Infectious Diseases, University Medical Center, Hamburg, Germany, [6]HIV i-Base, London, United Kingdom, [7]Institute of Infection & Global Health, University of Liverpool, Liverpool, United Kingdom, [8]Centre for Viral Diseases and the Copenhagen HIV Programme, University of Copenhagen, Copenhagen, Denmark

Session O-4 Oral Abstracts

10:00 AM – 12:00 PM **Room 312**

Host Factors and HIV/SIV Replication

Moderators

Renate R. Köenig, *Paul-Ehrlich-Institut, Langen, Germany*

Alan N. Engelman, *Dana-Farber Cancer Institute, Boston, MA, United States*

45 **Inhibition of Cul4A Neddylation Causes a Reversible Block To SAMHD1-Mediated Restriction of HIV-1**

Henning Hofmann, Thomas D. Norton, Eric C. Logue, Megan L. Schultz, Sylvie B. Polsky, Nicole Sunseri, Nathaniel R. Landau

NYU School of Medicine, New York, NY, United States

46 **MX2, an Interferon-Induced Inhibitor of HIV-1 Infection**

Melissa Kane[1], Shalini S. Yadav[1, 2], Julia Bitzegeio[1], Sebla B. Kutluay[1], Trinity Zang[1, 2], Sam J. Wilson[1, 2], Daniel Blanco-Melo[1], Masahiro Yamashita[3], Theodora Hatziioannou[3], Paul D. Bieniasz[1, 2]

[1]The Rockefeller University, New York, NY, United States, [2]Howard Hughes Medical Institute, New York, NY, United States, [3]Aaron Diamond AIDS Research Center, New York, NY, United States

47 **BCA2/Rabring7 Targets HIV-1 Gag for Lysosomal Degradation in a Tetherin-Independent Manner**

Ruth Serra-Moreno

Harvard Medical School, Southborough, MA, United States

48 **Crystal Structure of APOBEC3F Elucidates HIV-1 Vif Interaction and Dynamic Oligomerization**

Markus-Frederik Bohn, Shivender M. D. Shandilya, Mohan Somasundaran, Celia A. Schiffer

Biochemistry, UMass Medical School, Worcester, MA, United States

49LB **Crystal Structure of a TRIM Coiled-Coil: Implications for HIV-1 Capsid Recognition by TRIM5α**

Jacint G. Sanchez[1], Katarzyna Okreglicka[1], Viswanathan Chandrasekaran[2], Jordan M. Welker[1], Wesley I. Sundquist[2], **Owen Pornillos**[1]

[1]Molecular Physiology and Biological Physics, University of Virginia, Charlottesville, VA, United States, [2]Biochemistry, University of Utah, Salt Lake City, UT, United States

50 **Global Identification of the RNA Targets of HIV-1 Gag During Particle Genesis**

Sebla B. Kutluay[1], Daniel Blanco-Melo[1], Trinity Zang[1], Paul D. Bieniasz[1, 2]

[1]Aaron Diamond AIDS Research Center, New York, NY, United States, [2]Rockefeller University & Howard Hughes Medical Institute, New York, NY, United States

51 **Gorillas Transmitted SIV To Humans: Identification of HIV-1 Group P and O Ancestors**

Mirela D'arc[1], Ahidjo Ayouba[2], Amandine Esteban[2], Avelin Aghokeng[2, 3], Sabrina Locatelli[2], Lucie Etienne[2], Beatrice Hahn[4], Eric Delaporte[2], Eitel Mpoudi Ngole[5], Martine Peeters[2]

[1]Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, [2]UMI 233, IRD and University of Montpellier 1, Montpellier, France, [3]Projet PRESICA and IMPM/CREMER, Yaoundé, Cameroon, [4]University of Pennsylvania, Philadelphia, PA, United States, [5]Projet PRESICA and IMPM/CREME, Yaoundé, Cameroon

52LB **A Gorilla Reservoir for Human T-lymphotropic Virus Type 4 (HTLV-4)**

Matthew LeBreton[1,2], William M. Switzer[3], Cyrille F. Djoko[2], Amethyst Gillis[1], Hongwei Jia[3], **Walid Heneine**[3], Anupama Shankar[3], HaoQiang Zheng[3], Bradley S. Schneider[1], Nathan D. Wolfe[1,4]

[1]Metabiota, San Francisco, CA, United States, [2]Global Viral Cameroon, Yaounde, Cameroon, [3]CDC, Atlanta, GA, United States, [4]Global Viral, San Francisco, CA, United States

Session TD1 Themed Discussion

1:30 PM – 2:30 PM **Room 309**

Acute HCV Infection

Discussion Leader

Georg M. Lauer, *Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States*

676 **Seminal HCV RNA Level May Mirror Dynamics of Plasma HCV RNA in HIV-Positive Men With Acute HCV**

Daniel Bradshaw[1], Francois Lamoury[1], Beth Catlett[2], Tanya L. Applegate[1], John Mcallister[2], Gregory J. Dore[1], Gail Matthews[1], Mark Danta[3]

[1]Kirby Institute, University of New South Wales, Sydney, Australia, [2]St Vincent's Hospital, Sydney, Australia, [3]Faculty of Medicine, University of New South Wales, Sydney, Australia

675 **Higher Risk of Sexually Acquired HCV Coinfection in MSM With Wide HIV Transmission Bottleneck**

Roger D. Kouyos[1], Andri Rauch[2], Dominique Braun[1], Sabine Yerly[3], Jürg Böni[4], Thomas Klimkait[5], Vincent Aubert[6], Bruno Ledergerber[1], Hulrdrych Günthard[1], The Swiss HIV Cohort Study (SHCS)

[1]University Hospital Zurich, University of Zurich, Zurich, Switzerland, [2]Inselspital Bern, Bern, Switzerland, [3]University of Geneva, Geneva, Switzerland, [4]University of Zurich, Zurich, Switzerland, [5]University of Basel, Basel, Switzerland, [6]University of Lausanne, Lausanne, Switzerland

674 **Assessing HCV Acquisition Routes in HIV-Infected MSM Using Single Genome Sequencing—A Pilot Study**

Daniel S. Fierer[1], Andrew H. Talal[2], Kristen M. Marks[3], Wouter O. van Seggelen[1], Andrea D. Branch[4], Shirish Huprikar[1], Shuyi Wang[5], George M. Shaw[5], Hui Li[5]

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681 **CD3+CD56+ Natural Killer-Like T Cells in HIV(+) Patients With Acute Hepatitis C**

Pavlos Kokordelis[1, 2], Benjamin Krämer[1, 2], Christoph Boesecke[1, 2], Esther Voigt[3], Patrick Ingiliz[4], Andreas Glässner[1, 2], Ulrich Spengler[1, 2], Jürgen K. Rockstroh[1, 2], Jacob Nattermann[1]

[1]Internal Medicine I, University of Bonn, Bonn, Germany, [2]German Center for Infection Research (DZIF), Bonn, Germany, [3]Internal Medicine I, Praxis am Ebertplatz, Cologne, Germany, [4]Medical Center for Infectious Diseases (MID), Berlin, Germany

Session TD2 Themed Discussion

1:30 PM – 2:30 PM **Ballroom A**

Restriction Factors

Discussion Leader

Paul W. Spearman, *Emory University, Atlanta, GA, United States*

188 **Degradation of SAMHD1 Specifically Decreases the Efficacy of Thymidine HIV RT Analog Inhibitors**

Ester Ballana, Gerard Terradas, Eva Riveira-Muñoz, Bonaventura Clotet, Eduardo Pauls, José A. Esté

IrsiCaixa AIDS Research Institute, Badalona, Spain

182 **Characterizing Novel N-Terminal Domains of APOBEC3G**

Meiling R. May[1], Ann M. Sheehy[2]

[1]College of the Holy Cross, Worcester, MA, United States, [2]Biology, College of the Holy Cross, Worcester, MA, United States

188A **Natural Resistance To HIV-1 by Select APOBEC3H Haplotypes**

Eric W. Refsland[1], Judd F. Hultquist[1], Elizabeth M. Luengas[1], Rachel Prosser[2], Keith Henry[2], Michael Emerman[3], Reuben S. Harris[1]

[1]Biochemistry, Molecular Biology, and Biophysics, University of Minnesota, Minneapolis, MN, United States, [2]Hennepin County Medical Center, Minneapolis, MN, United States, [3]Fred Hutchinson Cancer Research Center, Seattle, WA, United States

186 **Nuclear Import of APOBEC3F-Labeled HIV-1 Preintegration Complexes**

Ryan C. Burdick, Wei-Shau Hu, **Vinay K. Pathak**

HIV Drug Resistance Program, National Cancer Institute, Frederick, MD, United States

Session TD3 Themed Discussion

1:30 PM – 2:30 PM **Room 304**

Heart Failure, Cardiac Steatosis, and HIV

Discussion Leader

Wendy S. Post, *The Johns Hopkins University School of Medicine, Baltimore, MD, United States*

725 **ST2 and GDF-15 Are Associated With Structural Heart Disease and Mortality in HIV**

Eric Secemsky, Rebecca Scherzer, Elaine Nitta, Alan Wu, David Lange, Steven Deeks, Jeffrey Martin, James Snider, Peter Ganz, Priscilla Hsue

University of California San Francisco, San Francisco, CA, United States

723 **Elevated NT-proBNP Levels Predict Mortality in HIV-Infected Women**

Matthew R. Gingo[1], Kidane Ghebrehawariat[1], Jong-Hyeon Jeong[1], Yanxia Chu[1], Quanwei Yang[1], Lorrie Lucht[1], David Hanna[2], Jason Lazaar[3], Mark Gladwin[1], Yingze Zhang[4], Alison Morris[1]

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726 **Depression and HIV Are Risk Factors for Incident Heart Failure Among Veterans**

Jessica R. White[1], Chung-Chou H. Chang[1, 2], Adeel A. Butt[2, 3], Hilary A. Tindle[2], Maria C. Rodriguez Barradas[4, 5], David Rimland[6, 7], David Leaf[8, 9], Matthew Budoff[10, 11], Amy C. Justice[12, 13], Matthew S. Freiberg[2, 3]

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724 **Cardiac Steatosis Increased in HIV: Related To Gender, Visceral Fat and ARV Exposure**

Julia B. Purdy[1], Chia-Ying Liu[2], Sabrina Mangat[3], Horacio Duarte[4], Diana Thiara[5], Nancyanne Schmidt[6], Jamie Hur[7], Christopher T. Sibley[2], David A. Bluemke[2], Colleen Hadigan[3]

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Session TD4 Themed Discussion

1:30 PM – 2:30 PM **Room 312**

Response To Early ART Initiation in Infants

Discussion Leader

Mark F. Cotton, *Stellenbosch University, Cape Town, South Africa*

922 Routine Antibody Tests Have No Place in Determining HIV Status After Early ART: Evidence From CHER

Helen Payne[1,2], Nonhlanhla Mkhize[3], Lynn Morris[3], Kennedy Otwombe[4], Ravindre Panchia[4], Avy Violari[4], Nigel Klein[1], Abdel G. Babiker[5], Mark F. Cotton[2], Diana M. Gibb[5]

[1]Infectious Diseases and Microbiology, Institute of Child Health, London, United Kingdom, [2]Children's Infectious Diseases Clinical Research Unit, Faculty of Medicine and Health Sciences, University of Stellenbosch, Cape Town, South Africa, [3]Centre for HIV and STIs, National Institute for Communicable Diseases, Johannesburg, South Africa, [4]Perinatal HIV Research Unit, University of the Witwatersrand, Johannesburg, South Africa, [5]Clinical Trials Unit, Medical Research Council, London, United Kingdom

923 Different Profiles of HIV in Early Treated HIV-Infected Children Seronegative by ELISA in Cameroon

Mathurin C. Tejiokem[1], Anfumbom Kfutwah[2], Francis Ateba Ndongo[3], Suzie Tetang Ndiang[4], Ida Calixte Penda[5,6], William Mbanzouen[2], Félicité Owona[1], Josiane Warszawski[7,8], Christine Rouzioux[9,10], Albert Faye[11,12]

[1]Service d'Épidémiologie et de Santé Publique, Centre Pasteur du Cameroun, Membre du Réseau International des Instituts Pasteur, Yaoundé, Cameroon, [2]Service de Virologie, Centre Pasteur du Cameroun, Membre du Réseau International des Instituts Pasteur, Yaoundé, Cameroon, [3]Unité de Jour, Centre Mère et Enfant, Fondation Chantal Biya, Yaoundé, Cameroon, [4]Service de Pédiatrie, Centre Hospitalier d'Essos, Yaoundé, Cameroon, [5]Hôpital de Jour, Hôpital Laquintinie de Douala, Douala, Cameroon, [6]Université de Douala, Faculté de Médecine et des Sciences Pharmaceutiques, Douala, Cameroon, [7]EPF, Equipe 4 (VIH et IST), INSERM U1018 (CESP), Le Kremlin Bicêtre, France, [8]Université de Paris Sud 11, Paris, France, [9]Laboratoire de Virologie, Assistance Publique des Hôpitaux de Paris, Hôpital Necker, Paris, France, [10]Université Paris Descartes, EA 3620, Paris, France, [11]Pédiatrie Générale, Assistance Publique des Hôpitaux de Paris, Hôpital Robert Debré, Paris, France, [12]Université Paris 7 Denis Diderot, Paris Sorbonne Cité, Paris, France

924 Greater Virologic Control in Infants Initiated On ART Before 6 Months of Age

Stephanie Shiau[1], Ashraf Coovadia[2], Karl-Gunter Technau[2], Renate Strehlau[2], Leigh Martens[2], Francoise Pinillos[2], Elaine J. Abrams[1], Louise Kuhn[1]

[1]Columbia University, New York, NY, United States, [2]University of the Witwatersrand, Johannesburg, South Africa

925 Early Viral Suppression Improves Neurocognitive Outcomes in HIV-Infected Children

Claudia S. Crowell[1], Yanling Huo[2], Katherine Tassiopoulos[2], Kathleen M. Malee[3], Ram Yogev[3], Rohan Hazra[4], Richard M. Rutstein[5], Sharon L. Nichols[6], Renee A. Smith[7], William J. Muller[3], for the IMPAACT 219C Study Team and the PediatricHIV/AIDS Cohort Study

[1]Pediatrics, University of Washington, Seattle, WA, United States, [2]Epidemiology, Harvard School of Public Health, Boston, MA, United States, [3]Northwestern University Feinberg School of Medicine, Chicago, IL, United States, [4]National Institute of Child Health and Human Development, Bethesda, MD, United States, [5]Children's Hospital of Philadelphia, Philadelphia, PA, United States, [6]University of California San Diego, La Jolla, CA, United States, [7]University of Illinois at Chicago, Chicago, IL, United States

926 Early Cytomegalovirus Viraemia and Clinical Outcomes of HIV-Infected Children in the Early ART Era

Nei-yuan Hsiao[1], Kennedy Otwombe[2], Landon Myer[3], Avy Violari[2], Diana Gibb[4], Ravindre Panchiar[2], Abdel Babiker[4], Patrick Jean-Phillipe[5], Mark Fredric Cotton[6]

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Session TD5 Themed Discussion

1:30 PM – 2:30 PM **Room 311**

Treatment Cascade and Loss To Follow-Up

Discussion Leader

David R. Bangsberg, *Massachusetts General Hospital Center for Global Health, Boston, MA, United States*

1060 Comparative Effectiveness of HIV Care and Treatment Programs in East Africa

Elvin Geng[1], Thomas Odeny[2], Rita Lyamuya[3], Alice Nakiwogga-Muwanga[4], Mwebesa Bwana[5], Paula Braitstein[6], Andrew Kambugu[4], Elizabeth Bukusi[7], Geoffrey Somi[8], Lameck Diero[9], Jeffrey Martin[10]

[1]Medicine, University of California San Francisco, San Francisco, CA, United States, [2]KEMRI, Nairobi, Kenya, [3]Medicine, NACP, Dar es Salaam, Tanzania, United Republic of, [4]IDI, Kampala, Uganda, [5]Medicine, MUST, Mbarara, Uganda, [6]AMPATH, Eldort, Kenya, [7]Medicine, KEMRI, Nairobi, Kenya, [8]NACP, Dar es Salaam, Tanzania, United Republic of, [9]AMPATH, Eldoret, Kenya, [10]University of California San Francisco, San Francisco, CA, United States

1063 HIV Care Cascade Among Hard To Reach Populations in India: Need To Expand HIV Counseling and Testing

Shruti H. Mehta[1], Gregory M. Lucas[2], Suniti Solomon[3], Aylur K. Srikrishnan[3], Allison McFall[1], P. Nandagopal[3], Pachamuthu Balakrishnan[3], Muniratnam S. Kumar[3], David D. Celentano[1], Sunil S. Solomon[2,3]

[1]Epidemiology, The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States, [2]The Johns Hopkins University School of Medicine, Baltimore, MD, United States, [3]YR Gaitonde Centre for AIDS Research and Education, Chennai, India

1061 Loss To Follow-up: Determining Outcomes for Adults Enrolled in HIV Services in Kenya

William Reidy[1], Mansi Agarwal[1], Matthew Lamb[1], Mark Hawken[1], Duncan Chege[1], Batya Elul[1], Elaine J. Abrams[1], Elvin Geng[2]

[1]Mailman School of Public Health, ICAP-Columbia University, New York, NY, United States, [2]School of Medicine, University of California at San Francisco, San Francisco, CA, United States

1064 Unplanned Interruptions in HIV Care in Nigeria: Rates and Implications

Aima A. Ahonkhai[1], Bolanle Banigbe[2], Juliet Adeola[2], Ifeyinwa Onwuatuelo[2], Ingrid V. Bassett[3], Elena Losina[4], Kenneth A. Freedberg[1], Propser Okonkwo[2], Susan Regan[1]

[1]Massachusetts General Hospital, Boston, MA, United States, [2]AIDS Prevention Initiative Nigeria, Abuja, Nigeria, [3]Infectious Disease, Massachusetts General Hospital, Boston, MA, United States, [4]Brigham and Women's Hospital, Boston, MA, United States

1065 Using the Side Door: Non-Linear Patterns Within the HIV Treatment Cascade in Zambia

Charles B. Holmes[1,2], Angela Bengtson[1,2], Izukanji Sikazwe[1,2], Carolyn Bolton-Moore[1,2], Lloyd B. Mulenga[1], Patrick Musonda[1,3], Benjamin H. Chi[1,2]

[1]Centre for Infectious Disease Research in Zambia, Lusaka, Zambia, [2]University of North Carolina School of Medicine, Chapel Hill, NC, United States, [3]University of East Anglia, East Anglia, United Kingdom

POSTER SESSIONS

2:30 PM – 4:00 PM

(Use the Poster Abstract section of the Program at a Glance, page 37 to 106, for specific posters in each session)

Session P-A1 SAMHD1
Session P-A2 Integration/Nuclear Import
Session P-B1 Transmission Networks
Session P-C1 The Gut and Lymph Nodes in HIV Pathogenesis
Session P-C2 Immune Activation and Pathogenesis
Session P-C3 NK Cells in HIV Pathogenesis
Session P-C4 CD8 T-Cell Pathogenesis
Session P-C5 Exhaustion Markers
Session P-D1 It's All About the Gut
Session P-E1 Modulating Immune Activation
Session P-E2 Therapeutic Vaccines and Immunotherapies
Session P-F1 Mechanisms of HIV Latency
Session P-F2 Dynamics of Persistent and Rebound HIV
Session P-F3 Effect of ART Early in HIV Infection
Session P-G1 CNS Viral Escape and Neuroinflammation on ART
Session P-G2 HAND in Aging Populations
Session P-H1 Clinical Pharmacology of TB and HCV Co-infection
Session P-H2 Pharmacogenetics: Drug Disposition To Therapeutics
Session P-I1 Preclinical Studies of Novel ART Approaches: Entry
Session P-I2 Preclinical Studies of Novel ART Approaches: Post-Entry
Session P-K1 Viral Set Point and Elite Controllers
Session P-L1 Primary Drug Resistance
Session P-L2 Acquired HIV Drug Resistance
Session P-M1 HIV Early Detection: Application of New Assays
Session P-N1 HCV Testing and Epidemiology
Session P-N2 HCV Pre-Clinical Studies and Pharmacology
Session P-O1 Lymphoma/Liver/Gammopathy
Session P-O2 Cancer: Natural History and Epidemiology
Session P-P1 Heart Failure, Cardiac Steatosis, and HIV
Session P-P2 Immune Activation, Immunodeficiency, and CVD
Session P-Q1 Biomarkers and Non-AIDS Events
Session P-Q2 Frailty: Physical Function and Telomeres
Session P-Q3 Diabetes and Insulin Resistance
Session P-S1 Reproductive Hormones in Women: Impact on Risk and Barrier Dysfunction
Session P-T1 Clinical Outcomes of HIV-Exposed Uninfected Infants
Session P-T2 Neonatal Sequelae of In Utero ART Exposure
Session P-U1 ART in Children and Adolescents
Session P-U2 HIV Drug Resistance and Tropism in Children and Youth
Session P-U3 ARV Pharmacokinetics, Pharmacogenetics, and Safety in Children and Adolescents
Session P-W1 Cascade of Care and Testing
Session P-W2 Cascade of Care, Linkage, and Retention
Session P-W3 Cascade of Care, Community Viral Load, and Viral Suppression
Session P-W4 Cascade of Care
Session P-X1 HIV Testing in Low-Income Settings
Session P-X2 HIV Treatment and Care

Session S1 Symposium

4:00 PM – 6:00 PM **Ballroom B/C**

Toward a Cure: A Challenging Game of Hide and Seek

Target audience: This session is directed to clinicians, basic researchers, and affected persons interested in the latest developments in HIV cure research.

Level of knowledge: It is assumed that learners are familiar with basic aspects of HIV replication and latency as well as standard therapeutic options.

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

- Understand the effects of early treatment on the establishment of the latent reservoir
- Understand the roles of different T-cell subsets in maintaining the latent reservoir
- Describe how different animal models can be used to investigate cure strategies prior to clinical trials

Conveners

Christine Rouzioux, *Université Paris Descartes, Paris, France*



Hiroyu Hatano, *University of California San Francisco, San Francisco, CA, United States*



53 **Impact of Early ART On HIV Eradication in Children**
Katherine F. Luzuriaga
University of Massachusetts Medical School, Worcester, MA, United States



54 **T Memory Stem Cells: The Stem Cell Reservoir for HIV?**
Mathias Lichterfeld
Massachusetts General Hospital, Boston, MA, United States



55 **Inflammation as an Obstacle for Remission: Lessons Learned From Non-Human Primate Models**
Michaela Müller-Trutwin
Institut Pasteur, Paris, France



56 **Humanized Mouse Models for Studies On HIV Latency, Reservoirs, and Eradication Strategies**
J. Victor Garcia-Martinez
University of North Carolina at Chapel Hill, Chapel Hill, NC, United States

Session S2 Symposium

4:00 PM – 6:00 PM **Ballroom A**

HCV and Beyond

Target audience: This session is directed to clinicians and researchers interested in viral hepatitis, including the latest information on the epidemiology of HEV, the biology of HCV, and efforts to cure HCV and HBV infections.

Level of knowledge: It is assumed that learners are familiar with basic principles of virology, epidemiology, and immunology.

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

- Recognize the nonhuman reservoirs for HEV infection
- Compare the innate immune responses to HCV and HIV infections
- Compare efforts to cure HIV and HBV infections
- Identify the major strategies for interferon alfa–sparing treatment of HCV

Conveners

Arthur Y. Kim, *Harvard Medical School, Boston, MA, United States*

Camila S. Graham, *Beth Israel Deaconess Medical Center, Boston, MA, United States*




57 **HEV: State of the Art**

Kenneth E. Sherman

University of Cincinnati College of Medicine, Cinncinnati, OH, United States



58 **HBV Eradication: Similarities To and Differences From HIV**

Shyam Kottilil

National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, United States



59 **Humoral Immunity and the Innate Response To HCV**

Andrea L. Cox

The Johns Hopkins University School of Medicine, Baltimore, MD, United States



60 **Interferon Alfa-Free Treatment of HCV**

Jean-Michel Pawlotsky

Henri Mondor Hospital, University of Paris-Est, Créteil, France



Session S3 Symposium

4:00 PM – 6:00 PM **Room 304**

PrEP: Use It or Lose It

Target audience: This session is directed to clinicians and scientists who are interested in understanding the differences in pre-exposure prophylaxis (PrEP) trial results and how PrEP can best be implemented for populations at high risk of HIV acquisition.

Level of knowledge: It is assumed that learners are familiar with the current status of PrEP for HIV prevention, the results from major clinical trials, and the challenges associated with the success of PrEP.

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

- Discuss potential reasons for differences in trial results
- Identify benefits and challenges in PrEP implementation in different settings
- Identify which populations may gain the greatest benefit from PrEP

Conveners

Lisa K. Fitzpatrick, *United Medical Center, Washington, DC, United States*

Suwat Chariyalertsak, *Chiang Mai University, Chiang Mai, Thailand*




61 **HIV Pre-Exposure Prophylaxis: Clinical Pharmacology Insights**

Craig W. Hendrix

The Johns Hopkins University School of Medicine, Baltimore, MD, United States



62 **Notes From the Field: Implementing PrEP in Resource Constrained Settings**

Nelly R. Mugo

Kenya Medical Research Institute, Nairobi, Kenya



63 **A Community Perspective On PrEP**

Christopher Balthazar and London Dorris

Stroger Hospital of Cook County, Chicago, IL, United States




64 **Choosing Populations for Maximal Impact**

David V. Glidden

University of California San Francisco, San Francisco, CA, United States



WEDNESDAY MARCH 5, 2014

Session PL3 Plenary

8:30 AM – 9:00 AM **Auditorium**

65 **B-Cell Responses To HIV Infection: Challenges and Opportunities**

Susan L. Moir, *National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, United States*



Session PL4 Plenary

9:00 AM – 9:30 AM **Auditorium**

66 **NeuroHIV in 2014: Beyond Dementia**

Serena S. Spudich, *Yale University, New Haven, CT, United States*



Session O-5 Oral Abstracts

10:00 AM – 12:15 PM **Room 304**

Critical Issues in MTCT: Maternal Health and HIV Treatment in Children

Moderators

Amita Gupta, *The Johns Hopkins University School of Medicine, Baltimore, MD, United States*

A. Sarah Walker, *Medical Research Council Clinical Trials Unit, London, United Kingdom*

67 **A 15-Year Review of Maternal Deaths in a Background of Changing HIV Management Guidelines**

Coceka N. Mnyani[1,2], Eckhart Buchmann[2], Karlyn Frank[2], Helen Struthers[1], James McIntyre[1]

[1]Anova Health Institute, Johannesburg, South Africa, [2]University of the Witwatersrand, Johannesburg, South Africa

68 **Incidence and Cofactors of Acute HIV During Pregnancy and Postpartum**

John Kinuthia[1], Alison Drake[2], Daniel Matemo[1], Barbra Richardson[3], R. Scott McClelland[4], Grace John-Stewart[5]

[1]Obstetrics and Gynaecology, University of Nairobi, Nairobi, Kenya, [2]Global Health, University of Washington, Seattle, WA, United States, [3]Biostatistics, University of Washington, Seattle, WA, United States, [4]Medicine, Global Health, Epidemiology, University of Washington, Seattle, WA, United States, [5]Global Health, Epidemiology, Medicine, Pediatrics, University of Washington, Seattle, WA, United States

69 **Efficacy and Safety of LPV/r Versus EFV in HIV+ Pregnant and Breast-Feeding Ugandan Women**

Deborah Cohan[1], Paul Natureeba[2], Albert Plenty[3], Flavia Luwedde Julia Mwesigwa[2], Veronica Ades[4], Edwin Charlebois[3], Tamara Clark Bridget Nzarubara[2], Moses Kamya[5], Pius Okong[6], Diane Havlir[3]

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70 **Infant Lopinavir/r Versus 3TC To Prevent Postnatal HIV-1 Transmission: The ANRS 12174 Trial**

Chipepo Kankasa[1], Nicolas Nagot[2,3], Nicolas Meda[4,5], James K. Tumwine[6], Amwe Aku[7], Debra Jackson[7], Roselyne Vallo[2,8], Thorkild Tylleskar[9], Philippe Van de Perre[2,3], ANRS 12174 Trial Group

[1]Department of Paediatrics and Child Health, University Teaching Hospital, Lusaka, Zambia, [2]INSERM U1058, Montpellier, France, [3]CHU Montpellier, Montpellier, France, [4]Centre de Recherche Internationale pour la Santé (CRIS), Université de Ouagadougou, Ouagadougou, Burkina Faso, [5]Centre Muraz, Bobo-Dioulasso, Burkina Faso, [6]Department of Paediatrics and Child Health, Makerere University, Kampala, Uganda, [7]School of Public Health, University of Western Cape, Cape Town, South Africa, [8]Université de Montpellier I, Montpellier, France, [9]Centre for International Health, University of Bergen, Bergen, Norway

71 **Lower Newborn Bone Mineral Content Associated With Maternal Use of Tenofovir Disoproxil Fumarate**

George K. Siberry[1], Denise L. Jacobson[2], Heidi Kalkwarf[3], Julia W. Wu[4], Linda A. DiMeglio[5], Ram Yogev[6,7], Katherine M. Knapp[8], Justin Wheeler[9], Rohan Hazra[1], Kenneth C. Rich[10]

[1]NICHD, Maternal and Pediatric Infectious Disease Branch, NIH, Bethesda, MD, United States, [2]Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, MA, United States, [3]Division of General and Community Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States, [4]Department of Epidemiology, Harvard School of Public Health, Boston, MA, United States, [5]Pediatric Endocrinology/Diabetology, Riley Hospital for Children at Indiana University Health, Indianapolis, IN, United States, [6]Ann & Robert Lurie Children's Hospital of Chicago, Chicago, IL, United States, [7]Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, United States, [8]Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, TN, United States, [9]Gerald J. and Dorothy R. Friedman School of Nutrition Science and Policy, Tufts University, Boston, MA, United States, [10]Department of Pediatrics, University of Illinois at Chicago, Chicago, IL, United States

72 **Virologic Control by 1 Year of Age Significantly Reduces HIV-1 Reservoirs in Perinatal Infection**

Deborah Persaud[1], Kunjal Patel[2], Brad Karalius[2], Carrie Ziemniak[1], Kaitlin Rainwater-Lovett[1], Ya Chen[1], Douglas D. Richman[3], George K. Siberry[4], Russell VanDyke[5], Katherine Luzuriaga[6], Pediatric HIV/AIDS Cohort Study (PHACS) and IMPAACT Network

[1]Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, MD, United States, [2]Epidemiology, Harvard School of Public Health, Boston, MA, United States, [3]Pathology and Medicine, University of California San Diego, San Diego, CA, United States, [4]Eunice Kennedy Shriver National Institutes of Child Health and Human Development, Bethesda, MD, United States, [5]Pediatrics, Tulane University Health Sciences Center, New Orleans, LA, United States, [6]Pediatrics, University of Massachusetts Medical School, Boston, MA, United States

73 **Virologic Efficacy of Efavirenz Maintenance Therapy in Nevirapine Prophylaxis-Exposed Children**

Ashraf Coovadia[1], Elaine Abrams[2], Renate Strehlau[1], Stephanie Shiau[2], Francoise Pinillos[1], Leigh Martens[1], Gillian Hunt[3], Wei-Yann Tsai[2], Lynn Morris[3], Louise Kuhn[2], NEVEREST 3 Study Team

[1]University of the Witwatersrand, Johannesburg, South Africa, [2]Columbia University, New York, NY, United States, [3]National Institute of Communicable Diseases, Johannesburg, South Africa

74LB **Final Results of Koncert: A Randomized Noninferiority Trial of QD Vs BD LPV/r Dosing in Children**

Hermione Lyall, KONCERT Trial Team

Imperial College London, London, United Kingdom

75LB **Very Early Combination Antiretroviral Therapy in Perinatal HIV Infection: Two Case Studies**

Deborah Persaud[1], Audra Deveikis[2], Hannah Gay[3], Jagmohan Batra[2], Tempe Chen[2], David E. Michalik[2], Kaitlin Rainwater-Lovett[1], Carrie Ziemniak[1], Katherine Luzuriaga[4], Yvonne Bryson[5]

[1]Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, MD, United States, [2]Pediatrics, Miller Children's Hospital, Long Beach, CA, United States, [3]Pediatrics, University of Mississippi Medical Center, Jackson, MS, United States, [4]Pediatrics, University of Massachusetts Medical School, Worcester, MA, United States, [5]Pediatrics, UCLA School of Medicine, Los Angeles, CA, United States

Session O-6 Oral Abstracts

10:00 AM – 12:00 PM Room 312

HIV/SIV Pathogenesis

Moderators

Marcus Altfeld, *Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology, and Harvard, Cambridge, MA, United States*

R. Keith Reeves, *Harvard Medical School, Boston, MA, United States*

76 **Pyroptosis Drives Both CD4 T Cell Death and Chronic Inflammation in HIV-Infected Lymphoid Tissues**

Gilad Doitsh[1], Nicole Galloway[1], Xin Geng[1], Kathryn Monroe[1], Zhiyuan Yang[1], Orlando Zepeda[2], Peter Hunt[2], Hiroyu Hatano[2], Stefanie Sowinski[1], Warner C. Greene[1]

[1]Gladstone Institute of Virology and Immunology, San Francisco, CA, United States, [2]University of California, San Francisco, San Francisco, CA, United States

77 **Early ART Initiation Prevents Disruption of the Mucosal Barrier and Subsequent T-Cell Activation**

Alexandra Schuetz[1], Yuwadee Phuang-Ngern[1], Rungsun Rerknimitr[2], Eugene Kroon[1, 3], Nitiya Chomchey[3], Praphan Phanuphak[3], Merlin Robb[4], Jerome Kim[4], Mark de Souza[3], Jintanat Ananworanich[2, 3], on behalf of the RV254/SEARCH 010 and RV304 StudyGroups

[1]Retrovirology, USAMC-AFRIMS, Bangkok, Thailand, [2]Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, [3]SEARCH, Bangkok, Thailand, [4]US Military HIV Research Program, Silver Spring, MD, United States

78 **Characterizing the IFNα Resistance of Transmitted Founder HIV-1**

Shilpa S. Iyer[1], Angharad E. Fenton-May[2], Andrew G. Smith[1], Weiyu Zhang[1], John C. Kappes[3], Feng Gao[4], Frederic Bibollet-Ruche[1], Hui Li[1], George M. Shaw[1], Persephone Borrow[5], Beatrice Hahn[1]

[1]Departments of Medicine and Microbiology, University of Pennsylvania, Philadelphia, PA, United States, [2]Nuffield Department of Clinical Medicine, Oxford, United Kingdom, [3]Departments of Medicine, University of Alabama at Birmingham, Birmingham, AL, United States, [4]Duke Human Vaccine Institute and Department of Medicine, Duke University Medical Centre, Durham, NC, United States, [5]Nuffield Department of Clinical Medicine, University of Oxford, Oxford, United Kingdom

79LB **Identification of IFI16 as HIV Restriction Factor**

Amalio Telenti[1], Ali Gawanbacht[2], Dominik Hotter[3], Christian Krapp[3], Nitisha Pyndiah[1], Greg Jordan[4], Søren R. Paludan[5], Martin R. Jakobsen[5], Frank Kirchhoff[2]

[1]University of Lausanne, Lausanne, Switzerland, [2]Institute of Molecular Virology, Ulm University Medical Center, Ulm, Germany, [3]Institute of Molecular Virology, Ulm University Medical Center, Ulm, Germany, [4]European Bioinformatics Institute, Cambridge, United Kingdom, [5]Department of Biomedicine and Aarhus Research Center for Innate Immunology, Aarhus, Denmark

80 **Central Memory and Effector Memory CD4 T Cells From HIV Controllers Harbor Distinct HIV Strains**

Eli Boritz[1], Luke Swaszek[1], Rebecca Hoh[2], Jeffrey Martin[3], Steven Deeks[2], Daniel Douek[1]

[1]Human Immunology Section, Vaccine Research Center, Bethesda, MD, United States, [2]Department of Medicine, University of California San Francisco, San Francisco, CA, United States, [3]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA, United States

81 **Accelerated Viral Load Increase and CD4 Decline in HIV-1 Superinfected Women**

Keshet Ronen[1], Barbra Richardson[1], Susan Graham[2], Kishor Mandaliya[3], Walter Jaoko[4], Scott McClelland[2], Julie Overbaugh[1]

[1]Fred Hutchinson Cancer Research Center, Seattle, WA, United States, [2]University of Washington, Seattle, WA, United States, [3]Coast Provincial General Hospital, Mombasa, Kenya, [4]University of Nairobi, Nairobi, Kenya

82 **Selection for Active SAMHD1 Antagonism in Natural Infections of SIVagm**

Chelsea Spragg[1, 2], Michael Emerman[2]

[1]Molecular and Cellular Biology, University of Washington, Seattle, WA, United States, [2]Human Biology, Fred Hutchinson Cancer Research Center, Seattle, WA, United States

83 **Probiotic and IL-21 Treatment Promotes Th17 Cell Recovery in ARV-Treatment of Pigtail Macaques**

Alexandra M. Ortiz[1], Zachary A. Klase[1], Kirby M. Carmack[1], Carol L. Vinton[1], Molly R. Perkins[1], Francois Villinger[2], Mirko Paiardini[2], Jason M. Brenchley[1]

[1]LMM, NIH, Bethesda, MD, United States, [2]Yerkes National Primate Research Center, Atlanta, GA, United States

Session O-7 Oral Abstracts

10:00 AM – 12:15 PM Ballroom B/C

Randomized Controlled Trials and Antiretroviral Resistance

Moderators

Urvi M. Parikh, *University of Pittsburgh, Pittsburgh, PA, United States*

Edmund C. Tramont, *National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, United States*

84LB **First-Line RAL + DRV/r Is Non-Inferior To TDF/FTC + DRV/r: The NEAT001/ANRS143 Randomised Trial**

François Raffi[1], Abdel G. Babiker[2], Laura Richert[3], Jean-Michel Molina[4], Elizabeth C. George[2], Andrea Antinori[5], Jose Arribas[6], Stefano Vella[7], Geneviève Chêne[3], Anton L. Pozniak[8], NEAT001/ANRS143 Study Group

[1]University Hospital, Nantes, France, [2]MRC Clinical Trials Unit at UCL, London, United Kingdom, [3]INSERM U897, Bordeaux, France, [4]St Louis Hospital, Paris, France, [5]INMI L Spallanzani, Rome, Italy, [6]Hospital La Paz, Madrid, Spain, [7]Istituto Superiore di Sanità, Rome, Italy, [8]Chelsea and Westminster Hospital, London, United Kingdom

85 **Efficacy and Tolerability of Atazanavir, Raltegravir, or Darunavir With FTC/Tenofovir: ACTG 5257**

Raphael J. Landovitz[1], Heather J. Ribaudo[2], Ighovwerha Ofotokun[3], Hongying Wang[2], Bryan P. Baugh[4], Randi Y. Leavitt[5], James F. Rooney[6], Daniel Seekins[7], Judith S. Currier[1], Jeffrey L. Lennox[3]

[1]Center for Clinical AIDS Research & Education, University of California Los Angeles, Los Angeles, CA, United States, [2]Harvard Center for Biostatistics in AIDS Research, Boston, MA, United States, [3]Division of Infectious Diseases, Emory University, Atlanta, GA, United States, [4]Janssen Therapeutics, Titusville, NJ, United States, [5]Merck & Co, Whitehouse Station, NJ, United States, [6]Gilead Sciences, Foster City, CA, United States, [7]Bristol-Myers Squibb, Wallingford, CT, United States

86 **Attachment Inhibitor Prodrug BMS-663068 in ARV-Experienced Subjects: Week 24 Analysis**

Jacob Lalezari[1], Gulam H. Latiff[2], Cynthia Brinson[3], Juan Echevarría[4], Sandra Treviño-Pérez[5], Johannes R. Bogner[6], David Stock[7], Samit R. Joshi[7], George J. Hanna[8], Max Lataillade[7], for the AI438011 study team

[1]Quest Clinical Research, San Francisco, CA, United States, [2]Maxwell Clinic, Durban, South Africa, [3]Central Texas Clinical Research, Austin, TX, United States, [4]Hospital Nacional Cayetano Heredia, Lima, Peru, [5]Mexico Centre for Clinical Research, Mexico City, Mexico, [6]Hospital of the University of Munich, Munich, Germany, [7]Bristol-Myers Squibb, Wallingford, CT, United States, [8]Bristol-Myers Squibb, Princeton, NJ, United States

87 **Sensitive Screening Reveals Widespread Underestimation of Transmitted HIV Drug Resistance**

Jin-fen Li, David Kim, Laurie Linley, Richard Kline, Walid Heneine, **Jeffrey A. Johnson**

Division of HIV/AIDS Prevention, CDC, Atlanta, GA, United States

88 **Transmitted HIV-1 Drug Resistance Between Partner-Pairs**

Joanne Stekler[1], Rachel Payant[2], Ingrid Beck[2], Brandon Maust[1], Sarah Holte[1,3], Janine Maenza[1], Claire E. Stevens[1], James I. Mullins[1], Ann C. Collier[1], Lisa M. Frenkel[1,2]

[1]University of Washington, Seattle, WA, United States, [2]Seattle Children's Hospital, Seattle, WA, United States, [3]Fred Hutchinson Cancer Research Center, Seattle, WA, United States

89 **Silent Mutations in HIV-1 Subtype B Reverse Transcriptase Selected by ART Restore Viral Fitness**

Sushama Telwatte[1,2], Anna C. Hearps[1,3], Adam Johnson[1], Con Sonza[4], Nicolas P. Sluis-Cremer[5], Richard P. Harrigan[6], Gilda Tachedjian[1,2]

[1]Centre for Biomedical Research, Burnet Institute, Melbourne, Australia, [2]Department of Microbiology, Monash University, Melbourne, Australia, [3]Department of Infectious Diseases, Monash University, Melbourne, Australia, [4]Department of Microbiology and Immunology, University of Melbourne, Melbourne, Australia, [5]Division of Infectious Diseases, University of Pittsburgh, Pittsburgh, PA, United States, [6]Drug Treatment Program, BC Centre for Excellence in HIV/AIDS, British Columbia, BC, Canada

90 **Reduced In Vivo Replicative Capacity of Drug-Resistant SHIV During Acute Infection**

Mian-er Cong, Chou-Pong Pau, Walid Heneine, **J. Gerardo Garcia-Lerma**

Division of HIV/AIDS Prevention, CDC, Atlanta, GA, United States

91LB **744 and Rilpivirine as Two-Drug Oral Maintenance Therapy: LAI116482 (LATTE) Week 48 Results**

David Margolis[1], Cynthia Brinson[2], Joseph Eron[3], Gary Richmond[4], Roger LeBlanc[5], Sandy Griffith[1], Marty St. Clair[1], Marita Stevens[6], Peter Williams[6], William Spreen[1]

[1]GSK, RTP, NC, United States, [2]Central Texas Clinical Research, Austin, TX, United States, [3]University of North Carolina, Chapel Hill, NC, United States, [4]HIV Clinic, Ft. Lauderdale, FL, United States, [5]Clinique Opus Inc, Montreal, QC, Canada, [6]Janssen, Beerse, Belgium

92LB **Safety and Antiviral Effect of MK-1439, A Novel NNRTI (+FTC/TDF) in ART-Naive HIV-Infected Patients**

Javier O. Morales-Ramirez[1], Jose M. Gatell[2], Debbie P. Hagins[3], Melanie Thompson[4], Keikawus Arastéh[5], Christian Hoffmann[6], Charlotte Harvey[7], Xia Xu[7], Hedy Teppler[7]

[1]Clinical Research Puerto Rico, San Juan, Puerto Rico, [2]University of Barcelona, Barcelona, Spain, [3]Chatham County Health Dept, Savannah, GA, United States, [4]AIDS Research Consortium of Atlanta, Atlanta, GA, United States, [5]EPIMED/ Vivantes Auguste-Viktoria-Klinikum, Berlin, Germany, [6]ICH Study Center, Hamburg, Germany, [7]Merck, Whitehouse Station, NJ, United States

Session O-8 Oral Abstracts

10:00 AM – 12:00 PM **Ballroom A**

TB and Other Coinfections

Moderators

Anne F. Luetkemeyer, *University of California San Francisco, San Francisco, CA, United States*

Alison D. Grant, *London School of Hygiene and Tropical Medicine, London, United Kingdom*

93 **A Phase 2 Trial of a Rifapentine Plus Moxifloxacin-Based Regimen for Pulmonary TB Treatment**

Marcus B. Conde[1], Solange C. Cavalcante[2,3], Margareth Dalcolmo[4], Fernanda Mello[1], Rafael Duarte[5], Carla Loredo[5], Valeria Rolla[4], Betina Durovni[2,3], Silvia Cohn[6], Richard E. Chaisson[6], **Susan E. Dorman**[6]

[1]Thoracic Diseases Institute, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil, [2]Municipal Health Secretariat, Rio de Janeiro, Brazil, [3]Instituto de Pesquisa Clínica Evandro Chagas, Rio de Janeiro, Brazil, [4]Centro de Referencia Professor Helio Fraga, ENSP-Fiocruz, Rio de Janeiro, Brazil, [5]Federal University of Rio de Janeiro, Rio de Janeiro, Brazil, [6]The Johns Hopkins University School of Medicine, Baltimore, MD, United States

94 **Tuberculosis Infection in Early Childhood in Uganda and the Influence of HIV Exposure**

Carina Marquez[1], Gabriel Chamie[1], Jane Achan[2], Anne F. Luetkemeyer[1], Mary Kyohere[3], Grant Dorsey[1], Moses R. Kamya[2], Edwin D. Charlebois[1], Diane V. Havlir[1]

[1]University of California, San Francisco, San Francisco, CA, United States, [2]Makerere University College of Health Sciences, Kampala, Uganda, [3]Infectious Diseases Research Collaboration, Kampala, Uganda

95 **Effect of Xpert MTB/RIF On Early Mortality in Adults With Suspected TB: A Pragmatic Randomized Trial**

Gavin Churchyard[1], Kerrigan McCarthy[1], Katherine L. Fielding[2], Wendy Stevens[3], Violet Chihota[1], Mark Nicol[4], Norbert Ndjeka[5], Alison D. Grant[2], David Mametja[5]

[1]Aurum Institute, Houghton, South Africa, [2]London School of Hygiene and Tropical Medicine, London, United Kingdom, [3]National Health Laboratory Service, Sandringham, South Africa, [4]University of Cape Town, Cape Town, South Africa, [5]South African Department of Health, Pretoria, South Africa

96LB **Xpert as the First-Line TB Test in South Africa: Yield, Initial Loss To Follow-Up, Proportion Treated**

Katherine L. Fielding[1], Kerrigan M. McCarthy[2], Helen Cox[3], Linda Erasmus[4], Sibuse Ginindza[2], Anna Vassall[1], Lindiwe Mvusi[5], Chris Dye[6], Alison D. Grant[1], Gavin J. Churchyard[2]

[1]London School of Hygiene & Tropical Medicine, London, United Kingdom, [2]Aurum Institute, Johannesburg, South Africa, [3]University of Cape Town, Cape Town, South Africa, [4]National Health Laboratory Service, Johannesburg, South Africa, [5]South African Department of Health, Pretoria, South Africa, [6]World Health Organization, Geneva, Switzerland

97LB **14 Day EBA Study of PA-824, Bedaquiline, Pyrazinamide and Clofazimine in Smear-Positive TB Patients**

Andreas Diacon[1], Rodney Dawson[2], Christo Van Niekerk[3], Jane Hutchings[3], Stephen Murray[4], Robert Schall[5], Divan Burger[6], Dan Everitt[4], Carl Mendel[4]

[1]Department of Medical Biochemistry, Stellenbosch University, Cape Town, South Africa, [2]Medicine, University of Cape Town Lung Institute, Cape Town, South Africa, [3]Clinical Development, TB Alliance, Pretoria, South Africa, [4]Clinical Development, TB Alliance, New York, NY, United States, [5]Mathematical Statistics and Actuarial Science, Univeristy of The Free State, Bloemfontein, South Africa, [6]Mathematical Statistics and Actuarial Science, University of the Free State, Bloemfontein, South Africa

98 **CTX Prophylaxis Discontinuation Among ART-Treated Adults: A Randomized Non-Inferiority Trial**

Christina S. Polyak[1], Krista Yuhas[2], Benson Singa[3], Monica Khaemba[3], Judd Walson[2], Barbra Richardson[2], Grace John-Stewart[2]

[1]Military HIV Research Program, Walter Reed Army Institute of Research, University of Washington, Bethesda, MD, United States, [2]Global Health, University of Washington, Seattle, WA, United States, [3]Kenya Medical Research Institute/ University of Washington, Nairobi, Kenya

Session TD6 Themed Discussion

1:30 PM – 2:30 PM **Room 309**

Frailty and Functional Impairment

Discussion Leader

Kevin E. Yarasheski, *Washington University School of Medicine, St Louis, MO, United States*

766 **Geriatric Syndromes Are Common Among Older HIV-Infected Adults**

Meredith Greene[1,2], Victor Valcour[1,3], Yinghui Miao[2,4], Ken Covinsky[1,2], Joy Madamba[5], Monica Mattes[6], Harry Lampiris[2,7], Jeffrey Martin[8], Steven Deeks[5]

[1]Medicine-Geriatrics, University of California San Francisco, San Francisco, CA, United States, [2]San Francisco VA Medical Center, San Francisco, CA, United States, [3]Neurology, University of California San Francisco, San Francisco, CA, United States, [4]NCIRE, San Francisco, CA, United States, [5]Medicine-HIV/ AIDS, University of California San Francisco, San Francisco, CA, United States, [6]University of Central Florida College of Medicine, Orlando, FL, United States, [7]Medicine-Infectious Diseases, University of California San Francisco, San Francisco, CA, United States, [8]Epidemiology & Biostatistics, University of California San Francisco, San Francisco, CA, United States

767 **Physical Function Impairment On Quality of Life Among Persons Aging With HIV Infection**

Kristine M. Erlandson, Amanda A. Allshouse, Catherine M. Jankowski, Samantha MaWhinney, Wendy M. Kohrt, Thomas B. Campbell

University of Colorado Anschutz Medical Campus, Aurora, CO, United States

764 **Cell-Mediated CMV Responses in HIV-Infected Persons With Impaired Physical Function**

Kristine M. Erlandson, Amanda A. Allshouse, Rick Rapaport, Brent E. Palmer, Cara C. Wilson, Samantha MaWhinney, Thomas B. Campbell

University of Colorado Anschutz Medical Campus, Aurora, CO, United States

762 **Frailty, Inflammation and Mortality Among Aging HIV-Infected and At-Risk Injection Drug Users**

Damani A. Piggott, Ravi Varadhan, Shruti H. Mehta, Todd T. Brown, Sean X. Leng, Gregory D. Kirk

The Johns Hopkins University, Baltimore, MD, United States

763 **Brisk Walking Improves Inflammatory Markers in cART-Treated Patients**

Valeria Longo[1], Matteo Bonato[2], Simona Bossolasco[1], Laura Galli[1], Andrea Caumo[2], Gaspare Pavei[3], Adriano Lazzarin[1], Giampiero Merati[3], Antonio La Torre[2], Paola Cinque[1]

[1]Infectious Diseases, San Raffaele Scientific Institute, Milano, Italy, [2]Biomedical Sciences for Health, Università degli Studi di Milano, Milano, Italy, [3]Pathophysiology and Transplantation Department, Università degli Studi di Milano, Milano, Italy

Session TD7 Themed Discussion

1:30 PM – 2:30 PM **Ballroom A**

Clinical Pharmacology in Patient Care

Discussion Leader

Stephen Taylor, *Birmingham Heartlands Hospital, Birmingham, United Kingdom*

496 **Pharmacokinetics of Raltegravir 400 vs 800 mg BID With Intermittent Rifampicin Dosed Thrice Weekly**

Helen E. Reynolds[1], Deirdre Egan[1], Laura Else[1], Mas Chaponda[2], Ales Chrdle[2], David J. Back[1], **Saye H. Khoo**[1]

[1]University of Liverpool, Liverpool, United Kingdom, [2]Royal Liverpool University Hospital, Liverpool, United Kingdom

494 **Relationship Between Efavirenz Trough & CYP2B6 Genotypes With Rifampin-Based TB Therapy in STRIDE**

Anne Luetkemeyer[1], Susan L. Rosenkranz[2], Darlene Lu[3], Beatriz Grinsztejn[4], Jorge Sanchez[5], Michael Ssemmanda[6], Ian Sanne[7], Helen McIlleron[8], Diane Havlir[1], David Haas[9], ACTG A5221 & A5243 Study Teams

[1]HIV/AIDS Division, San Francisco General Hospital, University of California, San Francisco, San Francisco, CA, United States, [2]Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, MA, United States, [3]HIV/AIDS Division, Center for Biostatistics in AIDS Research, Harvard School of Public Health, San Francisco, CA, United States, [4]Instituto de Pesquisa Clinica Evandro Chagas, Fundacao Oswaldo Cruz, Rio de Janeiro, Brazil, [5]Asociación Civil Impacta Salud y Educacioó, Lima, Peru, [6]Joint Clinical Research Center, Kampala, Uganda, [7]Clinical HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, [8]Division of Clinical Pharmacology, University of Cape Town, Cape Town, South Africa, [9]Vanderbilt University School of Medicine, Nashville, TN, United States

497 **Pharmacokinetics of Faldaprevir and Antiretrovirals in Patients With HIV/HCV Coinfection**

Jürgen K. Rockstroh[1], Marc-Antoine Valantin[2], Josep Mallolas[3], Massimo Puoti[4], Juan Antonio Pineda[5], Patrick Ingiliz[6], Marina Núñez[7], Fenglei Huang[8], Richard Vinisko[8], Douglas Dieterich[9]

[1]Department of Medicine I, University of Bonn, Bonn, Germany, [2]Service des Maladies Infectieuses et Tropicales, Hôpital Pitié-Salpêtrière, Paris, France, [3]Hospital Clinic-University of Barcelona, Barcelona, Spain, [4]Department of Infectious Diseases, AO Ospedale Niguarda Ca' Granda Milano, Milan, Italy, [5]Unit of Infectious Diseases and Microbiology, Hospital Universitario de Valme, Seville, Spain, [6]Medical Center for Infectious Diseases, Berlin, Germany, [7]Wake Forest University Health Sciences, Winston-Salem, NC, United States, [8]Boehringer Ingelheim Pharmaceutical, Inc, Ridgefield, CT, United States, [9]Mount Sinai Medical Center, New York, NY, United States

504 **Relative Genetic Contribution To the Pharmacokinetics of Commonly Prescribed Antiretrovirals**

Marco S. Siccardi[1], Adeniyi Olagunju[1, 2], Marco Simiele[3], Antonio D'Avolio[3], Andrea Calcagno[3], Giovanni Di Perri[3], Stefano Bonora[3], Andrew Owen[1]

[1]Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, United Kingdom, [2]Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Nigeria, [3]Amedeo di Savoia Hospital, University of Turin, Turin, Italy

505 **Leveraging Genomics in HIV Treatment Decisions**

Paul J. McLaren[1], Margalida Rotger[1], Manel Aouri[1], Huldrych Günthard[2], Catia Marzolini[3], Laurent Decosterd[1], Amalio Telenti[1]

[1]The Swiss HIV Cohort, Lausanne, Switzerland, [2]The Swiss HIV Cohort, Zurich, Switzerland, [3]The Swiss HIV Cohort, Basel, Switzerland

Session TD8 Themed Discussion

1:30 PM – 2:30 PM **Room 304**

How Transmission Networks Drive Epidemics

Discussion Leader

Roger D. Kouyos, *University Hospital Zurich, University of Zurich, Zurich, Switzerland*

213 **HIV Transmission in the United States: The Roles of Risk Group, Race/Ethnicity, and Geography**

Alexandra M. Oster[1], Joel O. Wertheim[2], Angela L. Hernandez[1], Marie C. B. Ocfemia[1], Neeraja Saduvala[3], David Kim[1], H. I. Hall[1]

[1]Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, Atlanta, GA, United States, [2]ICF International and University of California San Diego, San Diego, CA, United States, [3]ICF International, Atlanta, GA, United States

205 **Ongoing HIV-1 Subtype B Transmission Networks in the Netherlands**

Daniela Bezemer[1], Oliver Ratmann[2], Ard van Sighem[1], Bas E. Dutilh[3], Nuno Faria[4], Rob van den Hengel[1], Luuk Gras[1], Peter Reiss[1], Frank de Wolf[2], Christophe Fraser[2], ATHENA observational cohort

[1]Research, HIV Monitoring Foundation, Amsterdam, Netherlands, [2]Imperial College, London, United Kingdom, [3]Centre for Molecular and Biomolecular Informatics, Nijmegen, Netherlands, [4]University, Oxford, United Kingdom

206 **Using HIV Networks To Inform Real Time Prevention Interventions**

Susan J. Little[1], Sergei L. K. Pond[1], Christy M. Anderson[1], Jason A. Young[1], Joel O. Wertheim[1], Sanjay R. Mehta[1], Susanne May[2], Davey M. Smith[1]

[1]Medicine, University of California San Diego, San Diego, CA, United States, [2]Biostatistics, University of Washington School of Public Health, Seattle, WA, United States

215 **Large MSM Group and Local Heterosexual Transmission Are Major Concerns in the HIV Epidemic in Japan**

Teiichiro Shiino[1], Kenji Sadamasu[2], Junko Hattori[3], Mami Nagashima[2], Yasumasa Iwatani[3], Yoshiyuki Yokomaku[3], Wataru Sugiura[3], The Japanese Drug Resistance HIV-1 Surveillance Network

[1]Infectious Diseases Surveillance Center, National Institute of Infectious Diseases, Tokyo, Japan, [2]Tokyo Metropolitan Institute of Public Health, Tokyo, Japan, [3]Clinical Research Center, Nagoya Medical Center, Nagoya, Japan

207 **Transmission Networks of HIV-1 Subtype B, CRF01_AE and CRF51_01B Among MSM in Singapore**

Kim Tien Ng[1], Kah Ying Ng[2], Wei Xin Khong[2], Oliver Laeyendecker[3, 4], Thomas C Quinn[3, 4], Adeeba Kamarulzaman[1], Oon Tek Ng[2], Kok Keng Tee[1]

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208 **HIV-1 Phylodynamics and Phylogeography Among High-Risk and General Populations in Uganda**

Gonzalo Yebra[1], Manon Ragonnet-Cronin[1], Deogratius Ssemwanga[2], Chris M. Parry[2], Pontiano Kaleebu[2], Andrew J. Leigh Brown[1]

[1]Institute of Evolutionary Biology, University of Edinburgh, Edinburgh, United Kingdom, [2]Research Unit on AIDS, MRC/Uganda Virus Research Institute, Entebbe, Uganda

Session TD9 Themed Discussion

1:30 PM – 2:30 PM **Room 312**

Gut and Immune Activation

Discussion Leader

Peter W. Hunt, *University of California San Francisco, San Francisco, CA, United States*

312 **Rapid Gut-Homing of Plasmacytoid Dendritic Cells During Acute SIV Infection**

Haiying Li, Jacqueline Gillis, **R. Keith Reeves**

NEPRC, Harvard Medical School, Southborough, MA, United States

313 **CCR6+ and CD161+ CD4 T Cell Loss Contributes To the Pathogenesis of SIV Infection in Rhesus Macaques**

Colleen S. McGary[1], Luca Micci[1], Emily S. Ryan[1], Maria J. Buzon[2], Amy Shaw[2], Mathias Lichterfeld[2], Guido Silvestri[1, 3], Aftab A. Ansari[3], Mirko Paiardini[1, 3]

[1]Department of Microbiology and Immunology, Emory University, Atlanta, GA, United States, [2]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, United States, [3]Department of Pathology and Laboratory Medicine, Emory University, Atlanta, GA, United States

315 **Decreased Diversity of Gut Microbiota Is Associated With Immune Status During HIV-1 Infection**

Piotr Nowak[1], Babilonia Barqasho[2], Ekatarina Avershina[3], Kajsa Noyan[2], Jan Vesterbacka[1], Marius Trosseid[4], Knut Rudi[3], Anders Sönnerborg[1]

[1]Department of Infectious Diseases, Karolinska Institute, Huddinge, Sweden, [2]Department of Laboratory Medicine, Karolinska Institute, Huddinge, Sweden, [3]Department of Chemistry, Biotechnology and Food Science, Norwegian University of Life Sciences, Aas, Norway, [4]Infectious Diseases, Oslo University Hospital, Oslo, Norway

317 **Dysbiotic Bacteria Translocate in Progressive SIV Infection**

Zachary Klase[1], Elias Schwartzman[1], Alexandra Ortiz[1], Lauren Canary[1], Mariam Quinones[2], Jason Brenchley[1]

[1]Laboratory of Molecular Microbiology, NIAID/NIH, Bethesda, MD, United States, [2]NIAID/NIH, Bethesda, MD, United States

311 **Breaches in Colonic Claudin-4 Expression Correlate With T-Cell Activation in HIV-1 Infection**

Louise Greathead[1], Anna Mroz[1], Hiromi Kudo[1], Brian Gazzard[2], Mark Nelson[2], Robert D. Goldin[1], Alan Steel[2], Peter Kelleher[1]

[1]Imperial College, London, United Kingdom, [2]Chelsea and Westminster Hospital NHS Trust, London, United Kingdom

310 **Increased Immune Activation After Gut Permeabilization in SIV-Infected African Green Monkeys**

Jan Kristoff[1], Thaidra Gaufin[2], Rajeev Gautam[3], Dongzhu Ma[1], Jacob Estes[4], Russell Tracy[5], Cristian Apetrei[1], Steve Nelson[6], Gregory Bagby[6], Ivona Pandrea[1]

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Session TD10 Themed Discussion

1:30 PM – 2:30 PM **Room 311**

Reproductive Hormones in Women: Impact On Risk and Barrier Dysfunction

Discussion Leader

Susan Cu-Uvin, *Brown University, Providence, RI, United States*

844 **Depot-Medroxyprogesterone Acetate Does Not Increase Genital SHIV Shedding in Macaques**

Jessica Radzio[1], Krisztina Hanley[2], Debra Hanson[1], James Mitchell[1], Leecresia Jenkins[1], Shanon Ellis[1], Frank Deyounks[1], Walid Heneine[1], J. Gerardo Garcia-Lerma[1]

[1]Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, Atlanta, GA, United States, [2]Pathology, Emory University, Atlanta, GA, United States

846 **Hormonal Contraceptives Increase Innate Immune Effector Molecules in Cervicovaginal Secretions**

Brandon L. Guthrie[1], Robert Y. Choi[2], Alison C. Roxby[2], Rose Bosire[3], Barbara Lohman-Payne[1, 2], Taha Hirbod[4], Carey Farquhar[1, 2], Kristina Broliden[4]

[1]Department of Global Health, University of Washington, Seattle, WA, United States, [2]Department of Medicine, University of Washington, Seattle, WA, United States, [3]Center for Public Health Research, Kenya Medical Research Institute, Nairobi, Kenya, [4]Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden

847 **Injectable Contraception and HIV Acquisition in the VOICE Study (MTN-003)**

Lisa M. Noguchi[1, 2], Barbra Richardson[3], Z. Mike Chirenje[4], Gita Ramjee[5], Gonasagrie Nair[6], Thesla Palanee[7], Pearl Selepe[8], Ravindre Panchia[9], Kailazarid Gomez[10], Jeanne Marrazzo[11], on behalf of the VOICE Study Team

[1]Epidemiology, The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States, [2]Microbicide Trials Network, Pittsburgh, PA, United States, [3]SCHARP, Seattle, WA, United States, [4]UZ-UCSF, Harare, Zimbabwe, [5]MRC, Durban, South Africa, [6]CAPRISA, Durban, South Africa, [7]WITS Reproductive Health and HIV Institute, Johannesburg, South Africa, [8]Aurum Institute, Klerksdorp, South Africa, [9]PHRU, Soweto, South Africa, [10]FHI 360, Durham, NC, United States, [11]University of Washington, Seattle, WA, United States

845 **Dysregulation of Estradiol Signaling Contributes To Mucosal Barrier Dysfunction HIV+ Women**

Sumathi Sankaran-Walters[1], Anne Fenton[1], Chris Gaulke[1], Lauren Nagy[1], Irina Grishina[1], Jason Flamm[2], Thomas Prindiville[3], Satya Dandekar[1]

[1]Medical Microbiology and Immunology, University of CA, Davis, Davis, CA, United States, [2]Internal Medicine, Kaiser Permanente, Sacramento, CA, United States, [3]Internal Medicine, University of CA, Davis, CA, United States

Session TD16 Themed Discussion

1:30 PM – 2:30 PM **Ballroom B/C**

Real-World Experiences With Hepatitis C

Discussion Leader

Marion G. Peters, *University of California San Francisco, San Francisco, CA, United States*

668 **Telaprevir in Treatment-Experienced HIV-HCV G1 Coinfected Patients (ANRS HC26 TelapreVIH)**

Laurent Cotte[1, 2], Corinne Vincent[3], Philippe Sogni[4, 5], Isabelle Fournier[3], Hugues Aumaître[6], Pierre De Truchis[7], Isabelle Rosa[8], Stéphane Chevaliez[9], Jean-Pierre Aboulker[10], Jean-Michel Molina[4, 11]

[1]Infectious Diseases, Hospices Civils de Lyon, Lyon, France, [2]U1052, INSERM, Lyon, France, [3]SC10-US019, INSERM, Villejuif, France, [4]Assistance Publique - Hôpitaux de Paris, Paris, France, [5]Paris Descartes University, Paris, France, [6]Saint Jean Hospital, Perpignan, France, [7]Assistance Publique - Hôpitaux de Paris, Garches, France, [8]Centre Hospitalier Intercommunal, Créteil, France, [9]Assistance Publique - Hôpitaux de Paris, Créteil, France, [10]INSERM, Villejuif, France, [11]University of Paris VII Denis Diderot, Paris, France

660 **Boceprevir/Telaprevir-Based Therapy in HIV-Infection: Interim Analysis of a Multicenter Cohort**

Karin Neukam[1, 2], Daniela Munteanu[3, 4], Antonio Rivero[5], Annette Haberl[6], Manuel Márquez[7], Patrick Ingiliz[8], Ignacio de los Santos-Gil[9], Thomas Lutz[10], Juergen K. Rockstroh[3], Juan A. Pineda[1]

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658 **Protease Inhibitors To Treat Hepatitis C in the Swiss HIV Cohort Study: High Efficacy But Low Uptake**

Sebastian Haubitz[1], Verena Schaerer[2], Juan Ambrosioni[3], Matthias Cavassini[4], Marcel Stoeckle[5], Patrick Schmid[6], Laurent Decosterd[4], Karin Metzner[2], Jan Fehr[2], **Andri Rauch**[1]

[1]Division of Infectious Diseases, Bern, Switzerland, [2]Division of Infectious Diseases, Zurich, Switzerland, [3]Division of Infectious Diseases, Geneva, Switzerland, [4]Division of Infectious Diseases, Lausanne, Switzerland, [5]Division of Infectious Diseases, Basel, Switzerland, [6]Division of Infectious Diseases, St Gallen, Switzerland

655 **Slow HCV-RNA Decay and Early Resistance Predict the Risk of Failure To TVR/BOC Treatment**

Francesca Ceccherini-Silberstein[1], Valeria Cento[1], Velia Chiara Di Maio[1], Daniele Di Paolo[2], Sergio Babudieri[3], Antonio Di Biagio[4], Massimo Andreoni[5], Giustino Parruti[6], Giuliano Rizzardini[7], Carlo Federico Perno[1]

[1]Department of Experimental Medicine and Surgery, University of Rome Tor Vergata, Rome, Italy, [2]Hepatology Unit, University Hospital of Rome Tor Vergata, Rome, Italy, [3]Infectious Diseases Unit, Department of Clinical and Experimental Medicine, University of Sassari, Sassari, Italy, [4]S. Martino Hospital, Genoa, Italy, [5]Infectious Diseases Unit, University Hospital of Rome Tor Vergata, Rome, Italy, [6]Infectious Diseases Unit, Pescara General Hospital, Pescara, Italy, [7]Division of Infectious Diseases, Hospital Sacco of Milan, Milan, Italy

661 **Favorable Adverse Event Profile of Sofosbuvir/Ribavirin Versus Standard of Care for Hepatitis C**

Kerry Townsend[1], Shivakumar Narayanan[2], Amy Nelson[1], Adrian Majid[2], Luciano Kapelusznik[2], Robert R. Redfield[2], Shyamasundaran Kottilil[1], Rohit Talwani[2], Anuoluwapo Osinusi[1, 2]

[1]LIR, NIAID, NIH, Bethesda, MD, United States, [2]Institute of Human Virology, Div. of Infectious Diseases, University of Maryland School of Medicine, Baltimore, MD, United States

641 **Sustained Virologic Response and the Risk of Liver Decompensation in HCV and HIV/HCV Patients**

Temitope O. Olufade[1], Li Wang[2], Scott Devine[1], Onur Baser[2], Vincent Lo Re[3]

[1]US Outcomes Research, Merck Sharpe & Dohme, North Wales, PA, United States, [2]STATinMED Research, Dallas, TX, United States, [3]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States

650 **Predicting Risk of ESLD in HIV/HCV Patients for Individualized HCV Therapy Decisions**

Vincent Lo Re[1], Janet P. Tate[2], Adeel A. Butt[3], Marina B. Klein[4], Cynthia Gibert[5], David Rimland[6], Matthew B. Goetz[7], Jay R. Kostman[1], Amy C. Justice[2], Russell Localio[1]

[1]University of Pennsylvania, Philadelphia, PA, United States, [2]VA Connecticut Healthcare System, West Haven, CT, United States, [3]University of Pittsburgh School of Medicine, Pittsburgh, PA, United States, [4]McGill University Health Centre, Montreal, QC, Canada, [5]Washington DC VA Medical Center, Washington, DC, United States, [6]Atlanta VA Medical Center, Atlanta, GA, United States, [7]VA Greater Los Angeles Healthcare System, Los Angeles, CA, United States

POSTER SESSIONS

2:30 PM–4:00 PM

(Use the Poster Abstract section of the Program at a Glance, page 37 to 106, for specific posters in each session)

Session P-A4 Late Events in HIV Replication
Session P-A5 Apobec, Apobec, Apobec
Session P-B2 Application of NGS To Viral Profiling
Session P-C6 Clades and Pathogenesis
Session P-C7 Correlative Marker Studies
Session P-C8 Elite Controllers
Session P-C9 Pathogenesis: Insights From Clinical Trials
Session P-C10 Innate Immunity and Pathogenesis
Session P-D2 New SIV Models
Session P-D3 SCID Mice
Session P-D4 Non-Pathogenic vs Pathogenic Hosts
Session P-E3 New Technologies in Immunology
Session P-E4 Monocytes, Dendritic Cells, NK Cells
Session P-E5 Pre-Clinical Vaccine Studies
Session P-F4 Methods for Measuring Reservoirs
Session P-F5 What and Where Is the Reservoir?
Session P-F6 What Can We Learn From Bone Marrow Transplantation?
Session P-G3 Neuropathogenesis
Session P-G4 Host Genetics in HAND
Session P-G5 PML and Other CNS Infections
Session P-G6 CNS Viral Genetics
Session P-H3 ARV Pharmacokinetics, Drug Interactions, and Pharmacodynamics
Session P-K2 ART Initiation, Monitoring, and Outcomes
Session P-L3 Mechanisms of HIV Drug Resistance
Session P-L4 HIV Drug Resistance Variants
Session P-M2 HIV Diagnostics
Session P-N3 HCV: Prognosis and Impact of Treatment, Including Liver Transplantation
Session P-N4 HCV Treatment: Real-World Experience
Session P-N5 HCV: The Cascade
Session P-O4 Kaposi Sarcoma, PEL, and KSHV
Session P-P3 Alcohol, Smoking, and Atherosclerosis
Session P-P4 Risk Factors and Incidence: MI and Stroke
Session P-Q4 Lung Disease and HIV
Session P-Q5 Bone Disease: Osteopenia Fracture Risk and Osteoarthritis
Session P-Q6 Hepatic Fibrosis and Other Hepatic Complications
Session P-R1 Epidemiology and Transmission of TB
Session P-R2 TB Screening and Diagnosis
Session P-R3 Latent TB Screening and Treatment
Session P-R4 Inflammatory and Immune Activation Markers in TB
Session P-R5 Impact of ART on TB Risk and Disease
Session P-T3 Pregnancy Incidence and Outcomes Among Women in ART Programs
Session P-T4 Cellular and Immune Correlates of MTCT
Session P-T5 Characteristics of Pregnant Women in PMTCT
Session P-T6 Early Infant HIV Diagnosis
Session P-U4 Host and Immune Response in Children and Adolescents

Session P-U5 Complications of HIV and ART in Children and Adolescents
Session P-V1 Pre-Clinical Studies of Microbicides
Session P-V2 Animal Model of Clinical Studies and PrEP
Session P-V3 Identifying and Reducing HIV Risk
Session P-V4 PrEP, PEP, TasP
Session P-V5 Circumcision
Session P-W5 Acute Infection
Session P-W6 Incidence Assays
Session P-X3 The Treatment Cascade and Loss To Follow-Up
Session P-X4 Mental Health in HIV Care

Session O-11 Oral Abstracts

4:00 PM – 6:00 PM **Room 312**

Malignancies and Pharmacology

Moderators

Kelly E. Dooley, *The Johns Hopkins University School of Medicine, Baltimore, MD, United States*

Margaret Z. Borok, *University of Zimbabwe, Harare, Zimbabwe*

99 **HIV and Elevated Cancer-Specific Mortality Following Cancer Diagnosis in the United States**

Anna E. Coghill, Meredith S. Shiels, Eric A. Engels

Division of Cancer Epidemiology and Genetics, National Cancer Institute, Washington, DC, United States

100 **Impact of Kaposi Sarcoma On Survival in HIV-Infected African Adults On Antiretroviral Therapy**

Stephen B. Asiimwe[1,2], Miriam Laker-Oketta[1,3], John Bennett[1], Adrienne Mocello[1], David Glidden[1], Jessica Haberer[4], Mwebesa Bwana[1], Peter Hunt[1], David Bangsberg[4], Edward Mbidde[1], Jeffrey Martin[1]

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101 **Prospective Characterization of Kaposi Sarcoma Herpesvirus Inflammatory Cytokine Syndrome**

Mark N. Polizzotto[1], Thomas S. Uldrick[1], Kathleen M. Wyvill[1], Karen Aleman[1], Vickie Marshall[2], Denise Whitby[2], Stefania Pittaluga[3], Seth Steinberg[4], Irini Sereti[5], Robert Yarchoan[1]

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102 **Quadrivalent HPV Vaccine Demonstrates Immune Memory in HIV-1-Infected Men**

Timothy Wilkin[1], Shelly Lensing[2], Mark Einstein[3], Jeannette Lee[4], Stephen Goldstone[5], Elizabeth A. Stier[6], Michael Berry[7], Naomi Jay[8], Ronald Mitsuyasu[9], Joel Palefsky[8]

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103 **HIV-1 Infection Alters Intestinal Expression of Antiretroviral Drug Transporters and Enzymes**

Olena Kis[1], Md. Tozammel Hoque[1], Sharon L. Walmsley[2,3], Sumathi Sankaran-Walters[4], Satya Dandekar[5], **Reina Bendayan**[1]

[1]Pharmaceutical Sciences, University of Toronto, Toronto, ON, Canada, [2]University of Toronto, Toronto, ON, Canada, [3]Division of Infectious Diseases, University Health Network, Toronto, ON, Canada, [4]Medical Microbiology and Immunology, University of California, Davis, CA, United States, [5]Medical Microbiology and Immunology, University of California, Davis, CA, United States

104 **Tenofovir-Emtricitabine Directly Observed Dosing: 100% Adherence Concentrations (HPTN 066)**

Craig W. Hendrix[1], Adriana Andrade[1], Angela D. Kashuba[2], Mark Marzinke[1], Peter L. Anderson[3], Ayana Moore[4], Vanessa Elharrar[5], Lei Wang[6], Kenneth H. Mayer[7], Kristine B. Patterson[2]

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105 **Efavirenz Pharmacokinetics in HIV+ Persons Receiving Rifapentine and Isoniazid for TB Prevention**

Anthony T. Podany[1], Yajing Bao[2], Richard E. Chaisson[3], Susan Swindells[4], Janet W. Andersen[2], Thando Mwelase[5], Khuanchai Supparatpinyo[6], Amita Gupta[3], Constance A. Benson[7], Courtney V. Fletcher[1]

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106 **Pharmacokinetic Variability in TB Therapy: Associations With HIV and Effect On Outcome**

Derek J. Sloan[1], Alessandro Schipani[2], David Waterhouse[3], Lisa Stone[3], Henry C. Mwandumba[1], Anthony E. Butterworth[4], Robert S. Heyderman[1], Elizabeth L. Corbett[1], Saye H. Khoo[2], Geraint R. Davies[1]

[1]Malawi Liverpool Wellcome Trust Clinical Research Programme, Blantyre, Malawi, [2]University of Liverpool, Liverpool, United Kingdom, [3]Liverpool School of Tropical Medicine, Liverpool, United Kingdom, [4]College of Medicine, University of Malawi, Blantyre, Malawi

Session S4 Symposium

4:00 PM – 6:00 PM **Ballroom B/C**

TB: Looking To the Future: Resistance, Persistence, Monitoring, and Control

Target audience: This session is directed to clinicians and scientists interested in the pathogenesis, diagnosis, treatment, and prevention of TB.

Level of knowledge: It is assumed that learners are familiar with basic aspects of the disease, drug therapies, and development of resistance and with current tools available for disease monitoring on an individual and population basis.

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

- Methods for sequencing MDR and XDR TB strains and factors beyond inadequate adherence that contribute to emergence of resistance
- The pathogenesis of latency, novel animal models of latency, and implications for treating latent TB infections
- Use of PET-CT, PET-MRI, and other novel imaging to detect mycobacterial replication, tissue inflammation, and responses to TB therapy
- Insights gained from population-based studies of TB prevention

Conveners




Neil A. Martinson, *University of the Witwatersrand, Johannesburg, South Africa*

Jean William Pape, *Weill Cornell Medical College, New York, NY, United States, and Centres GHESKIO, Port-au-Prince, Haiti*

107 **The Genetics and Pathogenesis of MDR and XDR TB Drug Resistance**



Megan B. Murray

Harvard Medical School, Boston, MA, United States

108 **Is Latent TB Infection Really Latent?**



Petros C. Karakousis

The Johns Hopkins University School of Medicine, Baltimore, MD, United States

109 **Quantifying TB Treatment Response Using PET/CT**



Clifton E. Barry III

National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, United States

110 **Population-Level Control of HIV-Related TB**



Peter Godfrey-Faussett

Joint United Nations Programme on HIV/AIDS (UNAIDS), Geneva, Switzerland

Session S5 Symposium

4:00 PM – 6:00 PM **Ballroom A**

Visualizing the Virus

Target audience: This session is directed to scientists and clinicians who are interested in current concepts of how the HIV viral particle is assembled and how it interacts with cellular proteins, particularly during entry. Learners will also learn about state-of-the-art technological approaches and breakthroughs that have enabled visualization and analysis of HIV virions and proteins in real time.

Level of knowledge: It is assumed that learners will have a basic understanding of the HIV virion components and virus life cycle.

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

- Appreciate technological advances that are being applied to study HIV particles, viral proteins, and protein-protein interactions involved in viral entry
- Describe current views of how the HIV virion is assembled and how key cellular interactions contribute to infection and virus production
- Describe recent advances in structural biology that have enabled complex viral proteins to be visualized

Conveners




Hans-Georg Kräusslich, *University of Heidelberg, Heidelberg, Germany*

Eric O. Freed, *National Cancer Institute, Frederick, MD, United States*

111 **An Ingenious Cloak for Subterfuge: The HIV Capsid Structure**



Angela M. Gronenborn

University of Pittsburgh, Pittsburgh, PA, United States

112 **Structure of a Soluble, Cleaved HIV-1 Env Trimer and Its Interaction With Broadly Neutralizing Antibodies**



Ian A. Wilson

The Scripps Research Institute, La Jolla, CA, United States

113 **Imaging the Molecular Dance of Single HIV-1 Env Molecules**



Walter H. Mothes

Yale University, New Haven, CT, United States

114 **Kill HIV by Starvation: SAMHD1 as a Potent Viral Restriction Factor and a Master Regulator of Cellular dNTP Metabolism**



Yong Xiong

Yale University, New Haven, CT, United States

Session S6 Symposium

4:00 PM – 6:00 PM **Room 304**

Know Your Epidemic: From Data To Action

This session aims to inform the attendees of the value of data in furthering the understanding of the epidemiology of the HIV epidemic and the critical role that data and evidence can play in informing research as well as policy decisions regarding HIV. The availability of various population-level surveys and the wealth of other research findings allow for a more effective response to the HIV epidemic.

Target audience: This session is directed to clinicians, researchers and policy makers who are interested in use of data and evidence to inform their work

Level of knowledge: It is assumed that learners are familiar with the global HIV epidemic, basic epidemiology of HIV, and affected populations

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

- Describe the complexity of the global epidemiology of HIV
- List available population surveys related to HIV
- Recognize the evolution of the HIV epidemic within subpopulations
- Identify ways in which data and evidence can be used to inform policy

Conveners




John Stover, *Futures Institute, Glastonbury, CT, United States*

Beatriz Grinsztejn, *Instituto de Pesquisa Clinica Evandro Chagas-Fiocruz, Rio de Janero, Brazil*

115 **Population Surveys: What Do They Show?**



Peter D. Ghys

Joint United Nations Programme on HIV/AIDS (UNAIDS), Geneva, Switzerland

116 **MSM in the UK: Prevention Effects of ART in Perspective**



Andrew Phillips

University College London, London, United Kingdom

117 **Understanding Networks of HIV Transmission**



Stéphane Helleringer

Columbia University, New York City, NY, United States

118 **From Evidence To Policy: Experience From Swaziland**



Velephi J. Okello

Swaziland National AIDS Programme, Mbabane, Swaziland

THURSDAY MARCH 6, 2014

Session PL5 Plenary

8:30 AM – 9:00 AM **Auditorium**

119 **HIV-1 Infection and Type-1 Interferon**



Michael H. Malim

King's College London, London, United Kingdom

Session PL6 Plenary

9:00 AM – 9:30 AM **Auditorium**

120 **PEPFAR/Global Fund at 10 years: Past, Present, and Future**



Stefano M. Bertozzi

University of California Berkeley School of Public Health, Berkeley, CA, United States

Session O-9 Oral Abstracts

10:00 AM – 12:15 PM **Room 312**

Interferon and Antibody at the Interface of Innate and Adaptive Immunity To HIV

Moderators

Xueling Wu, *Aaron Diamond AIDS Research Center, New York, NY, United States*

David T. Evans, *University of Wisconsin, Madison, WI, United States*

121 **Cryo-EM Structures of the HIV-1 Env Trimer Reveal the Full Extent of Neutralizing Antibody Epitopes**

Andrew B. Ward[1], Dmitry Lyumkis[1], Natalia de Val[1], Jean-Philippe Julien[1], Albert Cupo[2], Per Johan Klasse[2], Rogier Sanders[3], John Moore[2], Ian Wilson[1]

[1]Integrative Structural and Computational Biology, The Scripps Research Institute, La Jolla, CA, United States, [2]Weill Cornell Medical College, New York, NY, United States, [3]Academic Medical Center, Amsterdam, Netherlands

122LB **Immunogenicity of Cleaved, Soluble BG505 SOSIP.664 Native-Like Trimers in Rabbits**

John P. Moore

Microbiology/Immunology, Weill Medical College, New York, NY, United States

123 **Identification of a New Neutralization Target at the N262/N448 Glycosylation Sites On HIV-1 gp120**

Xueling Wu[1], **Tongqing Zhou**[2], Ivelin S. Georgiev[2], Sijy O'Dell[2], Mark Louder[2], Dennis R. Burton[3], Wayne C. Koff[3], Martin Markowitz[1], Peter D. Kwong[2], John R. Mascola[2]

[1]Aaron Diamond AIDS Research Center, New York, NY, United States, [2]Vaccine Research Center, Bethesda, MD, United States, [3]International AIDS Vaccine Initiative, New York, NY, United States

124 **CD169 Mediates HIV-1 Evasion From Detection by α-gp120 Neutralizing Antibodies in Dendritic Cells**

Hisashi Akiyama[1], Nora G. P. Ramirez[1], Manasa Gudheti[2], Suryaram Gummuluru[1]

[1]Microbiology, Boston University School of Medicine, Boston, MA, United States, [2]Vutara Inc., Salt Lake City, UT, United States

125 **Tetherin Antagonism by Vpu Protects HIV-Infected Cells From ADCC**

Juan F. Arias[1], Lisa N. Heyer[2], Benjamin von Bredow[1], Kim L. Weisgrau[3], Brian Moldt[4], Dennis R. Burton[4], Eva G. Rakasz[3], David T. Evans[1]

[1]Department of Pathology and Laboratory Medicine, University of Wisconsin, Madison, WI, United States, [2]Department of Microbiology and Immunobiology, Harvard Medical School, Southborough, MA, United States, [3]Wisconsin National Primate Research Center, University of Wisconsin, Madison, WI, United States, [4]Department of Immunology and Microbial Science, The Scripps Research Institute, La Jolla, CA, United States

126 **HIV Nef and Vpu Protect HIV-infected CD4+ T Cells From ADCC Through Downmodulation of CD4 and BST2**

Tram N. Q. Pham[1], Sabelo Lukhele[1], Fadi Hajjar[1], Jonathan Richard[1], Rajesh M. Valanparambil[2], Halima Medjahed[3], Mathieu Coutu[3], Andres Finzi[3, 4], Eric A. Cohen[1, 4]

[1]Institut de Recherches Cliniques de Montréal, Montreal, QC, Canada, [2]Department of Medicine, McGill University, Montreal, QC, Canada, [3]Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada, [4]Department of Microbiology, Infectiology and Immunology, Université de Montréal, Montreal, QC, Canada

127 **Identification of HIV-infected CD4+ T Cells Using HIV RNA and Broadly Neutralizing Antibodies**

Joseph P. Casazza[1], Alexander C. Vostal[1], Irene R. Primmer[1], David R. Ambrozak[1], Amarenda Pegu[2], Eli Boritz[3], Mark K. Louder[3], Daniel C. Douek[3], John R. Mascola[3], Richard A. Koup[1]

[1]Immunology Laboratory, NIAID, Bethesda, MD, United States, [2]Virology Laboratory, NIAID, Bethesda, MD, United States, [3]Human Immunology Section, NIAID, Bethesda, MD, United States

128 **Type I Interferon Signaling Is Critical for Early Control of Immune System Damage**

Netanya G. Sandler[1], Steven E. Bosinger[2], Jacob D. Estes[3], Eli Boritz[4], Brandon F. Keele[3], Jerome A. Langer[5], Jeffrey D. Lifson[3], Srini S. Rao[4], Gideon Schreiber[6], Daniel C. Douek[4]

[1]Internal Medicine, University of Texas Medical Branch at Galveston, Galveston, TX, United States, [2]Yerkes NHP Genomics Laboratory, Yerkes National Primate Research Center, Emory University, Atlanta, GA, United States, [3]Leidos Biomedical Research, Inc, AIDS and Cancer Virus Program, Frederick National Laboratory for Cancer Research, Frederick, MD, United States, [4]NIAID Vaccine Research Center, National Institutes of Health, Bethesda, MD, United States, [5]Pharmacology, Robert Wood Johnson Medical School, Rutgers University, Piscataway, NJ, United States, [6]Biological Chemistry, Weizmann Institute of Science, Rehovot, Israel

129 **miR-422a: A Solitary MicroRNA Biomarker of Interferon-α Anti-HIV-1 Activity In Vivo**

Mohamed Abdel-Mohsen[1, 2], Xutao Deng[2], Teri Liegler[1], Andri Rauch[3], Bruno Ledergerber[4], Huldrych F. Günthard[5], Joseph K. Wong[1, 6], Satish K. Pillai[1, 2]

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Session O-10 Oral Abstracts

10:00 AM – 12:00 PM **Ballroom B/C**

CV and Other Complications

Moderators

Jason V. Baker, *University of Minnesota, Hennepin County Medical Center, Minneapolis, MN, United States*

Cristina Mussini, *University of Modena and Reggio Emilia, Modena, Italy*

130 **Increased Arterial Inflammation Relates to High-Risk Coronary Plaque Morphology in HIV+ Patients**

Ahmed Tawakol[1], **Markella V. Zanni**[2], Janet Lo[2], Ezinne J. Ihenachor[2], Allison Han[2], Megan MacNabb[1], Bryan Wai[3], Udo Hoffmann[3], Suhny Abbara[3], Steven Grinspoon[2]

[1]Cardiology Division, Massachusetts General Hospital/Harvard Medical School, Boston, MA, United States, [2]Program in Nutritional Metabolism, Massachusetts General Hospital/Harvard Medical School, Boston, MA, United States, [3]Cardiovascular Radiology Division, Massachusetts General Hospital/Harvard Medical School, Boston, MA, United States

131 **Arterial Inflammation in HIV as Measured by FDG-PET/CT Is Associated With Splenic Activity**

Priscilla Y. Hsue[1], Megan MacNabb[2], Rebecca Kaplan[2], Elaine Nitta[1], Steven Deeks[3], Jeffrey Martin[3], Miguel Pampaloni[3], Peter Ganz[1], Ahmed Tawakol[2]

[1]Cardiology, University of California San Francisco, San Francisco, CA, United States, [2]Massachusetts General Hospital, Boston, MA, United States, [3]University of California San Francisco, San Francisco, CA, United States

132 **Replicative Senescence of Circulating Osteogenic Cells and Low BMD in Perinatally Infected Men**

John S. Manavalan, Stephen Arapdi, Jayesh Shah, Chiyuan A. Zhang, Marc Foca, Natalie Neu, Stavroula Kousteni, Michael T. Yin

Columbia University Medical Center, New York, NY, United States

133 **High-Dose Vitamin D and Calcium Attenuates Bone Loss With ART Initiation: Results From ACTG A5280**

Edgar T. Overton[1], Ellen S. Chan[2], Todd T. Brown[3], Pablo Tebas[4], Grace A. McComsey[5], Kathleen M. Melbourne[6], Andrew Napoli[7], Royce Hardin[8], Heather J. Ribaudo[2], Michael T. Yin[9], ACTG A5280 Study Team

[1]University of Alabama School of Medicine, Birmingham, AL, United States, [2]Harvard School of Public Health, Boston, MA, United States, [3]The Johns Hopkins University, Baltimore, MD, United States, [4]Hospital of the University of Pennsylvania, Philadelphia, PA, United States, [5]Pediatrics, Case Western Reserve University, Cleveland, OH, United States, [6]Gilead Sciences, Foster City, CA, United States, [7]Virology, Bristol-Myers Squibb, Plainsboro, NJ, United States, [8]Duke University Community Advisory Board, Durham, NC, United States, [9]Harvard School of Public Health, New York, NY, United States

134 **Rosuvastatin Improves Hip Bone Mineral Density But Worsens Insulin Resistance**

Grace A. McComsey[1], Ying Jiang[1], Kristine M. Erlandson[2], Sara M. Debanne[1]

[1]Case Western Reserve University, Cleveland, OH, United States, [2]University of Colorado Anschutz Medical Campus, Aurora, CO, United States

135 **Effects of Tesamorelin On Hepatic Fat in HIV Patients: A Randomized, Placebo-Controlled Trial**

Takara Stanley, Meghan Feldpausch, Jinhee Oh, Karen Branch, Martin Torriani, Steven Grinspoon

Massachusetts General Hospital, Boston, MA, United States

Session O-12 Oral Abstracts

10:00 AM – 12:15 PM **Ballroom A**

Persistence

Moderators

Nicolas Chomont, *Vaccine and Gene Therapy Institute of Florida, Port St. Lucie, FL, United States*

Mary Kearney, *National Cancer Institute, Frederick, MD, United States*

136LB **Early Treatment in Acute SIV Infection Limits the Size and Distribution of the Viral Reservoir**

Afam A. Okoye[1], Mukta Rohankhedkar[1], Matthew Reyes[1], Joseph Clock[1], Derick Duell[1], Yoshinori Fukazawa[1], Richard Lum[1], Haesun Park[1], Jeffrey D. Lifson[2], Louis J. Picker[1]

[1]Vaccine & Gene Therapy Institute and the Oregon National Primate Research Center, Oregon Health & Science University, Beaverton, OR, United States, [2]Frederick National Laboratory for Cancer Research, SAIC-Frederick, Inc, Frederick, MD, United States

137 **CD4 T-Cell Subset Composition of HIV Reservoirs in Gut, Lymph Node, and Blood During HAART**

Steven A. Yukl[1, 2], Teri Liegler[1], Mohamed Abdel-Mohsen[1], Elizabeth Sinclair[1], Hiroyu Hatano[1], Frederick Hecht[1], Ma Somsouk[1], Sarah Palmer[3, 4], Steven G. Deeks[1], **Joseph K. Wong**[1, 2]

[1]University of California San Francisco, San Francisco, CA, United States, [2]San Francisco Veterans Affairs Medical Center, San Francisco, CA, United States, [3]Karolinska Institute, Stockholm, Sweden, [4]Westmead Millennium Institute for Medical Research, Sydney, Australia

138 **Proliferation of Cells With HIV Integrated Into Regulatory Genes Is a Mechanism of Persistence**

Thor A. Wagner[1, 2], Sherry McLaughlin[1, 2], Kavita Garg[3], Hannah Huang[2], Sheila Styrchak[2], James I. Mullins[1], Lisa M. Frenkel[1, 2]

[1]University of Washington, Seattle, WA, United States, [2]Seattle Children's Hospital, Seattle, WA, United States, [3]Fred Hutchinson Cancer Research Center, Seattle, WA, United States

139 **Novel Ex Vivo Approaches Distinguish Effective and Ineffective Drugs for Reversing Latency In Vivo**

Gregory M. Laird, C. Korin Bullen, Janet D. Siliciano, Robert F. Siliciano

The Johns Hopkins University School of Medicine, Baltimore, MD, United States

140 **Effect of Vorinostat On Host Gene Expression in HIV Infected Patients On Antiretroviral Therapy**

Khader Ghneim[1], Jeff Ahlers[1], Julian Elliot[2], Miranda Smith[2], Fiona Wightman[2], Ajantha Solomon[2], Miles Prince[3], Steven Deeks[4], Rafick Sekaly[1], Sharon Lewin[2]

[1]VGTI-FL, Port Saint Lucie, FL, United States, [2]Department of Infectious Diseases, Monash University, Melbourne, Australia, [3]Department of Hematology, Peter Macallum Hospital, Melbourne, Australia, [4]Department of Medicine, University of California, San Francisco, CA, United States

141 **Cyclophosphamide Enhances SB-728-T Engraftment To Levels Associated With HIV-RNA Control**

Gary Blick[1], Jay Lalezari[2], Ricky Hsu[3], Edwin DeJesus[4], Trevor Hawkins[5], Ronald Mitsuyasu[6], Steven Deeks[7], Gary Lee[8], Winson Tang[8], Dale Ando[8]

[1]Circle Care Center, Norwalk, CT, United States, [2]Quest Clinical Research, San Francisco, CA, United States, [3]Private Practice, New York, NY, United States, [4]Orlando Immunology Center, Orlando, FL, United States, [5]Southwest Care, Santa Fe, NM, United States, [6]UCLA David Geffen School of Medicine, Los Angeles, CA, United States, [7]UCSF School of Medicine, San Francisco, CA, United States, [8]Sangamo BioSciences, Richmond, CA, United States

142 **Stimulation of Subdominant CTL Response Is Required for the Elimination of HIV-1 Latent Reservoir**

Kai Deng, Mihaela Pertea, Liang Shan, Robert Siliciano

The Johns Hopkins University, Baltimore, MD, United States

143 **Dendritic Cell-Based HIV Therapeutic Vaccine Increases Residual Viremia in Individuals On ART**

Bernard J. Macatangay[1], Mariam B. Lawani[1], Sharon A. Riddler[1], Nicole D. Wheeler[1], Margaret A. Bedison[1], Charles R. Rinaldo[2], John W. Mellors[1]

[1]University of Pittsburgh School of Medicine, Pittsburgh, PA, United States, [2]Infectious Disease and Microbiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA, United States

144LB **HIV-1 Rebound Following Allogeneic Stem Cell Transplantation and Treatment Interruption**

Timothy J. Henrich[1], Emily Hanhauser[2], Michael N. Sirignano[3], Jonathan Z. Li[1], Mathias Lichterfeld[4], Francisco M. Marty[1], Philippe Armand[5], Robert J. Soiffer[5], Marcus Altfeld[3], Daniel R. Kuritzkes[1]

[1]Brigham and Women's Hospital, Harvard Medical School, Cambridge, MA, United States, [2]Brigham and Women's Hospital, Cambridge, MA, United States, [3]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, United States, [4]Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States, [5]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, United States

Session O-13 Oral Abstracts

10:00 AM – 12:00 PM **Room 304**

Antiretroviral Scale-Up in Sub-Saharan Africa: Challenges and Opportunities

Moderators

Joep M.A. Lange, *Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands*

Harriet Nuwagaba-Biribonwoha, *International Center for AIDS Care and Treatment Programs (ICAP) in Swaziland, Columbia University Mailman School of Public Health, Mbabane, Swaziland*

145 **Age-Disparate Relationships and HIV Incidence Amongst Rural South Africa Women**

Guy Harling[1], Marie-Louise Newell[2, 3], Frank Tanser[3], Ichiro Kawachi[4], SV Subramanian[4], Till Bärnighausen[1, 3]

[1]Global Health and Population, Harvard School of Public Health, Boston, MA, United States, [2]University of Southampton, Southampton, United Kingdom, [3]Africa Centre for Health and Population Studies, Mtubatuba, South Africa, [4]Social and Behavioral Sciences, Harvard School of Public Health, Boston, MA, United States

146 **Introduction of HIV into Stable Heterosexual Couples in Rakai, Uganda Before and After ART**

Mary K. Grabowski[1], Justin Lessler[1], Fred Nalugoda[2], Steve J. Reynolds[3, 4], Robert Ssekubugu[5], Xiangrong Kong[1], Godfrey Kigozi[5], Maria Wawer[1, 5], David Serwadda[5, 6], Ronald H. Gray[1, 5]

[1]The Johns Hopkins University, Baltimore, MD, United States, [2]Epidemiology, Rakai Health Sciences Program, Kalisizo, Uganda, [3]Medicine, The Johns Hopkins University, Baltimore, MD, United States, [4]National Institutes of Health, Bethesda, MD, United States, [5]Rakai Health Sciences Program, Kalisizo, Uganda, [6]University of Makerere, Kampala, Uganda

147 **One Year Outcomes Following Community-Based HIV Self-Testing: A Prospective Study in Malawi**

Augustine T. Choko[1], Peter MacPherson[1, 2], Emily L. Webb[3], Helena Ball[3], Rodrick Sambakunsi[1], Aaron Mdolo[1], Simon D. Makombe[4], Nicola Desmond[1, 2], Richard Hayes[3], Elizabeth L. Corbett[1, 3]

[1]Malawi Liverpool Wellcome Trust Clinical Research Programme, Blantyre, Malawi, [2]Liverpool School of Tropical Medicine, Liverpool, United Kingdom, [3]London School of Hygiene & Tropical Medicine, London, United Kingdom, [4]HIV Unit, Ministry of Health, Lilongwe, Malawi

148 **Community HIV Testing and Linkage To Care Reduces Population Viral Load in South Africa and Uganda**

Ruanne V. Barnabas[1, 2], Heidi van Rooyen[3], Elioda Tumwesigye[4], Meighan Krows[1], Pam Murnane[1], Hllton Humphries[3], Bosco Turyamureeba[4], James P. Hughes[2, 5], Jared Baeten[6], Connie Celum[6]

[1]Global Health and Medicine, University of Washington, Seattle, WA, United States, [2]Fred Hutchinson Cancer Research Center, Seattle, WA, United States, [3]HIV/AIDS, STIs and Tuberculosis (HAST) Programme, Human Sciences Research Council, Sweetwaters, South Africa, [4]Integrated Community Based Initiatives, Kabwohe, Uganda, [5]Global Health and Epidemiology, University of Washington, Seattle, WA, United States, [6]Global Health, Epidemiology and Medicine, University of Washington, Seattle, WA, United States

149 **Enhanced HIV Surveillance To Evaluate the National Response To HIV/AIDS in Kenya**

William Maina[1], Davies Kimanga[1], Ibrahim Mohammed[1], Mamo Umuro[2], Macdonald Obudho[3], George Kichamu[4], Patrick Mureithi[5], Willis Akhwale[6], Kevin M. De Cock[7], Andrea A. Kim[7]

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150 **Unequal Benefits From ART: A Growing Male Disadvantage in Life Expectancy in Rural South Africa**

Till Barnighausen[1, 2], Abraham J. Herbst[2], Frank Tanser[2], Marie-Louise Newell[2, 3], Jacob Bor[2, 4]

[1]Global Health and Population, Harvard School of Public Health, Boston, MA, United States, [2]Africa Centre for Health and Population Studies, Mtubatuba, South Africa, [3]University of Southampton, Southampton, United Kingdom, [4]Department of International Health, Boston University School of Public Health, Boston, MA, United States

151 **A New Paradigm for Evaluating the HIV Care Cascade**

Margaret L. McNairy, Matthew Lamb, Batya Elul, Elaine Abrams, Wafaa El-Sadr, The Identifying Optimal Models of HIV Care in Africa Study

ICAP Columbia University, New York, NY, United States

152LB **Moderate HIV Incidence and High ART Coverage in Rural Kwazulu-Natal: First Population-Based Survey**

Helena Huerga[1], Médecins Sans Frontières, Adrian Puren[2], Malika Bouhenia[1], Jihane Ben Farhat[1], Alex Welte[3], Lubbe Wiesner[4], David Maman[1], Jean-François Etard[1, 5]

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Session TD11 Themed Discussion

1:30 PM – 2:30 PM **Room 309**

Kaposi Sarcoma

Discussion Leader

Thomas S. Uldrick, *National Cancer Institute, Bethesda, MD, United States*

709 **Guidelines On Kaposi's Sarcoma Treatment: Results From Two Cochrane Systematic Reviews**

Esther E. Freeman[1], Charles Okwundu[2], Oluwatoyin Gbabe[3], Miriam Laker[4], Philippa Easterbrook[5], Toby Maurer[6], Jeffrey Martin[4]

[1]Department of Dermatology, Harvard Medical School, Massachusetts General Hospital, Boston, MA, United States, [2]Centre for Evidence-Based Health Care, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, South Africa, [3]Centre for Evidence-Based Health Care, Faculty of Health Sciences, Stellenbosch University, Tygerberg, South Africa, [4]Department of Epidemiology and Biostatistics, University of California at San Francisco, San Francisco, CA, United States, [5]HIV Department, World Health Organization, Geneva, Switzerland, [6]Department of Dermatology, University of California at San Francisco, San Francisco, CA, United States

711 **Kaposi Sarcoma in the Era of Combination Antiretroviral Therapy**

Natascha Wyss, Matthias Egger, Julia Bohlius, Malignancy Working Group for COHERE in EuroCoord

Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

710 **Randomized Trial of Protease Inhibitor-Based Antiretroviral Therapy for Kaposi Sarcoma in Africa**

Jeffrey Martin[1], Miriam Laker-Oketta[1, 2], Victoria Walusansa[3], Jackson Orem[3], John Bennett[1], Adrienne Mocello[1], Toby Maurer[1], Peter Hunt[1], Andrew Kambugu[2], Edward Mbidde[2, 4]

[1]University of California San Francisco, San Francisco, CA, United States, [2]Infectious Diseases Institute, Kampala, Uganda, [3]Uganda Cancer Institute, Kampala, Uganda, [4]Uganda Virus Research Institute, Entebbe, Uganda

708 **The Effect of Protease Inhibitor Use On Kaposi Sarcoma Incidence in a cART-Experienced Cohort**

Elizabeth Chiao, Marc Kowalkowski

Baylor College of Medicine, Houston, TX, United States

714 **Indoleamine 2, 3-Dioxygenase (IDO) Activity as a Determinant of Kaposi Sarcoma in Africa**

Helen Byakwaga[1, 2], Peter W. Hunt[1], Miriam Laker-Oketta[1, 3], David V. Glidden[1], Yong Huang[1], Mwebesa Mwebesa[2], Victoria Walusansa[4], David R. Bangsberg[5], Edward Mbidde[3], Jeffrey N. Martin[1]

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Session TD12 Themed Discussion

1:30 PM – 2:30 PM **Ballroom A**

Pulmonary Complications of HIV Infection

Discussion Leader

Marshall J. Glesby, *Weill Cornell Medical College, New York, NY, United States*

775 **HIV Infection and Related Biomarkers Are Independent Risk Factors for Radiographic Emphysema**

Engi F. Attia[1], Matthew B. Goetz[2], Maria C. Rodriguez-Barradas[3], David Rimland[4], Sheldon T. Brown[5], Guy Soo Hoo[2], Joon Kim[5], Cherry Wongtrakool[4], Kathleen Akgun[6], Kristina Crothers[1]

[1]Medicine, University of Washington, Seattle, WA, United States, [2]Medicine, West Los Angeles Veterans Affairs Medical Center and David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA, United States, [3]Medicine, Michael E. DeBakey Veterans Affairs Medical Center and Baylor College of Medicine, Houston, TX, United States, [4]Medicine, Atlanta Veterans Affairs Medical Center and Emory University, Atlanta, GA, United States, [5]Medicine, James J. Peters Veterans Affairs Medical Center and Icahn School of Medicine at Mt. Sinai, Bronx and NYC, NY, United States, [6]Medicine, West Haven Veterans Affairs Medical Center and Yale University, West Haven, CT, United States

776 **Factors Associated With Chronic Obstructive Pulmonary Disease in a High-Risk HIV-Infected Cohort**

Alain Makinson[1], Maurice Hayot[2], Sabrina Eymard-Duvernay[3], François Raffi[4], Laurence Thirard[5], Fabrice Bonnet[6], Pierre Tattevin[7], Sophie Abgrall[8], Jacques Reynes[1], Vincent Le Moing[1], ANRS EP48 HIV CHEST Study Team

[1]Infectious and Tropical Diseases Department, University Hospital Montpellier 1, UMI 233, Montpellier, France, [2]Department of Clinical Physiology, INSERM U1046, University Hospital Montpellier, Montpellier, France, [3]UMI 233, IRD, University Montpellier 1, Montpellier, France, [4]Infectious and Tropical Diseases Department, Nantes University Hospital, Nantes, France, [5]Tourcoing University Hospital, Tourcoing, France, [6]Internal Medecine and Infectious Diseases Department, University Hospital Bordeaux, INSERM U897, Bordeaux, France, [7]Infectious Diseases and ICU, Pontchaillou University Hospital, Rennes, France, [8]Infectious and Tropical Diseases Department, Groupement Hospitalier Nord, Bobigny, France

773 **HIV Infection Increases Risk of Acute Exacerbations of COPD**

Allison A. Lambert, Gregory D. Kirk, Jacquie Astemborski, Shruti H. Mehta, M. Bradley Drummond

The Johns Hopkins University, Baltimore, MD, United States

774 **Association of HIV Infection and Immune Activation With Decline in Lung Function**

Kristina Crothers[1], Carla V. Rodriguez[1], Cherry Wongtrakool[2], Guy Soo Hoo[3], Joon Kim[4], Sheldon T. Brown[4], David Rimland[2], Maria C. Rodriguez-Barradas[5], Matthew B. Goetz[3], Amy C. Justice[6]

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Session TD13 Themed Discussion

1:30 PM – 2:30 PM **Room 304**

Incidence Assays

Discussion Leader

Christine M. Rousseau, *Bill and Melinda Gates Foundation, Seattle, WA, United States*

1006 **Performance of the Limiting-Antigen Avidity EIA for Use With Dried Blood Spot Specimens**

Erin K. Rottinghaus, Trudy Dobbs, Bharat S. Parekh, Yen T. Duong

Centers for Disease Control and Prevention, Atlanta, GA, United States

1008 **Incorrect Identification of Recent HIV Infection Using a LAg-Avidity Assay in Adults in the US**

Andrew F. Longosz[1], Ron Brookmeyer[2], Shruti Mehta[3], Greg D. Kirk[3], Joseph B. Margolick[4], Joelle Brown[5], Thomas C. Quinn[1, 6], Susan H. Eshleman[7], Oliver Laeyendecker[1, 6]

[1]Laboratory of Immunoregulation, Division of Intramural Research, National Insitutes of Health, Baltimore, MD, United States, [2]Department of Biostatistics, University of California Los Angeles, Los Angeles, CA, United States, [3]Department of Epidemiology, The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States, [4]Department of Molecular Microbiology and Immunology, The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States, [5]Department of Epidemiology, University of California Los Angeles, Los Angeles, CA, United States, [6]Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD, United States, [7]Department of Pathology, The Johns Hopkins University School of Medicine, Baltimore, MD, United States

1007 **The Impact of HIV Subtype On Specificity of Cross-Sectional HIV Incidence Assays in Rakai, Uganda**

Andrew F. Longosz[1], David Serwadda[2, 3], Fred Nalugoda[3], Godfrey Kigozi[3], Veronica Franco[4], Ronald H. Gray[3, 5], Thomas C. Quinn[1, 4], Susan H. Eshleman[4], Oliver Laeyendecker[1, 4]

[1]NIAID, National Insitutes of Health, Baltimore, MD, United States, [2]Makerere University School of Public Health, Kampala, Uganda, [3]Rakai Health Sciences Program, Rakai, Uganda, [4]The Johns Hopkins University School of Medicine, Baltimore, MD, United States, [5]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States

1005 **Independent Evaluation of Predicate Incidence Assays for HIV Surveillance**

Reshma Kassanjee1, Christopher Pilcher[2], Sheila Keating[3], Shelley Facente[2], Matt Price[4], Jeffrey Martin[2], Susan Little[5], **Alex Welte**[0], Michael Busch[3], Gary Murphy[6], Consortium for the Evaluation and Performance of HIV Incidence Assays (CEPHIA)

[1]The South African DST/NRF Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA), Stellenbosch University, Stellenbosch, South Africa, [2]University of California San Francisco, San Francisco, CA, United States, [3]Blood Systems Research Institute, San Francisco, CA, United States, [4]Department of Medical Affairs, International AIDS Vaccine Initiative (IAVI), New York City, NY, United States, [5]Department of Medicine, University of California San Diego, La Jolla, CA, United States, [6]Health Public England, London, United Kingdom

Session TD14 Themed Discussion

1:30 PM – 2:30 PM **Room 312**

What We Learn From Bone Marrow Transplants

Discussion Leader

Paula M. Cannon, *University of Southern California, Los Angeles, CA, United States*

418 **Impact of Systemic Cytotoxic Chemotherapy for Malignancies On HIV-1 Reservoir Persistence**

Timothy J. Henrich[1], Emily Hanhauser[2], Jonathan Z. Li[1], Andrea Heisey[2], Jeremy S. Abramson[3], Ayad Hamdan[4], Philippe Armand[5], Ann S. LaCasce[5], Daniel R. Kuritzkes[1]

[1]Brigham and Women's Hospital, Harvard Medical School, Cambridge, MA, United States, [2]Brigham and Women's Hospital, Cambridge, MA, United States, [3]Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States, [4]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States, [5]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, United States

417 **Dynamics of HSPC Repopulation in Nonhuman Primates Revealed by a Decade-Long Clonal Tracking**

Sanggu Kim[1], Namshin Kim[2], Angela Presson[1], Dong Sung An[1], Robert E. Donahue[3], Irvin S. Y. Chen[1]

[1]University of California, Los Angeles, Los Angeles, CA, United States, [2]Korean Bioinformatics Center, Daejeon, Korea, Republic of, [3]National Heart, Lung and Blood Institute, Bethesda, MD, United States

416 **Targeting SIV Reservoirs via Autologous Hematopoietic Stem Cell Transplant in Rhesus Macaques**

Maud Mavigner[1], Benjamin Watkins[2, 3], Benton O. Lawson[1], Ann Chahroudi[1, 2], Leslie S. Kean[2, 3], Guido Silvestri[1]

[1]Yerkes National Primate Research Center, Emory University, Atlanta, GA, United States, [2]Department of Pediatrics, Emory University, Atlanta, GA, United States, [3]Emory Transplant Center, Emory University, Atlanta, GA, United States

419 **Modeling Functional Cure of HIV in Nonhuman Primates Using Gene-Modified Hematopoietic Stem Cells**

Hans-Peter Kiem[1], Christopher W. Peterson[1], Patrick M. Younan[1], Shiu-Lok Hu[2], Patricia Polacino[2], Michael Holmes[3], Philip Gregory[3], Jianbin Wang[3]

[1]Transplantation Biology, Fred Hutchinson Cancer Research Center, Seattle, WA, United States, [2]University of Washington, Seattle, WA, United States, [3]Sangamo Biosciences, Richmond, CA, United States

Session TD15 Themed Discussion

1:30 PM – 2:30 PM **Room 311**

CNS Viral Escape and Neuroinflammation on ART

Discussion Leaders

Dennis L. Kolson, *University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA, United States*

Scott L. Letendre, *University of California San Diego, San Diego, CA, United States*

447 **CNS Outcomes of cART vs. cART plus Maraviroc and Raltegravir Intensification During Acute HIV**

Victor Valcour[1], Serena Spudich[2], Napaporn Sailasuta[3], Sukalaya Lerdlum[4], **James L. K. Fletcher[5]**, Eugene D. M. B. Kroon[5], Peeriya Mangyu[5], Bonnie Slike[6], Jerome Kim[6], Jintanat Ananworanich[7], on behalf of the SEARCH 010/RV254 Study Group

[1]Memory and Aging Center, UCSF, San Francisco, CA, United States, [2]Neurology, Yale University, New Haven, CT, United States, [3]Huntington Medical Research Institutes, Pasedena, CA, United States, [4]Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, [5]SEARCH, The Thai Red Cross AIDS Research Center, Bangkok, Thailand, [6]U.S. Military HIV Research Program, Walter Reed Army Institute of Research, Silver Springs, MD, United States, [7]Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

442 **HIV-1 RNA Detection in CSF in ART-Treated Subjects With Incomplete Viral Suppression in Plasma**

Sam Nightingale, the PARTITION Study Group

Institute of Infection and Global Health, University of Liverpool, Liverpool, United Kingdom

443 **CSF Viral Escape in Patients Without Neurological Disorders: Prevalence and Associated Factors**

Carmela Pinnetti[1], Patrizia Lorenzini[1], Federica Forbici[1], Adriana Ammassari[1], Raffaella Libertone[1], Maria Letizia Giancola[1], Maria Rosaria Capobianchi[1], Carlo Federico Perno[2], Andrea Antinori[1]

[1]National Institute for Infectious Disease, Rome, Italy, [2]University of Rome, Rome, Italy

445 **Cerebrospinal Fluid Viral Blips and Persistent Escape in HIV-Infected Patients On ART**

Arvid Eden[1], Lars-Magnus Andersson[1], Dietmar Fuchs[2], Lars Hagberg[1], Staffan Nilsson[3], Bo Svennerholm[1], Aylin Yilmaz[1], Henrik Zetterberg[1], Magnus Gisslen[1]

[1]University of Gothenburg, Gothenburg, Sweden, [2]Innsbruck Medical University, Innsbruck, Austria, [3]Chalmers University of Technology, Gothenburg, Sweden

446 **Mitochondrial DNA Is Associated With Inflammation and Neurocognitive Deficits in HIV Infection**

Josué Pérez-Santiago[1], Sanjay R. Mehta[1], Sara Gianella[1], Rachel D. Schrier[1], Mariana Cherner[1], Susanna R. Var[1], Tyler R. C. Day[1], Miguel Ramirez-Gaona[2], Davey M. Smith[1, 3], Scott L. Letendre[1]

[1]Medicine, University of California San Diego, La Jolla, CA, United States, [2]Bioinformatics, University of Alberta, Edmonton, AB, Canada, [3]Veterans Administration San Diego Healthcare System, San Diego, CA, United States

444 **Early Monocyte Inflammation Among Treatment-Naïve Acute HIV-Infected Thai Subjects**

Lishomwa C. Ndhlovu[1], Mary Margaret Byron[1], Guangxiang Zhang[2], Duanghathai Sutthichom[3], Somprartthana Rattanamanee[3], Rapee Trichavaroj[4], Nittaya Phanuphak[3], Victor Valcour[5], Merlin Robb[6], Jintanat Ananworanich[7]

[1]Hawaii Center for AIDS, University of Hawaii, Honolulu, HI, United States, [2]University of Hawaii, Honolulu, HI, United States, [3]SEARCH, The Thai Red Cross AIDS Research Center, Bangkok, Thailand, [4]Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand, [5]University of California San Francisco, San Francisco, CA, United States, [6]US Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD, United States, [7]SEARCH, HIV-NAT, The Thai Red Cross AIDS Research Center, Bangkok, Thailand

POSTER SESSIONS

2:30 PM–4:00 PM

(Use the Poster Abstract section of the Program at a Glance, page 37 to 106, for specific posters in each session)

Session P-A6 HIV Entry
Session P-A7 Factor Potpourri
Session P-B3 Viral Subtype: Expansion, Migration, and Recombination
Session P-C11 CD4/CD8, Aging, and Immune Senescence
Session P-C12 Mucosal CD4 and TH17 Cells
Session P-C13 In Vitro Studies
Session P-C14 Genomics and Endogenous Retroviruses
Session P-D5 Compartmentalization
Session P-D6 New Themes in Host Control
Session P-E6 Human Vaccine Trial Results
Session P-E7 Immune Response To Infection
Session P-F7 Effect of ART on Persistence
Session P-F8 Immunology for Cure
Session P-F9 Toward A Cure...
Session P-G7 ART Effects on HAND and CNS Reservoirs
Session P-G8 CNS Inflammation, Immune Activation, and HAND Biomarkers
Session P-H4 New Clinical and Preclinical Formulations
Session P-J1 RCTs in Second-Line ART and Virologic Failure
Session P-J2 RCTs in First-Line ART in Treatment Naïve Patients
Session P-J3 ART Simplification, Intensification, and Switch Studies
Session P-K3 ART: Adherence and Retention
Session P-K4 Second-Line ART
Session P-K5 HIV-2
Session P-L5 Laboratory Detection of Drug Resistance and Tropism
Session P-L6 Cost Effectiveness Studies of ART and Drug Resistance Testing
Session P-N6 Acute HCV Infection: Pathogenesis
Session P-N7 HCV Infection and Cellular and Humoral Immune Responses
Session P-N8 HCV-Related Outcomes: Cardiac and Non-Liver
Session P-N9 HBV and HDV
Session P-N10 HEV
Session P-O5 Cervical Cancer, HPV, and HPV Vaccine
Session P-O6 Anal Cancer and HPV
Session P-P5 Antiretroviral Therapy, Lipids, and CVD
Session P-P6 Statins and ARV Effects in HIV
Session P-Q7 Renal Disease: ART, Genetic Factors, and Long-Term Outcomes
Session P-Q8 Obesity: ART and Animal Models
Session P-Q9 Genetic Factors and ART Outcomes
Session P-Q10 ART and Suicidality
Session P-R6 Cryptococcal Disease
Session P-R7 OIs other than TB and Cryptococcal Disease

Session P-S2 HIV in Women: Pregnancy, Progression, Pap, and Bones
Session P-S3 Immune Mediators and Immune Activation in Women
Session P-S4 Immune Response To Vaccination in HIV+ Women
Session P-T7 Risk Factors for MTCT
Session P-T8 PMTCT Approaches: Implementation and Outcome
Session P-T9 ART Pharmacokinetics During Pregnancy and Breast Feeding
Session P-U6 Response To Early ART Initiation in Infants
Session P-U7 Co-Infections and Treatment Responses in Children and Adolescents
Session P-U8 Outcomes Among Adolescents – Perinatally and Behaviorally Acquired HIV Infection
Session P-W7 Disease Progression/Mortality
Session P-W8 Co-Morbidities
Session P-W9 Transmission/Risk Factors

Session S7 Symposium
4:00 PM – 6:00 PM **Room 304**

Interferon: Whatever Turns You On

Target audience: This session is directed to basic, translational, and clinical researchers interested in the role played by mechanisms of antiviral innate immunity — and, specifically, the type I interferons — in HIV-infected individuals in both protecting against virus replication and potentially inducing immunopathology in the host.

Level of knowledge: It is assumed that learners are familiar with the basic aspects of virology, immunology, and pathogenesis of HIV infection and AIDS.

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

- Recognize the potential antiviral as well as pro-inflammatory roles of type I IFNs during HIV infection
- Understand the role of type I IFNs in HIV transmission and pathogenesis
- Describe the similarities and differences of the role played by type I IFNs in HIV and HCV infections

Conveners

Nina Bhardwaj, *Icahn School of Medicine at Mount Sinai, New York, NY, United States*

Michael M. Lederman, *Case Western Reserve University, Cleveland, OH, United States*




154 **HIV-1 Evades Innate Immune Recognition Through Specific Co-Factor Recruitment**
Greg J. Towers
University College London, London, United Kingdom



155 **Interferon Treatments for Chronic Hepatitis C**
Markus H. Heim
University Hospital Basel, Basel, Switzerland



156 **Perturbing Interferon Signaling in SIV Infection**
Daniel C. Douek
National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, United States



157 **Type 1 Interferon-Mediated Selective Pressure On HIV-1 Transmission**
Persephone Borrow
University of Oxford, Oxford, United Kingdom

Session S8 Symposium
4:00 PM – 6:00 PM **Room 311**

The Road To Elimination: Preventing and Treating HIV Infection in Infants

Target audience: This session is directed to individuals interested in prevention of perinatal transmission and early antiretroviral therapy for HIV-exposed infants at high risk for perinatal transmission.

Level of knowledge: It is assumed that learners are familiar with pathophysiology of perinatal HIV transmission, approaches to prevention of infant infection and HIV management of pregnant and breast-feeding women. In addition, learners should have a basic understanding of manifestations and treatment of HIV infection during infancy and early childhood.

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

- Describe the rationale for and implementation experience with the Option B+ approach to prevention of perinatal HIV transmission
- Identify short- and long-term effects of antiretroviral exposure during pregnancy and breast-feeding
- Recognize new approaches to early diagnosis and treatment of HIV-exposed and -infected newborns

Conveners

Dalton C. Wamalwa, *University of Nairobi, Nairobi, Kenya*

Coceka N. Mnyani, *University of the Witwatersrand, Anova Health Institute, Johannesburg, South Africa*



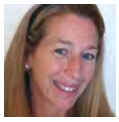

158 **Treatment of Pregnant and Breast-Feeding Women: Evidence and Rationale for Option B+**
Saeed Ahmed
Baylor College of Medicine, Lilongwe, Malawi



159 **Achievements and Challenges With Option B+ Implementation in the Field To Date**
Edward Bitarakwate
Elizabeth Glaser Pediatric AIDS Foundation, Kampala, Uganda



160 **No Free Rides: Consequences of Fetal & Infant ARV Exposure Among Children Remaining HIV Uninfected**
Kathleen M. Powis
Harvard Medical School, Boston, MA, United States



161 **Treatment of HIV-Infected Newborns: Why, When, and What To Start?**
Ellen G. Chadwick
Northwestern University, Feinberg School of Medicine, Chicago, IL, United States

Session S9 Symposium

4:00 PM – 6:00 PM **Room 312**

Intimate Infections: What's Love Got To Do With It?

Target audience: This session is directed to clinicians and scientists interested in sexually transmitted infections affecting HIV-infected and -at risk persons.

Level of knowledge: It is assumed that learners are familiar with basic HIV epidemiology and sexually transmitted infections.

Objective: At the completion of the session, learners will be able to:

- Describe the epidemiology, clinical manifestations, association with HIV infection, and approaches to prevention and treatment of human papilloma virus (HPV), bacterial vaginosis (BV), meningococcus, and lymphogranuloma venerium (LGV)

Conveners

Christine Katlama, *Pitié-Salpêtrière Hospital, Paris, France*



Bernard Liautaud, *GHESKIO Centers, Port-au-Prince, Haiti*



162 **Oral Human Papillomavirus (HPV): Epidemiology and Role in Oropharyngeal Cancer**
Gypsyamber D'Souza
The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States



163 **Bacterial Vaginosis**
Landon Myer
University of Cape Town, Cape Town, South Africa



164 **Outbreak of Invasive Meningococcal Disease Among Men Who Have Sex With Men — New York City, 2010-2013**
Alison D. Ridpath
New York City Department of Health and Mental Hygiene, New York, NY, United States



165 ***Lymphogranuloma venereum***
David A. Lewis
National Institute for Communicable Diseases, Johannesburg, South Africa



POSTER LISTINGS

Session P-A1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

SAMHD1

166 **CDK2 But Not CDK1 Phosphorylates SAMHD1 in Primary Macrophages**

Alba Ruiz[1], Eduardo Pauls[1], Ester Ballana[1], Albert Gubern[2], Mar Álvarez[3], Luis Menéndez-Arias[3], Francesc Posas[2], Bonaventura Clotet[1], José A. Esté[1]

[1]IrsiCaixa AIDS Research Institute, Hospital Germans Trias i Pujol, Universitat Autònoma de Barcelona, Badalona, Spain, [2]Cell Signaling Unit, Departament de Ciències Experimentals i de la Salut, Universitat Pompeu Fabra, Parc de Recerca Biomèdica de Barcelona, Barcelona, Spain, [3]Centro de Biología Molecular Severo Ochoa, Consejo Superior de Investigaciones Científicas, Universidad Autónoma de Madrid, Madrid, Spain

167LB **p21 Regulates the HIV-1 Restriction Factor SAMHD1**

Alba Ruiz[1], Eduardo Pauls[1], Eva Riveira-Muñoz[1], Marc Permanyer[1], Roger Badia[1], Oliver T. Keppler[2], Bonaventura Clotet[1], Ester Ballana[1], **Jose Este**[1]

[1]AIDS Research Institute - IrsiCaixa, Badalona, Spain, [2]Institute for Medical Virology, Frankfurt, Germany

168 **Inhibitors of CDK2 and CDK6 Block HIV-1 RT Through the Control of SAMHD1 Activity**

Ester Ballana, Roger Badia, Marc Permanyer, Eva Riveira-Muñoz, Bonaventura Clotet, Eduardo Pauls, José A. Esté

IrsiCaixa AIDS Research Institute, Badalona, Spain

169 **Vpx Mediated Degradation of SAMHD1 Does Not Render HSCs More Permissive To Lentiviral Gene Transfer**

Duo Li[1], Erika Schlaepfer[1], Caitlin Knowlton[2], Baek Kim[2], Annette Audigé[1], Roberto Speck[1]

[1]Division of Infectious Diseases and Hospital Epidemiology, University Hospital of Zurich, Zurich, Switzerland, [2]Center for Drug Discovery, Department of Pediatrics, Emory University, Atlanta, GA, United States

Session P-A2 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Integration/Nuclear Import

170 **BET Proteins Mediate Integration Site Selection of MLV Much Alike LEDGF/p75 in HIV Integration**

Jan De Rijck[1], Christine de Kogel[1], Jonas Demeulemeester[1], Sofie Vets[1], Nirav Malani[2], Frederic Bushman[2], **Frauke Christ**[1], Rik Gijsbers[1], Zeger Debyser[1]

[1]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium, [2]Department of Microbiology, University of Pennsylvania, Philadelphia, PA, United States

171 **Zinc-Finger Endonuclease Targeting LEDGF/p75 Inhibits HIV-1 Integration**

Roger Badia, Ester Ballana, Bonaventura Clotet, José Esté

IrsiCaixa AIDS Research Institute, Badalona, Spain

172 **Small-Molecule Inhibits HIV-1 Replication by Interacting With HIV Capsid**

Atsuko Hachiya[1,2], Anna Gres[2], Karen A. Kirby[2], Michailidis Eleftherios[2], Masami Maejima[1], Wataru Sugiura[1], Kyeongeun Lee[3], Vineet KewalRamani[3], Kamlendra Singh[2], Stefan G. Sarafianos[2,4]

[1]Clinical Research Center, Laboratory of Infectious Diseases, National Hospital Organization, Nagoya Medical Center, Nagoya, Japan, [2]C. S. Bond Life Sciences Center & Department of Molecular Microbiology and Immunology, University of Missouri School of Medicine, Columbia, MO, United States, [3]HIV Drug Resistance Program, National Cancer Institute, Frederick, MD, United States, [4]Department of Biochemistry, University of Missouri, Columbia, MO, United States

173 **Resistance To HIV-1 Infection in PBLs From LGMD1F Patients Carrying a Genetic Defect in TNPO3**

Mercedes Bermejo[1], Mayte Coiras[1], Sara Rodriguez-Mora[1], Elena Mateos[1], Ramón Martí[2], Juan Vilchez[3], Antonio Andreu[2], Jose Alcamí[1]

[1]AIDS Immunopathology Unit, Instituto de Salud Carlos III, El Centro Nacional de Microbiología, Majadahonda, Madrid, Spain, [2]Research Group on Neuromuscular and Mitochondrial Disorders, Vall d'Hebron Institut de Recerca, VHIR and CIBERER, Barcelona, Spain, [3]Hospital Universitari i Politècnic La Fe, Department of Neurology, Universitat de Valencia, and CIBERNED, Department of Medicine, Valencia, Spain

174 **HIV Integrase$^{R263A/K264A}$ Is Defective for TRN-SR2/IN Interaction and Nuclear Import of the PIC**

Stephanie Dehouwer, Jonas Demeulemeester, Wannes Thys, Zeger Debyser, **Frauke Christ**

Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium

Session P-A4 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Late Events in HIV Replication

175 **SHAPE-Directed Discovery of a Novel Structure in the HIV-1 RNA Polyadenylation Signal**

Nathan A. Siegfried[1], Steven Busan[1], Greggory M. Rice[1], Christine E. Hajdin[1], **Julie A. E. Nelson**[2], Kevin M. Weeks[1]

[1]Chemistry, Univ of North Carolina at Chapel Hill, Chapel Hill, NC, United States, [2]UNC Center for AIDS Research and Microbiology & Immunology, Univ of North Carolina at Chapel Hill, Chapel Hill, NC, United States

176 **HIV-1 Assembly On Intracellular Plasma Membrane-Connected Compartments of Human Macrophages**

David O. Nkwe, Annegret Pelchen-Matthews, Mark Marsh

Laboratory for Molecular Cell Biology, University College London, London, United Kingdom

177 **LEDGIN (ALLINI) Disruption of HIV-1 Assembly Does Not Involve LEDGF/p75**

Hind J. Fadel[1], James Morrison[1], Dyana Saenz[1], Stephen C. Ekker[2], James R. Fuchs[3], Mamuka Kvaratskhelia[3], Eric M. Poeschla[1]

[1]Division of Infectious Diseases & Department of Molecular Medicine, Mayo Clinic, Rochester, MN, United States, [2]Department of Biochemistry and Molecular Biology, Mayo Clinic, Rochester, MN, United States, [3]Ohio State University Center for Retrovirus Research, Columbus, OH, United States

178 **Characterization of the Interaction Between Staufen-1 With HIV-1 Rev and HERV-K(HML-2) Rec**

Katharina Fiddeke, Alexander Rohde, Kirsten Hanke, Jula Wamara, Oliver Hohn, **Norbert Bannert**

HIV and Other Retroviruses, Robert Koch Institute, Berlin, Germany

179 **The Role of RNA Interference in HIV-1-Infected Primary Human Monocyte-Derived Macrophages**

Valentina Vongrad[1], Jochen Imig[2], Pejman Mohammadi[3], Shivendra Kishore[4], Lukasz Jaskiewicz[4], Mihaela Zavolan[4], Jonathan Hall[2], Niko Beerenwinkel[3], Huldrych F Günthard[1], Karin J Metzner[1]

[1]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Zurich, Switzerland, [2]Institute of Pharmaceutical Sciences, ETH Zurich, Zurich, Switzerland, [3]ETH Zurich, D-BSSE, Basel, Switzerland, [4]Computational and Systems Biology, University of Basel, Basel, Switzerland

180 **Induced Maturation of HIV-1 Virions**

Barbara Mueller[1], Simone Mattei[2], Maria Anders[1], John A. G. Briggs[2], Hans-Georg Kraeusslich[1]

[1]Infectious Diseases, Virology, University of Heidelberg, Heidelberg, Germany, [2]EMBL, Heidelberg, Germany

181 **Interplay of Cholesterol and Env Protein in the Lytic Deformation of HIV-1 by Peptide Triazoles**

R Venkat Kalyana Sundaram[1,2], Huiyuan Li[3], Lauren Bailey[4], A Rosemary Bastian[2,5], Steven Wrenn[6], Cameron Abrams[6], Irwin Chaiken[1]

[1]Biochemistry and Molecular Biology, Drexel University College of Medicine, Philadelphia, PA, United States, [2]School of Biomedical Engineering, Science and Health Systems, Drexel University, Philadelphia, PA, United States, [3]Shared Research Facility, West Virginia University, Morgantown, WV, United States, [4]Biochemistry, Drexel University College of Medicine, Philadlephia, PA, United States, [5]Biochemistry, Drexel University College of Medicine, Philadelphia, PA, United States, [6]Chemical and Biological Engineering, Drexel University, Philadelphia, PA, United States

Session P-A5 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Apobec, Apobec, Apobec

182 **Characterizing Novel N-Terminal Domains of APOBEC3G**

Meiling R. May[1], Ann M. Sheehy[2]

[1]College of the Holy Cross, Worcester, MA, United States, [2]Biology, College of the Holy Cross, Worcester, MA, United States

183 **SLBP (Stem-Loop Binding Protein) Regulates the Expression of APOBEC3G**

Ming Li, Lynne Tucker, Michelle Lally, Bharat Ramratnam

Alpert Medical School of Brown University, Providence, RI, United States

184 **Incomplete Apobec3G Neutralization by Vif Mutations Facilitates Evolution From CCR5 To CXCR4 Use**

Claudia Alteri[1], Matteo Surdo[1], Patrizia Saccomandi[1], Fabio Continenza[2], Daniele Armenia[1], Luca Carioti[1], Anna Artese[3], Francesca Ceccherini-Silberstein[1], Carlo Federico Perno[1,2], Valentina Svicher[1]

[1]Department of Experimental Medicine and Surgery, University of Rome Tor Vergata, Rome, Italy, [2]Istituto Nazionale per le Malattie Infettive "Lazzaro Spallanzani", Rome, Italy, [3]Department of Pharmacobiological Sciences, Magna Graecia University of Catanzaro, Roccelletta di Borgia (CZ), Italy

185 **17β-Estradiol Protects Primary Macrophages Against HIV Through Induction of IFNα and APOBEC3A**

Carley Tasker[1], Jian Ding[1], Mirco Schmolke[2], Amariliz Rivera-Medina[3], Adolfo García-Sastre[2], Theresa Chang[1]

[1]Department of Microbiology and Molecular Genetics, Rutgers Biomedical and Health Sciences, Newark, NJ, United States, [2]Department of Microbiology, Mount Sinai School of Medicine, New York, NY, United States, [3]Department of Medicine, Rutgers Biomedical and Health Sciences, Newark, NJ, United States

186 **Nuclear Import of APOBEC3F-Labeled HIV-1 Preintegration Complexes**

Ryan C. Burdick, Wei-Shau Hu, **Vinay K. Pathak**

HIV Drug Resistance Program, National Cancer Institute, Frederick, MD, United States

187 **Non-Integrating HIV-1 Is Sensitive To Inhibition by Target Cell Apobec3a**

Carsten Münk[1], Aikaterini Krikoni[1], Wolfgang Goering[2], Andre Franken[1], Daniela Marino[1], Gerald G. Schumann[3], Renate König[4], Wolfgang A. Schulz[2], Dieter Häussinger[1]

[1]Clinic for Gastroenterology, Hepatology and Infectiology, Heinrich-Heine University Düsseldorf, Düsseldorf, Germany, [2]Clinic for Urology, Heinrich-Heine University Düsseldorf, Düsseldorf, Germany, [3]Medical Biotechnology, Paul-Ehrlich-Institute, Langen, Germany, [4]Host-Pathogen-Interaction, Paul-Ehrlich-Institute, Langen, Germany

188 **Degradation of SAMHD1 Specifically Decreases the Efficacy of Thymidine HIV RT Analog Inhibitors**

Ester Ballana, Gerard Terradas, Eva Riveira-Muñoz, Bonaventura Clotet, Eduardo Pauls, José A. Esté

IrsiCaixa AIDS Research Institute, Badalona, Spain

188A **Natural Resistance To HIV-1 by Select APOBEC3H Haplotypes**

Eric W. Refsland[1], Judd F. Hultquist[1], Elizabeth M. Luengas[1], Rachel Prosser[2], Keith Henry[2], Michael Emerman[3], Reuben S. Harris[1]

[1]Biochemistry, Molecular Biology, and Biophysics, University of Minnesota, Minneapolis, MN, United States, [2]Hennepin County Medical Center, Minneapolis, MN, United States, [3]Fred Hutchinson Cancer Research Center, Seattle, WA, United States

Session P-A6 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

HIV Entry

189 **The Sphingosine-1-Phosphate Receptor 1 Dimerizes With CCR5 and Enhances HIV Infection**

Charline Duquenne[1], Sandrine Gimenez[1], Adeline Guigues[1], Laurent Prézeau[2], Noellie Campos[3], Jamal Tazi[3], Pierre Corbeau[1], **Vincent François**[1]

[1]Institute of Human Genetics, CNRS, Montpellier, France, [2]Institute of Functional Genomics, CNRS, Montpellier, France, [3]Institute of Molecular Genetics, CNRS, Montpellier, France

190 **Purinergic Receptor Antagonists as Potent Inhibitors of HIV-1 Infection by Blocking Early Entry**

Talia H. Swartz, Anthony M. Esposito, Natasha D. Durham, Benjamin K. Chen

Icahn School of Mount Sinai, New York, NY, United States

191 **Optical Sorting of HIV-1 Reveal the Minimum Number of Spikes Required for Optimal Viral Infectivity**

Wei Cheng

University of Michigan, Ann Arbor, MI, United States

192 **Application of an HIV Entry Assay To Identify HIV Target Cells in the Female Genital Tract**

Vineet R. Joag

University of Toronto, Toronto, ON, Canada

193 **Early Non-Mac-Tropic HIV-1 R5 Envs Efficiently Trans-Infect T Cells and Infect Ectocervices**

Paul J. Peters[1], Olivia O'Connell[1], Thomas Musich[2], Maria Paz Gonzalez-Perez[1], Tiffany Moore-Simas[3], Cynthia Derdeyn[4], Paul R. Clapham[1]

[1]Molecular Medicine, University of Massachusetts Medical School, Worcester, MA, United States, [2]National Cancer Institute, Bethesda, MD, United States, [3]Obstetrics & Gynecology, UMass Memorial Medical Center, Worcester, MA, United States, [4]Emory Vaccine Center, Atlanta, GA, United States

194 **Transmitter as Compared To Recipient Envelopes Confer Greater Replication and α4β7 Utilization**

Victor Pena-Cruz[1], *Behzad Etemad*[1], *Nikolaos Chatziandreou*[1], *Shannon Stock*[2], *Steven J. Reynolds*[3], *Oliver Layendecker*[3], *Ronald H. Gray*[3], *David Serwadda*[4], *Thomas C. Quinn*[3], **Manish Sagar**[1]

[1]Boston University, Boston, MA, United States, [2]College of the Holy Cross, Worcester, MA, United States, [3]The Johns Hopkins University, Baltimore, MD, United States, [4]Makerere University School of Public Health, Kampala, Uganda

195 **Differences in HIV Receptor Activity of CXCR4 Isoforms: Consequences for X4 Strains Emergence**

Charline Duquenne[1], Christina Psomas[2], Sandrine Gimenez[1], Marie-Josée Carles[3], Claudine Barbuat[4], Jean-Philippe Lavigne[3], Albert Sotto[4], Jacques Reynes[2], **Vincent François**[1], Pierre Corbeau[1]

[1]Institute of Human Genetics, CNRS, Montpellier, France, [2]Infectious Diseases, University Hospital, Montpellier, France, [3]Microbiology, University Hospital, Nîmes, France, [4]Infectious Diseases, University Hospital, Nîmes, France

196 **Defining Interactions of HIV With Rectal Epithelial Barriers and Rectal Mucus**

Luis M. Barcena[1], Minh Dinh[1], Peter A. Anton[2], Thomas J. Hope[1]

[1]Northwestern University Feinberg School of Medicine, Chicago, IL, United States, [2]UCLA, David Geffen School of Medicine, Los Angeles, CA, United States

Session P-A7 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Factor Potpourri

197LB **Platelet Factor 4 Oligomeric State Correlates With Antiviral Activity**

Zahra F. Parker[1], Ann Rux[2], Fang-Hua Lee[1], Amber Riblett[1], Mortimer Poncz[3], Bruce Sachais[4], Robert Doms[5]

[1]Microbiology, University of Pennsylvania, Philadelphia, PA, United States, [2]Pathology, University of Pennsylvania, Philadelphia, PA, United States, [3]Hematology, The Children's Hospital of Philadelphia, Philadelphia, PA, United States, [4]Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, United States, [5]Pathology and Laboratory Medicine, The Children's Hospital of Philadelphia, Philadelphia, PA, United States

198 **CRM-1: A Critical Regulator of HIV Replication in a Quest Towards a Small Animal Model for HIV**

Hila Elinav[1], Yuanfei Wu[2], Ayse Coskun[2], Katarzyna Hryckiewicz[2], Iris Kemler[3], Yani Hu[4], Bing Hao[5], Choukri Ben Mamoun[6], Eric Poeschla[3], Richard Sutton[2]

[1]Clinical Microbiology and Infectious Diseases, Hadassah Hebrew University Medical Center, Jerusalem, Israel, [2]Infectious diseases, Yale University, New Haven, CT, United States, [3]Department of Molecular Medicine, Mayo Clinic, Rochester, MN, United States, [4]Infectious Diseases, Yale University, New Haven, CT, United States, [5]Molecular, Microbial and Structural Biology, University of Connecticut Health Center, Farmington, CT, United States, [6]Infectious diseases, Yale University, Jerusalem, CT, United States

199 **Analyses of the Sequence-Function Relationships Among HIV-1 Vpr, SIVagmVpr, and SIVmacVpx**

Ana Beatriz DePaula-Silva, Patrick A. Cassiday, Vicente Planelles

Pathology, University of Utah, Salt Lake City, UT, United States

200 **Elevated Expression of Anti-HIV-1 Restriction Factors in Effector Memory CD4+ T Cells In Vivo**

Mohamed Abdel-Mohsen[1], Xutao Deng[2], Rui Andre Saraiva Raposo[1], Teri Liegler[1], Elizabeth Sinclair[1], Rebecca Hoh[1], Douglas F. Nixon[1], Joseph K. Wong[1], Steven G. Deeks[1], **Satish K. Pillai**[1]

[1]University of California, San Francisco, San Francisco, CA, United States, [2]Blood Systems Research Institute, San Francisco, CA, United States

201LB **TRIM5alpha Determinants for the Activation of Innate Immunity**

Marie-Édith Nepveu-Traversy, **Lionel Berthoux**

Medical Biology, UQTR, Trois-Rivières, QC, Canada

202 **HIV-1 Vpu Antagonizes Macaque and Chimpanzee BST-2 Through Cytoplasmic Domain Interactions**

Takeshi Yoshida[1,2], Yoshio Koyanagi[3], Hirofumi Akari[1], Klaus Strebel[2]

[1]Center for Human Evolution Modeling Research, Primate Research Institute, Kyoto University, Inuyama, Japan, [2]Laboratory of Molecular Microbiology, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD, United States, [3]Laboratory of Viral Pathogenesis, Institute for Virus Research, Kyoto University, Kyoto, Japan

203 **Investigating the Requirement of a NOD-Like Receptor for Early HIV Replication**

Manja Burggraf[1], Prashant Jain[2], Crystal Shih[2], Nicole Esly[1], John Marlett[3], John A. Young[3], Sumit K. Chanda[2], **Renate Koenig**[1]

[1]Host-Pathogen-Interactions, Paul-Ehrlich-Institute, Langen, Germany, [2]Sanford-Burnham Medical Research Institute, La Jolla, CA, United States, [3]The Salk Institute, La Jolla, CA, United States

204 **ITIH4: A Cellular Factor Targeted by HIV-1 Vpr**

Steven Santos[1], Yong-Hui Zheng[2], Michael Bukrinsky[1]

[1]The George Washington University, NW Washington, DC, United States, [2]Michigan State University, East Lansing, MI, United States

Session P-B1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Transmission Networks

205 **Ongoing HIV-1 Subtype B Transmission Networks in the Netherlands**

Daniela Bezemer[1], Oliver Ratmann[2], Ard van Sighem[1], Bas E. Dutilh[3], Nuno Faria[4], Rob van den Hengel[1], Luuk Gras[1], Peter Reiss[1], Frank de Wolf[2], Christophe Fraser[2], ATHENA observational cohort

[1]Research, HIV Monitoring Foundation, Amsterdam, Netherlands, [2]Imperial College, London, United Kingdom, [3]Centre for Molecular and Biomolecular Informatics, Nijmegen, Netherlands, [4]University of Oxford, Oxford, United Kingdom

206 **Using HIV Networks To Inform Real Time Prevention Interventions**

Susan J. Little[1], Sergei L. K. Pond[1], Christy M. Anderson[1], Jason A. Young[1], Joel O. Wertheim[1], Sanjay R. Mehta[1], Susanne May[2], Davey M. Smith[1]

[1]Medicine, University of California San Diego, San Diego, CA, United States, [2]Biostatistics, University of Washington School of Public Health, Seattle, WA, United States

207 **Transmission Networks of HIV-1 Subtype B, CRF01_AE and CRF51_01B Among MSM in Singapore**

Kim Tien Ng[1], Kah Ying Ng[2], Wei Xin Khong[2], Oliver Laeyendecker[3,4], Thomas C Quinn[3,4], Adeeba Kamarulzaman[1], Oon Tek Ng[2], Kok Keng Tee[1]

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208 **HIV-1 Phylodynamics and Phylogeography Among High-Risk and General Populations in Uganda**

Gonzalo Yebra[1], Manon Ragonnet-Cronin[1], Deogratius Ssemwanga[2], Chris M. Parry[2], Pontiano Kaleebu[2], Andrew J. Leigh Brown[1]

[1]Institute of Evolutionary Biology, University of Edinburgh, Edinburgh, United Kingdom, [2]Research Unit on AIDS, MRC/Uganda Virus Research Institute, Entebbe, Uganda

209 **Sustained Spread of HIV-1 Drug Resistance in Treatment-Naïve Patients in the United Kingdom**

Jean L. Mbisa[1], Esther Fearnhill[2], David T. Dunn[2], Deenan Pillay[3], David Asboe[4], Patricia Anne Cane[1], on behalf of the UK HIV Drug Resistance Database

[1]Virus Reference Department, Public Health England, London, United Kingdom, [2]Medical Research Council Clinical Trials Unit, University College London, London, United Kingdom, [3]Research Department of Infection, University College London, London, United Kingdom, [4]Directorate of HIV Medicine and Sexual Health, Chelsea and Westminster Hospital, London, United Kingdom

210 **Transmission Clustering Among Newly Diagnosed HIV+ Patients in Chicago, 2008 To 2011**

Sarah Hoehnen[1], Anna Hotton[2], **Audrey L. French**[1], Stacey Kincaid[3], David Barker[1], Ronald Lubelchek[1]

[1]Infectious Disease, Rush University Medical Center, Chicago, IL, United States, [2]Chicago Developmental Center for AIDS Research, Chicago, IL, United States, [3]Ruth M. Rothstein CORE Center, Chicago, IL, United States

211 **Can Molecular HIV Surveillance Identify Groups To Prioritize for Prevention?**

Alexandra M. Oster[1], Joel O. Wertheim[2], Angela L. Hernandez[1], Marie C. B. Ocfemia[1], Neeraja Saduvala[3], David Kim[1], H. I. Hall[1]

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212 **Investigation of HIV Transmission Dynamics Reveals "Active" Clusters of Men Who Have Sex With Men**

Philip A. Chan[1], Austin Huang[2], Allison DeLong[3], Joseph Hogan[3], Marissa Reitsma[1], Marco Salemi[4], Rami Kantor[1]

[1]Medicine, Brown University, Providence, RI, United States, [2]Computer Science, Brown University, Providence, RI, United States, [3]Center for Statistical Sciences, Brown University, Providence, RI, United States, [4]Pathology, University of Florida, Gainesville, FL, United States

213 **HIV Transmission in the United States: The Roles of Risk Group, Race/Ethnicity, and Geography**

Alexandra M. Oster[1], Joel O. Wertheim[2], Angela L. Hernandez[1], Marie C. B. Ocfemia[1], Neeraja Saduvala[3], David Kim[1], H. I. Hall[1]

[1]Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, Atlanta, GA, United States, [2]ICF International and University of California San Diego, San Diego, CA, United States, [3]ICF International, Atlanta, GA, United States

214 **Risk Factor Predicts Geographic Spread Within New York City HIV-1 Transmission Network and Beyond**

Joel O. Wertheim[1], Sanjay R. Mehta[1], Sergi L. Kosakovsky Pond[1], Davey M. Smith[1], Lisa A. Forgione[2], Lucia L. Torian[2]

[1]University of California, San Diego, San Diego, CA, United States, [2]New York City Department of Health and Mental Hygiene, New York, NY, United States

215 **Large MSM Group and Local Heterosexual Transmission Are Major Concerns in the HIV Epidemic in Japan**

Teiichiro Shiino[1], Kenji Sadamasu[2], Junko Hattori[3], Mami Nagashima[2], Yasumasa Iwatani[3], Yoshiyuki Yokomaku[3], Wataru Sugiura[3], The Japanese Drug Resistance HIV-1 Surveillance Network

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Session P-B2 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Application of NGS To Viral Profiling

216 **Full-Length HIV-1 Haplotype Reconstruction From Heterogeneous Virus Populations**

Armin Töpfer[1, 2], Francesca Di Giallonardo[3, 4], Melanie Rey[5], Sandhya Prabhakaran[5], Yannik Duport[3], Christine Leemann[3], Huldrych F. Günthard[3], Volker Roth[5], Niko Beerenwinkel[1, 2], Karin J. Metzner[3]

[1]D-BSSE, ETH Zurich, Basel, Switzerland, [2]SIB Swiss Institute of Bioinformatics, Basel, Switzerland, [3]University of Zurich, Zurich, Switzerland, [4]Life Science Zurich Graduate School, Zurich, Switzerland, [5]University of Basel, Basel, Switzerland

217 **Limited HIV-1 Superinfection in Seroconvertors From the CAPRISA 004 Microbicide Trial**

Andrew Redd[1], Caroline Mullis[2], Daniel Sheward[3], Carolyn Williamson[3], Lise Werner[4], Nigel Garrett[4], Stephen Porcella[5], Quarraisha Abdool Karim[4], Thomas Quinn[1], Salim Abdool Karim[4], TRAPS Study Team

[1]NIAID, Baltimore, MD, United States, [2]The Johns Hopkins, Baltimore, MD, United States, [3]University of Cape Town, Cape Town, South Africa, [4]CAPRISA, Durban, South Africa, [5]NIAID, Hamilton, MT, United States

218 **Analysis of PCR Bias Using Primer IDs and Illumina Sequencing of HIV RNA Populations**

Valerie F. Boltz[1], Wei Shao[2], Mary F. Kearney[1], John W. Mellors[3], Frank Maldarelli[1], John M. Coffin[4]

[1]Drug Resistance Program, National Cancer Institute, Frederick, MD, United States, [2]Advanced Biomedical Computing Center, Leidos Biomedical Research, Inc, Frederick, MD, United States, [3]Division of Infectious Disease, University of Pittsburgh, Pittsburgh, PA, United States, [4]Department of Molecular Biology and Microbiology, Tufts University, Boston, MA, United States

219 **HIV Surveillance and Parallel Virome Analysis Using Unbiased Next-Generation Sequencing**

Ka-Cheung Luk[1], **Michael Berg**[1], Samia Nacacche[2], Scot Federman[2], Charlotte Ngansop[3], Dora Mbanya[3], Lazare Kaptue[4], Charles Y. Chiu[2], John Hackett[1]

[1]Abbott Diagnostics, Abbott Park, IL, United States, [2]University of California, San Francisco, San Francisco, CA, United States, [3]Universite de Yaounde, Yaounde, Cameroon, [4]Universite des Montagnes, Bangangte, Cameroon

220 **Primer ID Deep Sequencing of HIV-1 env Region To Reveal Genetic Structure of Viral Population**

Shuntai Zhou[1], Maria Bednar[1], Christa Sturdevant[1, 2], Serena Spudich[3], Richard Price[4], Ronald Swanstrom[5, 6]

[1]Lineberger Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States, [2]Department of Microbiology and Immunology, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States, [3]Department of Neurology, Yale University, New Haven, CT, United States, [4]Department of Neurology, University of California at San Francisco, San Francisco, CA, United States, [5]UNC Center For AIDS Research, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States, [6]Department of Biochemistry and Biophysics, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States

221 **Using RNASeq To Characterize Viral Genetic Diversity in a Cohort of HIV-2 Monoinfected Individuals**

Katherine L. James[1], Louis-Marie Yindom[1], Thushan De Silva[2], Shokouh Makvandi-Nejad[1], Stephen Taylor[3], Hilton Whittle[4], Tim Vincent[5], Gilean McVean[6], Sarah Rowland-Jones[1]

[1]NDM, University of Oxford, Oxford, United Kingdom, [2]University of Sheffield, Sheffield, United Kingdom, [3]Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, United Kingdom, [4]London School of Hygiene and Tropical Medicine, London, United Kingdom, [5]Medical Council Research Unit, Fajara, Gambia, [6]Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, United Kingdom

222 **Next Generation Sequencing of Full-Length HIV-1 env During Primary Infection**

Melissa E. Laird[1], N. Lance Helpler[1], Colleen Ludka[2], Michael Brown[3], Stephen Espitia[4], Yan Guo[2], Douglas D. Richman[1, 4], Sergei Kosakovsky Pond[1], Ellen E. Paxinos[2], Davey M. Smith[1, 4]

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Session P-B3

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Viral Subtype: Expansion, Migration, and Recombination

223 **Spread of CRF33_01B and Emergence of Novel Recombinants Among People Who Inject Drugs in Malaysia**

Wei Zhen Chow[1], Lai Yee Ong[1], Hui Ting Cheong[1], Nur Ezreen Syafina[1], Maryam Nabiel Al-Khannaq[1], Yutaka Takebe[2], Clayton Koh[1], Haider Al-Darraji[1], Adeeba Kamarulzaman[1], Kok Keng Tee[1]

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224 **AHI Detection Among People Who Inject Drugs in Russia Reveals the HIV-1 Transmission Bottleneck**

Elena Dukhovlinova[1], Alexey Masharsky[2, 3], Sergei Verevochkin[3], Olga Toussova[3, 4], Andrey Shevchenko[3, 5], David Montefiori[6], Irving Hoffman[7], William Miller[7, 8], Andrei Kozlov[2, 3], Ronald Swanstrom[1, 9]

[1]CFAR and Lineberger CCC, University of North Carolina, Chapel Hill, NC, United States, [2]Saint Petersburg State University, Saint Petersburg, Russian Federation, [3]the Biomedical Center, Saint Petersburg, Russian Federation, [4]Pavlov State Medical University, Saint Petersburg, Russian Federation, [5]Theodosius Dobzhansky Center for Genome Bioinformatics, Saint Petersburg, Russian Federation, [6]Laboratory for AIDS Vaccine Research and Development, Duke University, Durham, NC, United States, [7]Center for Infectious Diseases, University of North Carolina, Chapel Hill, NC, United States, [8]Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC, United States, [9]Department of Biochemistry and Biophysics, University of North Carolina, Chapel Hill, NC, United States

225 **Migration of HIV-1 Subtypes in East Africa Is Associated With Proximity To Highway Corridor**

Nuno R. Faria[1], Kim C. E. Sigaloff[2], David A. M. C. van de Vijver[3], Andrew J. Tatem[4], Andrea C. Pineda[5], Carolle L. Wallis[6], Marc A. Suchard[7], Tobias F. Rinke de Wit[2], Raph L. Hamers[2], Philippe Lemey[5], Nicaise Ndembi[8]

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226 **Ongoing Cross-Species Transmission of Simian Retroviruses and High HIV Prevalence in Cameroon**

Julius Chia[1, 2], Avelin Aghokeng[1, 2], Emilande Guichet[2], Ahidjo Ayouba[2], Steve Ahuka-Mundeke[2], Nicole Vidal[2], William Switzer[3], **Eric Delaporte**[2], Eitel Mpoudi Ngole[1], Martine Peeters[2]

[1]Projet PRESICA and IMPM/CREMER, Yaoundé, Cameroon, [2]IRD, Montpellier, France, [3]Centers for Disease Control and Prevention, Atlanta, GA, United States

227 **An Emerging HIV-1 Recombinant (CRF58_01B) Disseminating Among People Who Inject Drugs in Malaysia**

Wei Zhen Chow[1], Yutaka Takebe[2], Nur Ezreen Syafina[1], Malarvelli Soorya Prakasa[1], Haider Al-Darraji[1], Clayton Koh[1], Adeeba Kamarulzaman[1], Kok Keng Tee[1]

[1]Centre of Excellence for Research in AIDS (CERiA), Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia, [2]National Institute of Infectious Diseases, AIDS Research Center, Toyama, Shinjuku-ku, Tokyo, Japan

228 **Exploring the Hidden Interrelationship of HIV-1 Epidemics in Asia and Beyond**

Yutaka Takebe[1], Makiko Kondo[2]

[1]AIDS Research Center, National Institute of Infectious Diseases, Tokyo, Japan, [2]Department of Microbiology, Kanagawa Prefectural Institute of Public Health, Chigasaki, Japan

229 **CRF01_AE and Subtype B Transmission Networks Cross Over; A New AE-B Recombinant Emerges in Japan**

Masumi Hosaka[1], Seiichiro Fujisaki[2], Junko Hattori[1], Teiichiro Shiino[2], Atsuko Hachiya[1], Masakazu Matsuda[1], Yasumasa Iwatani[1, 3], Yoshiyuki Yokomaku[1], Wataru Sugiura[1, 3]

[1]National Hospital Organization Nagoya Medical Center, Nagoya, Japan, [2]National Institute of Infectious Diseases, Tokyo, Japan, [3]Nagoya Graduate School of Medicine, Nagoya, Japan

230 **Phylodynamic Analysis of a Regional HIV Epidemic**

Jeffrey B. Joy, Richard Liang, Conan K. Woods, Susan Shurgold, Guillaume Colley, Chanson Brumme, Robert S. Hogg, Julio S. G. Montaner, P. Richard Harrigan, Art F. Y. Poon

Medicine, BC Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada

Session P-C1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

The Gut and Lymph Nodes in HIV Pathogenesis

231 **Damage of Gut Junctional Complexes Features HIV-Infected Immunological Non Responders**

Camilla Tincati[1], Giuseppe Ancona[1], Paola Braidotti[1], Delfina Tosi[1], Federica Savi[1], Elisa Borghi[1], Alessandra Barassi[1], Esther Merlini[1], Nicolas Chomont[2], Giulia Marchetti[1]

[1]Department of Health Sciences, University of Milan, Milan, Italy, [2]Vaccine and Gene Therapy Institute, Port St. Lucie, FL, United States

232 **Gut Homing and HIV-1 Permissiveness Are Specifically Regulated by Retinoic Acid in CCR6+ T-Cells**

Delphine Planas[1, 2], Sandrine Da Fonseca[1, 2], Jean-Philippe Goulet[3], Annie Gosselin[1], Aurélie Cléret-Buhot[1, 2], Mohammad-Ali Jenabian[4], Jean-Pierre Routy[5, 6], Petronela Ancuta[1, 2]

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233 **Dysregulated Gut Dendritic Cells Correlate With T-Cell Activation During Untreated HIV Infection**

Stephanie M. Dillon[1], Eric J. Lee[1], Gregory L. Austin[1], Sara Gianella[2], Davey M. Smith[2], Basile Siewe[3], Alan L. Landay[3], Cara C. Wilson[1]

[1]University of Colorado AMC, Aurora, CO, United States, [2]University of California San Diego, La Jolla, CA, United States, [3]Rush University Medical Center, Chicago, IL, United States

234 **HIV-1 RNA+ Cells Are Concentrated in the Germinal Centers of Activated Lymph Nodes In Vivo**

Tessa Arends[1], Joy Folkvord[1], Martin McCarter[1], Amie Meditz[2], Elizabeth Connick[1]

[1]University of Colorado Anschutz Medical Campus, Aurora, CO, United States, [2]Boulder Community Hospital, Boulder, CO, United States

235 **Duodenal and Rectal Mucosa Immune Reconstitution Differ After ART Initiation**

Talia Sainz[1], Sergio Serrano-Villar[2], Anthony Albanese[3], Tammy Yotter[4], Paolo Troia-Cancio[4], Darin Lartimore[4], Steve Deeks[5], Elizabeth Sinclair[5], Vera Go[4], David Asmuth[6]

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236 **Gut Microbiota of HIV Infected Subjects Induce Inflammatory Cytokines But Not T Regulatory Cells**

Charles P. T. Neff, Andrew Fontenot, Catherine Lozupone, Brent E. Palmer

Allergy and Clinical Immunology, University of Colorado, Aurora, CO, United States

Session P-C2 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Immune Activation and Pathogenesis

264LB **An SMS Intervention To Improve HIV Linkage To Care: A Randomized, Comparative Effectiveness Trial**

Mark J. Siedner[1], Data Santorino[2], Alexander J. Lankowski[3], Michael Kanyesigye[4], Bosco Mwebesa Bwana[4], Jessica E. Haberer[1], David R. Bangsberg[1]

[1]Medicine, Massachusetts General Hospital, Boston, MA, United States, [2]Mbarara Univeristy of Science and Technology, Mbarara, Uganda, [3]University of Philadelphia, Philadelphia, PA, United States, [4]Mbarara University of Science and Technology, Mbarara, Uganda

265 **CD4 T-Cell Responses in Relationship With Immune Activation and Viral Load in Primary HIV Infection**

Mathieu F. Chevalier[1], Céline Didier[1], Gaël Petitjean[1], Pierre-Marie Girard[2], Françoise Barré-Sinoussi[1], Daniel Scott-Algara[1], Laurence Weiss[3, 4]

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266 **Herpesvirus Infections in HIV+ Individuals On ART Are Not Associated With Immune Activation**

Bernard J. Macatangay[1], Yue Chen[2], Arlene Bullotta[2], Aarika Yates[2], Eric Fialkovich[2], Luann Borowski[2], William Buchanan[2], Phalguni Gupta[2], Charles Rinaldo[2]

[1]Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States, [2]Infectious Disease and Microbiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA, United States

267 **Chronic Inflammation in HIV-1 Infected Individuals Reduces T-Cell Responsiveness To Vaccines**

Jean Boyer[1], Lorenzo Ramirez[1], Ian Frank[2], Pablo Tebas[2]

[1]University of Pennsylvania, Philadelphia, PA, United States, [2]Hospital of the University of Pennsylvania, Philadelphia, PA, United States

268 **Persistently Activated CD27+CD80+ B Cells Following ART Correlate With Macrophage Activation**

Stephanie N. Hudey[1], Bret J. Rudy[2], Xinrui Zhang[3], Susan Lukas[4], Maureen Goodenow[3], John Sleasman[5]

[1]University of South Florida Morsani College of Medicine, Tampa, FL, United States, [2]New York University School of Medicine, New York City, NY, United States, [3]University of Florida, Gainesville, FL, United States, [4]University of South Florida Morsani College of Medicine, St. Petersburg, FL, United States, [5]Duke School of Medicine, Durham, NC, United States

269 **Novel Exosomal HIV miRNAs may Contribute To Chronic Immune Activation**

Mark A. Bernard, Simon C. Yue, Asha Anandaiah, Henry Koziel, Souvenir D. Tachado

Division of Pulmonary, Critical Care and Sleep Medicine, Beth Israel Deaconess Medical Center, Boston, MA, United States

270LB **Interleukin-21 Reduces Residual Immune Activation in ART-Treated SIV-Infected Rhesus Macaques**

Luca Micci[1], Emily Ryan[1], Colleen McGary[1], Sara Paganini[1], Guido Silvestri[1], Jason Brenchley[2], Francois Villinger[1], **Mirko Paiardini**[1]

[1]Department of Microbiology and Immunology, Emory University, Atlanta, GA, United States, [2]NIH/NIAID, Bethesda, MD, United States

271 **Immune Activation and Risk of HIV-1 Transmission Among HIV-1 Serodiscordant Couples**

Erin M. Kahle[1], Michael Bolton[2], James Hughes[1], Deborah Donnell[2], Connie Celum[1], Jairam Lingappa[1], Allan Ronald[3], Guy de Bruyn[4], Julie McElrath[2], Jared M. Baeten[1]

[1]University of Washington, Seattle, WA, United States, [2]Fred Hutchinson Cancer Research Center, Seattle, WA, United States, [3]University of Makerere, Kampala, Uganda, [4]University of Witwatersrand, Johannesburg, South Africa

272 **Inflammation in Acute HIV Infection Correlates With Blood and Gut CD4 T-Cell Loss and Viral Burden**

Netanya G. Sandler[1], Jintanat Ananworanich[2, 3], Suteeraporn Pinyakorn[2, 3], Adam Rupert[4], Alexandra Schuetz[5], James L. K. Fletcher[2], Daniel C. Douek[6], Nicholas Chomont[7], Jerome H. Kim[8], Irini Sereti[9]

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Session P-C3 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

NK Cells in HIV Pathogenesis

273 NK Cell Subsets Responding To HIV-Infected Autologous CD4 T Cell in Protective KIR/HLA Genotypes

Irene Lisovsky[1,2], Rujun Song[2,3], Bertrand Lebouché[4], Jean-Pierre Routy[1,5], Julie Bruneau[6], Nicole F. Bernard[2,7]

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274 Siglec-7 Binds HIV-1 GP120 and Facilitates Infection of CD4pos T Cells and Macrophages

Stefania Varchetta[1], Paolo Lusso[2], Dalila Mele[1], Stefania Paolucci[1], Raffaello Cimbro[2], Mauro Malnati[3], Agostino Riva[4], Renato Maserati[1], Mario U. Mondelli[1], **Domenico Mavilio[5]**

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275 Monocyte and NK Cell Dysfunctional Responses To Mycobacteria During Chronic HIV-1 Infection

Melanie A. Gasper[1,2], David R. Sherman[1], Donald L. Sodora[1]

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276 Identification of a New Isoform of MLL5: A Surrogate Marker of the CD4 Depletion in HIV-1

Vincent Vieillard[1], Florence Baychelier[1], Alexis Sennepin[1], Myriam Ermonval[2], Karim Dorgham[1], **Patrice Debre[1]**

[1]INSERM UMR-S 945, Paris, France, [2]Département de Virologie, Institut Pasteur, Paris, France

277 Do KIR3DL1/HLA-B Combinations Influence ADCC Responses of HIV-1 Infected Slow Progressors?

Gamze Isitman[1,2], Zoya Padamsi[1,2], Pilar Zanoni[1,2], Matthew Parsons[3], Marianne Harris[4], Jean-Pierre Routy[1,5], Cecile L. Tremblay[6], Nicole F. Bernard[1,2]

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278 CD8+ NK Cells in HIV-1 Infection Are Associated With Slower Disease Progression Towards AIDS

Fareed Ahmad[1], Henoch S. Hong[1,2], I-Na Lu[1], Marc Jäckel[3], Nupur Bhatnagar[1], Johanna M. Eberhardt[1], Benjamin A. Bollmann[1], Reinhold E. Schmidt[1], Dirk Meyer-Olson[3,4]

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Session P-C4 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

CD8 T-Cell Pathogenesis

279 HLA-B*35:05 Is a Protective Allele With a Unique Structure Amongst CRF01_AE-Infected Thais

Masahiko Mori[1,2], Nuanjun Wichukchinda[3], Reiko Miyahara[1], Archawin Rojanawiwat[3], Panita Pathipvanich[4], Tomoyuki Maekawa[1], Philip Goulder[2], Michio Yasunami[1], Koya Ariyoshi[1], Pathom Sawanpanyalert[3]

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280 Eomes and T-Bet Are Differentially Linked To CD8+ T-Cell Exhaustion in HIV Infection

Johanna Tauriainen[1], Marcus Buggert[1], Takuya Yamamoto[2], Bo Hejdeman[3], Richard A. Koup[2], Marianne Jansson[4], Anders Sonnerborg[1], Michael R. Betts[5], Annika C. Karlsson[1]

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281 Increased Frequencies of HLA-G+ HIV-1-Specific Regulatory CD8 T Cells in HIV-1 Controllers

Selena Vigano[1], Chun Li[1], Jordi Negron[1], Florencia Pereyra[1], Mathias Lichterfeld[2], Xu Yu[1]

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282 CD8+CD28-CD127^{lo}CD39+ Treg: A New Biomarker for HIV Infection

Chiara Dentone[1,2], Daniela Fenoglio[1,3], Alessia Parodi[1], Francesca Kalli[1], Antonio Di Biagio[4], Paolo Fraccaro[5], Giancarlo Orofino[6], Giovanni Cenderello[7], Mauro Giacomini[1,5], Gilberto Filaci[1,3]

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Session P-C5 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Exhaustion Markers

283 Determinants of PD-1 Expression On CD4+ and CD8+ T Cells in Treated and Untreated HIV Disease

Leslie R. Cockerham[1], Vivek Jain[1], Elizabeth Sinclair[2], David V. Glidden[3], Wendy Hartogenesis[1], Hiroyu Hatano[1], Peter W. Hunt[1], Jeffery N. Martin[3], Frederick M. Hecht[1], Steven G. Deeks[1]

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284 CD160 Is the Most Specific Co-Inhibitory Molecule Associated With CD8 T Cell Functional Impairment

Selena Vigano, Riddhima Banga, Florence Bellanger, Alex Farina, Denis Comte, Giuseppe Pantaleo, **Matthieu Perreau**

Division of Immunology and Allergy, Lausanne University Hospital, Lausanne, Switzerland

285 **Expansion of TIGIT-Expressing CD8+ T Cells Persists in Virally Suppressed HIV-1 Infection**

Glen M. Chew[1], Tsuyoshi Fujita[1], Ravi Tandon[1], Jeffrey N. Martin[2], Steven Deeks[2], Lishomwa C. Ndhlovu[1]

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286 **PD-1 Expression Is Associated With Preserved CD4+ T Cell Homeostasis in Viremic Non-Progressors**

Melicent C. Peck[1], Elizabeth Sinclair[1], Nichole R. Klatt[2], Lorrie Epling[1], Jeffrey N. Martin[3], Frederick M. Hecht[1], Steven G. Deeks[1], David Camerini[4], Peter W. Hunt[1]

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287 **PD-1 Homolog Expression Regulates Spontaneous Cytokine Production in HIV Infection**

Preeti Bharaj, Harendra S. Chahar, Lizette Rodarte, Ogechika Alozie, Manjunath Swamy, Premlata Shankar

COEID, Texas Tech University, El Paso, TX, United States

Session P-C6 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Clades and Pathogenesis

288 **HIV Virulence Has Not Increased in the UK Subtype B Epidemic**

Emma B. Hodcroft[1], Jarrod Hadfield[2], Esther Fearnhill[3], Andrew Phillips[4], David Dunn[3], Deenan Pillay[5], Andrew Leigh Brown[1], UK HIV Drug Resistance Database

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289 **Subjects Infected With Clade C-Containing HIV Exhibit Higher CD4+ T Cell Activation**

Priscilla R. Costa[1], Wendy Hartogensis[2], Ricardo S. Diaz[1], Peter Bacchetti[2], Rick Hecht[2], Breno R. Santos[3], AMPLIAR study team, Esper G. Kallas[1], **Chris Pilcher**[2]

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Session P-C7 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Correlative Marker Studies

290 **Telomere Length Predicts Immunological Recovery in Older HIV Patients Treated With cART**

Jose-Ramon Blanco[1], Inmaculada Jarrin[2], Alfredo Martinez[3], Eva Siles[4], Ana Cañuelo[4], Felix Gutierrez[5], Jorge del Romero[6], Jesus Santos[7], Santiago Moreno[8], CoRIS

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291 **The Clinical Impact of Viral Load Copy Years in Antiretroviral-Naïve HIV Seroconverters**

Matthias an der Heiden[1], Alexander Zoufaly[2], Caroline Sabin[3], Jan van Lunzen[4], Hans-Jürgen Stellbrink[5], Barbara Gunsenheimer-Bartmeyer[1], Philippe Vanhems[6], Santiago Perez-Hoyos[7], Geneviève Chêne[8], Osamah Hamouda[1], on behalf of CASCADE Collaboration in EuroCoord

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292 **Interleukin-32: Expression, Interaction With IFN, and Clinical Significance in HIV-1 Infection**

Carolina Scagnolari[1], Katia Montenleone[1], Carla Selvaggi[1], Francesca Falasca[1], Pierluigi Di Maio[1], Ivano Mezzaroma[2], Gabriella d'Ettorre[3], Ombretta Turriziani[1], Guido Antonelli[1]

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293 **TNFα in Viral Control and Early Disease Progression in Patients With HIV-1 Infection**

Sagar A. Vaidya[1, 2], Christian Korner[1], Michael Sirignano[1], Molly Amero[1], Sue Bazner[2], Jenna Rychert[2], Todd Allen[1], Eric S. Rosenberg[2], Ronald J. Bosch[3], Marcus Altfeld[1, 4]

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294 **Monocyte Activation Markers in HIV Infected Subjects: A Biomarker for HIV Immunotherapy**

Joumana Zeidan[1], Elizabeth Sinclair[2], Gary Lee[3], Shelley Wang[3], Martin Giedlin[3], Geoff Nichol[3], Winson Tang[3], Steven Deeks[2], Dale Ando[3], Rafick-Pierre Sekaly[1]

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295 **Down-Regulation of CD39/CD73 On B Cells of HIV Patients Coincides With a Disturbed Ig Class Switch**

Eun-Seong Kim[1], Ilona Tòth[1], Claudia Beisel[1], Johanna Eberhard[1], Silke Kummer[1], Ansgar W. Lohse[1], Friedrich Haag[2], Jan van Lunzen[1], Julian Schulze zur Wiesch[1]

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Session P-C8 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Elite Controllers

296 **Transcriptional Signatures of CD4 T Cell Subsets and Control of HIV Reservoirs in Elite Controllers**

Adele de Masson[1], Amos Kirilovsky[1], Rima Zoorob[1], Veronique Avettand-Fenoel[2], Veronique Morin[1], Anne Oudin[1], Benjamin Descours[1], Christine Rouzioux[2], Brigitte Autran[1], the ALT ANRS-Co15 Study Group

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298 **Elite Suppressor CD4+ and CD8+ T Cells Suppress Viral Replication in Monocyte-Derived Macrophages**

Victoria E. K. Walker-Sperling[1], Robert W. Buckheit[2], Robert F. Siliciano[3, 4], Joel N. Blankson[3]

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299 **Effective Control of Virus Replication in HIV-1 Elite Controllers by Active SAMHD1**

Eduardo Pauls[1], Alba Ruiz[1], Beatriz Mothe[1], Manel Crespo[2], Menéndez-Arias Luis[3], Bonaventura Clotet[1], Oliver T. Keppler[4], Francesc Posas[5], Christian Brander[1, 6], José A. Esté[1]

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Session P-C9 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Pathogenesis: Insights From Clinical Trials

300 Effect of Raltegravir Intensification in the Cytokine Profile of Treated HIV+ Individuals

Marta Massanella[1], Josep M. Llibre[2], Silvia Marfil[3], Maria C. Puertas[3], Jordi Puig[2], Eugènia Negredo[2], Douglas D. Richman[4, 5], Javier Martinez-Picado[3], Bonaventura Clotet[2, 3], Julià Blanco[3]

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301 Analyses of HIV-1 Viral Dynamics During Treatment With a Regimen Including an Integrase Inhibitor

Jeremie Guedj[1], Ruy Ribeiro[2], Adriana Andrade[3], Susan L. Rosenkranz[4], Darlene Lu[5], Douglas Richman[6], Mathew Strain[6], John Mellors[7], Daniel R. Kuritzkes[8], **Alan S. Perelson[2]**

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302 Characterization of Functional Profile of HIV-Specific CD4+ T Cells in VISCONTI Group of Patients

Assia Samri[1], Charline Bacchus[1], Laurent Hocqueloux[2], Asier Saez-Cirion[3], Amandine Emarre[1], Christine Rouzioux[4], Brigitte Autran[1], and VISCONTI ANRS Study

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303 Immune Activation and Defective pTFHs Are Associated With Impaired Immunity in Aging HIV+ Persons

Varghese K. George[1], Suresh Pallikkuth[1], Anita Parmigiani[2], Maria L. Alcaide[1], Margaret Fischl[1], Savita Pahwa[1]

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304 Fresh Cohort: Acute HIV-1 Infection in Cohort of High Risk HIV Negative Women in KZN, South Africa

Krista Dong[1, 2], Amber Moodley[1], Thumbi Ndungu[1, 3], Bruce Walker[1, 4]

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305 Vitamin D Significantly Changes the Immune Transcriptome and Augments CD4 Recall Responses in HIV

Raskit Lachmann[1], Margaret-Anne Bevan[2], Sangmi Kim[1], Nishma Patel[1], Riddhima Banga[1], Nagasuma Chandra[3], Sudha Rao[4], Catherine Hawrylowicz[5], Annapurna Vyakarnam[1], **Barry Peters[1]**

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306 Impact of Methamphetamine Use On Immunologic and Virologic Markers During Suppressive ART

Marta Massanella[1], Sara Gianella[1], Douglas D. Richman[1, 2], Susan J. Little[1], Constance B. Benson[1], Eric S. Daar[3], Michael D. Dube[4], Richard H. Haubrich[1], Davey M. Smith[1, 5], Sheldon R. Morris[1], the CCTG 592 Team

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307 Vitamin D-Receptor Gene Polymorphisms: Association With Virologic Failure and Mortality

Simbarashe Takuva[1, 2], Lynne McNamara[3], Tobias Chirwa[4], Ian Sanne[3], Adrian R. Martineau[5], Patrick A. MacPhail[3]

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308 Statins Use Is Associated With Greater CD4 Gains in HIV-Infected US Veterans

Henning J. Drechsler[1, 2], James Cutrell[1, 2], Pablo Tebas[3], Roger Bedimo[1, 2]

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309 Maraviroc Intensification in HIV-Infected Patients Induces Increased CCR5 Expression On T Cells

Assia Samri[1], Gael Mouillot[1], Christina Psomas[2], Melanie Lavenu[1], Selma Trabelsi[3], Lise Cuzin[4], Pierre Corbeau[5], Brigitte Autran[1], Philippe Flandre[3]

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Session P-C10 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Innate Immunity and Pathogenesis

237 CD161+Vα7.2+IL18R+ MAIT Cells Are Reduced in HIV Infection Regardless of the Disease Status

Johanna M. Eberhard[1], Philip Hartjen[1, 2], Ashwin Balagopal[3], Clara Lehmann[4], Dominik Ebert[1], Ilona Tóth[1], Silke Kummer[1], Reinhold E. Schmidt[5], Jan van Lunzen[1], Julian Schulze zur Wiesch[1]

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238 HIV-1 Alters Plasmacytoid Dendritic Cell Phenotype and Function by Modulating ILT Receptors

Adel Benlahrech, Amina Yasmin, Peter Kelleher, Nesrina Imami, Steven Patterson

Immunology, Imperial College London, London, United Kingdom

239 Innate Immune Reconstitution With Viral Suppression in HIV-1 Infection

Eileen Scully[1, 2], Ainsley Lockhart[1], Chelsey Musante[1], JJ Chang[1], Molly Amero[1], Eric Rosenberg[3], Ronald J. Bosch[4], Marcus Altfeld[1, 5]

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Session P-C11 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

CD4/CD8, Aging, and Immune Senescence

240 **CD4:CD8 Ratio Remains Significantly Depressed Despite Viral Suppression With Effective ART**

Brinda Emu[1], Jeffrey Martin[2], Douglas Nixon[2], Steven G. Deeks[2], Joseph M. McCune[2]

[1]Yale University, New Haven, CT, United States, [2]University of California, San Francisco, San Francisco, CA, United States

241 **CMV Reactivation and Immune Aging in HIV-Infected Individuals Virologically Suppressed On ART**

Helen M. McGuire[1], Philip M. Grant[2], Holden Maecker[3], Jorg J. Goronzy[4], Mark M. Davis[3, 5], Andrew R. Zolopa[2]

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242 **A Low CD4/CD8 Ratio During Effective ART Predicts Immunosenescence and Morbidity/Mortality**

Sergio Serrano-Villar[1], Talía Sainz[2], Sulggi A. Lee[3], Peter W. Hunt[3], Elizabeth Sinclair[3], April L. Ferre[4], Vivek Jain[3], Frederick M. Hetch[3], Santiago Moreno[1], Steve G. Deeks[3]

[1]Infectious Diseases, University Hospital Ramón y Cajal, Madrid, Spain, [2]Infectious Diseases, University Hospital Gregorio Marañón, Madrid, Spain, [3]University of California San Francisco, San Francisco, CA, United States, [4]University of California Davis, Davis, CA, United States

243 **CMV and HIV: A Double Hit On the CD4/CD8 Ratio**

Talia Sainz[1], Sergio Serrano-Villar[2], Sulggi A. Lee[3], Peter W. Hunt[3], Elizabeth Sinclair[3], Jeffrey N. Martin[3], Joseph M. McCune[3], Steven G. Deeks[3]

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Session P-C12 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Mucosal CD4 and TH17 Cells

244 **Severe Depletion of Lung CD4 T Cells During HIV Infection Impairs Alveolar Macrophage Function**

Bjorn Corleis[1], Maud Deruaz[2], Melis N. Anahtar[1], Gregory Olson[1], Brittany Bowman[1], Vladimir Vrbanac[2], Andrew M. Tager[2], Douglas S. Kwon[1]

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

245 **Impaired IL-23 Signalling and Th17 Dysfunction in HIV Infection**

Jason R. Fernandes[1], Ashok Kumar[2, 3], Jonathan B. Angel[1, 3]

[1]Chronic Diseases, The Ottawa Hospital Research Institute, Ottawa, ON, Canada, [2]Pathology, Children's Hospital of Eastern Ontario Research Institute, Ottawa, ON, Canada, [3]Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada

246 **Th17 and Tregs at Early HIV Infection Influence Disease Progression and HIV Specific CD8+ Responses**

Juliana Falivene[1], Yanina A. Ghiglione[1], Natalia L. Laufer[1, 2], María E. Socías[3], María J. Ruiz[1], Pedro Cahn[2, 3], Omar Sued[2, 3], Horacio Salomón[1], Gabriela Turk[1], María M. Gherardi[1]

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247 **Profound Lung CD4+ T-Cell Depletion in HIV-Associated Chronic Obstructive Pulmonary Disease**

Iulia Popescu[1], M. Bradley Drummond[2], Lucio Gama[2], Christian Merlo[2], Robert Wise[2], Janice Clements[2], Gregory D. Kirk[3], **John F. McDyer**[1]

[1]Medicine, University of Pittsburgh, Pittsburgh, PA, United States, [2]Medicine, The Johns Hopkins University, Baltimore, MD, United States, [3]School of Public Health, The Johns Hopkins University, Baltimore, MD, United States

248 **Site Specific HIV-Infection of Th17 Cells in the Human Female Reproductive Tract**

Marta Rodriguez-Garcia, Fiona D. Barr, John V. Fahey, Charles R. Wira

Physiology and Neurobiology, Geisel School of Medicine at Dartmouth, Lebanon, NH, United States

249 **Transcriptional Profiling Identifies New Mechanisms of HIV Permissiveness in Primary Th17 Cells**

Aurélie Cleret-Buhot[1, 2], Jean-Philippe Goulet[3, 4], Patricia Monteiro[1, 2], Annie Bernier[1, 2], Annie Gosselin[1, 2], Mohammad-Ali Jenabian[5], Jean-Pierre Routy[5], Elias Haddad[6], Rafick Pierre Sekaly[6], Cécile Tremblay[1, 2], **Petronela Ancuta**[1, 2]

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Session P-C13 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

In Vitro Studies

250 **Elevated Soluble CD40 Ligand During HIV Infection Suppresses Dendritic Cell Function**

Meagan O'Brien, Elizabeth Miller, Nina Bhardwaj

Mount Sinai School of Medicine, New York, NY, United States

251 **Chronic Exposure To Type-I IFN Under Lymphopenic Conditions Alters CD4 T Cell Homeostasis**

Cecile Le Saout[1], Rebecca B. Hasley[1], Hiromi Imamichi[1], Zonghui Hu[2], Megan A. Luckey[3], Jung-Huyn Park[3], Adam Rupert[4], Michael Sneller[1], H. Clifford Lane[1], **Marta Catalfamo**[1]

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252 **IL-15 Induces Id2 To Drive Effector Differentiation of CD8 TM and EM Cells While Maintaining CM Pools**

Alessandra Noto[1], Francesco A. Procopio[1], Julien van Grevenynghe[2], Cheryl Cameron[1], Courtney Steel[1], Amit Sabnis[1], Hiroshi Takata[1], Franck Dupuy[1], Jeff Ahlers[1], Rafick-Pierre Sekaly[1]

[1]Vaccine and Gene Therapy Institute, PORT SAINT LUCIE, FL, United States, [2]Lady Davis Institute, McGill University, Montreal, QC, Canada

253 **Double Stranded RNA Stimulates IL-1β Secretion in Cervical Epithelial Cells via the Inflammasome**

Melis N. Anahtar, Maud Deruaz, Andrew M. Tager, Douglas S. Kwon

Ragon Institute, Massachusetts General Hospital, Cambridge, MA, United States

254 **Alpha-Defensins Modulate HIV Transcytosis: Role of STI-Mediated Enhancement of HIV Transmission**

Kimyata Valere[1], Aprille Rapista[2], Alison J. Quayle[3], Wuyan Lu[4], Eliseo Eugenin[1], Theresa Chang[1]

[1]Public Health Research Institute, Department of Microbiology and Molecular Genetics, Rutgers University-New Jersey Medical School, Newark, NJ, United States, [2]Public Health Research Institute, Newark, NJ, United States, [3]Louisiana State University Health Sciences Center, New Orleans, LA, United States, [4]Institute of Human Virology, University of Maryland School of Medicine, Baltimore, MD, United States

255 **Exposure To IFNα Leads To Generation of IL-10-Producing Tr1 Cells**

Clara Lehmann[1], Kristina Koch[1], Nora Koch[1], Pia Hartmann[1, 2], Gerd Fätkenheuer[1], Fabio Romerio[3]

[1]First Department of Internal Medicine, University of Cologne, Cologne, Germany, [2]Institute for Medical Microbiology, Immunology and Hygiene, University of Cologne, Cologne, Germany, [3]Institute of Human Virology, University of Maryland School of Medicine, Baltimore, MD, United States

256 **TNF Drives Foam Cell Formation by Monocytes From HIV+ Donors in an In Vitro Atherosclerosis Model**

Anna Maisa[1], Candida F. Pereira[2,3], Thomas A. Angelovich[1,4], Jing-Ling Zhou[1], William A. Muller[5], **Anna C. Hearps[1,6]**, Suzanne M. Crowe[1,3], Anthony Jaworowski[1,3]

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257 **HIV-Altered mRNA Expressions of Type 1 IFN Pathway Related To Activation/Exhaustion in CD4+ T Cells**

Chi-Lin Lee[1], Erik Serrao[2,3], Toni Frederick[1], Chia-Hao Wang[1], **Andrea Kovacs[1]**

[1]Department of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles, CA, United States, [2]Medicine, Harvard University, Boston, MA, United States, [3]Pharmacology and Pharmaceutical Sciences, University of Southern California, Los Angeles, CA, United States

258 **Dysfunctional High Density Lipoprotein Directly Upregulates T Cell Activation in HIV-1 Infection**

Theodoros Kelesidis, Judith Currier, Diana Huynh, Sangeun Park, Hwee Ng, Otto O. Yang

Medicine, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, United States

259 **Dysfunctional High Density Lipoprotein Directly Reduces HIV-1-Specific Antiviral Responses**

Theodoros Kelesidis, Judith Currier, Diana Huynh, Sangeun Park, Hwee Ng, Otto Yang

Medicine, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, United States

Session P-C14 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Genomics and Endogenous Retroviruses

260 **HLA Gene Loci Associated With HIV Load in CSF and Blood Plasma in the CHARTER Cohort**

Benjamin B. Gelman[1], Sunil K. Ahuja[2], Ronald J. Ellis[3], Scott Letendre[4], Christina M. Marra[5], Justin McArthur[6], Susan Morgello[7], David B. Clifford[8], Igor Grant[9], Florin Vaida[10], The CHARTER Group

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261 **GUAVAh: A Compendium of Host Genetic Data in HIV Biology and Disease**

Istvan Bartha[1,2], Paul J. McLaren[1,2], Angela Ciuffi[2], Jacques Fellay[1,2], Amalio Telenti[2]

[1]École Polytechnique Fédérale De Lausanne, Lausanne, Switzerland, [2]Institute of Microbiology, University Hospital Lausanne, Lausanne, Switzerland

262 **HIV-1 Infection Leads To Increased Expression of HML-2 Proviruses In Vivo But Not Virion Production**

Neeru Bhardwaj[1], Frank Maldarelli[2], John Mellors[3], John M. Coffin[1]

[1]Tufts University, Boston, MA, United States, [2]National Cancer Institute, Frederick, MD, United States, [3]University of Pittsburgh, Pittsburgh, PA, United States

263 **Exome Sequencing To Evaluate the Impact of Rare Coding Variation On HIV-1 Control**

Paul J. McLaren[1], Patrick R. Shea[2], David B. Goldstein[2], Jacques Fellay[1]

[1]Life Sciences, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland, [2]Center for Human Genome Variation, Duke University School of Medicine, Durham, NC, United States

Session P-D1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

It's All About the Gut

310 **Increased Immune Activation After Gut Permeabilization in SIV-Infected African Green Monkeys**

Jan Kristoff[1], Thaidra Gaufin[2], Rajeev Gautam[3], Dongzhu Ma[1], Jacob Estes[4], Russell Tracy[5], Cristian Apetrei[1], Steve Nelson[6], Gregory Bagby[6], Ivona Pandrea[1]

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311 **Breaches in Colonic Claudin-4 Expression Correlate With T-Cell Activation in HIV-1 Infection**

Louise Greathead[1], Anna Mroz[1], Hiromi Kudo[1], Brian Gazzard[2], Mark Nelson[2], Robert D. Goldin[1], Alan Steel[2], Peter Kelleher[1]

[1]Imperial College, London, United Kingdom, [2]Chelsea and Westminster Hospital NHS Trust, London, United Kingdom

312 **Rapid Gut-Homing of Plasmacytoid Dendritic Cells During Acute SIV Infection**

Haiying Li, Jacqueline Gillis, **R. Keith Reeves**

NEPRC, Harvard Medical School, Southborough, MA, United States

313 **CCR6+ and CD161+ CD4 T Cell Loss Contributes To the Pathogenesis of SIV Infection in Rhesus Macaques**

Colleen S. McGary[1], Luca Micci[1], Emily S. Ryan[1], Maria J. Buzon[2], Amy Shaw[2], Mathias Lichterfeld[2], Guido Silvestri[1,3], Aftab A. Ansari[3], Mirko Paiardini[1,3]

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314 **SIV Vaccine Controllers Prevent Aberrant Accumulation of Follicular CD4 T Cells in Rectal Mucosa**

Geetha H. Mylvaganam[1,2], Vijayakumar Velu[1,2], Jung-Joo Hong[2,3], Shanmugalakshmi Sadagopal[1,2], Suefen Kwa[1,2], Rahul Basu[1,2], Benton Lawson[2], Francois Villinger[2,3], Rama R. Amara[1,2]

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315 **Decreased Diversity of Gut Microbiota Is Associated With Immune Status During HIV-1 Infection**

Piotr Nowak[1], **Babilonia Barqasho[2]**, Ekatarina Avershina[3], Kajsa Noyan[2], Jan Vesterbacka[1], Marius Trosseid[4], Knut Rudi[3], Anders Sönnerborg[1]

[1]Department of Infectious Diseases, Karolinska Institute, Huddinge, Sweden, [2]Department of Laboratory Medicine, Karolinska Institute, Huddinge, Sweden, [3]Department of Chemistry, Biotechnology and Food Science, Norwegian University of Life Sciences, Aas, Norway, [4]Infectious Diseases, Oslo University Hospital, Oslo, Norway

316 **Dysregulated miR-34a-SIRT1-Acetyl-p65 Axis Induces Immune Activation in Chronic SIV-Infection**

Mahesh Mohan, Andrew Alan Lackner, Xavier Alvarez

Comparative Pathology, Tulane National Primate Research Center, Covington, LA, United States

317 **Dysbiotic Bacteria Translocate in Progressive SIV Infection**

Zachary Klase[1], Elias Schwartzman[1], Alexandra Ortiz[1], Lauren Canary[1], Mariam Quinones[2], Jason Brenchley[1]

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Session P-D2 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

New SIV Models

318LB **Viral Suppression Was Induced by Anti-PD-L1 Following ARV-Interruption in SIV-Infected Monkeys**

Stephen W. Mason[1], Srisowmya Sanisetty[2], Christa Osuna-Gutierrez[3], So-Yon Lim[3], Susan Chaniewski[1], Shalyn Campellone[1], Daniel Tenney[1], Scott Balsitis[1], James B. Whitney[3]

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319 **A Novel HIV-1mt Encoding CCR5-Tropic Env Established Persistent Infection in Cynomolgus Macaques**

Akatsuki Saito[1,2], Kazuhiro Matsuoka[2,3], Hirotaka Ode[2,3], Hiroyuki Otsuki[4], Takeshi Yoshida[1], Yasumasa Iwatani[3], Wataru Sugiura[3], Tetsuro Matano[5], Tomoyuki Miura[4], **Hirofumi Akari**[1]

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320 **New SIVsmm Strains To Achieve Control of Virus Replication With Conventional ART in Rhesus Macaques**

George Haret-Richter[1], Dongzhu Ma[1], Hui Li[2], Samantha Ross[1], Rachit Anand[1], Cuiling Xu[1], George M. Shaw[2], Beatrice H. Hahn[2], John W. Mellors[3], Ivona Pandrea[1], **Cristian Apetrei**[1]

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Session P-D3 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

SCID Mice

321 **Immune-Pathogenesis/-Therapy of Persistent HIV-1 Infection in Humanized Mice**

Lishan Su

Microbiology and Immnuology, UNC-Chapel Hill, Chapel Hill, NC, United States

322 **Dual Roles of Plasmacytoid Dendritic Cells in HIV-1 Infection and Pathogenesis**

Guangming Li[1], Menglan Cheng[2], Jun-ichi Nunoya[1], Liang Cheng[1], Haitao Guo[1], Haisheng Yu[2], Yong-jun Liu[3], Liguo Zhang[2], Lishan Su[1]

[1]University of North Carolina at Chapel Hill, Chapel Hill, NC, United States, [2]Institute of Biophysics, Chinese Academy of Sciences, Beijing, China, [3]Baylor Research Institute, Dallas, TX, United States

323 **Characterizing the Acute Spread of Cell-Associated HIV in Humanized Mice**

Kenneth M. Law, Alice W. Yewdall, Benjamin K. Chen

Infectious Disease, Icahn School of Medicine at Mount Sinai, New York, NY, United States

Session P-D4 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Non-Pathogenic vs Pathogenic Hosts

324 **Differential TCR Activation and TRAIL Regulation in Sooty Mangabeys and Rhesus Macaques**

Shan Yu[1], Kenneth Rogers[2], Francois Villinger[2], Amitinder Kaur[3]

[1]Division of Immunology, Harvard Medical School, Southborough, MA, United States, [2]Division of Pathology, Emory University, Atlanta, GA, United States, [3]Harvard Medical School, Southborough, MA, United States

325 **Divergent CD4+ T Memory Stem Cell Dynamics in Pathogenic and Nonpathogenic SIV Infections**

Emily K. Cartwright[1], Colleen McGary[1], Barbara Cervasi[1], Benton Lawson[1], Steven E. Bosinger[1], Thomas H. Vanderford[1], Mirko Paiardini[1], Ann M. Chahroudi[2], Guido Silvestri[1]

[1]Yerkes National Primate Research Center, Emory Vaccine Center, Atlanta, GA, United States, [2]Department of Pediatrics, Emory University, Atlanta, GA, United States

326 **Double-Negative T Cells Are Functionally Distinct and Maintained in SIV-Infected Sooty Mangabeys**

Namita Rout[1], James M. Billingsly[1], Shan Yu[1], Alexandra Grzywna[2], Premeela A. Rajakumar[1], Arnaud Colantonio[1], Robert P. Johnson[1], Jim Else[3], Amitinder Kaur[1]

[1]Immunology, NEPRC-HMS, Southborough, MA, United States, [2]Wellesley College, Wellesley, MA, United States, [3]Animal Resources, Yerkes National Primate Research Center, Atlanta, GA, United States

327 **CD39/CD73/Adenosine Pathway in Progressive vs Non-Progressive Infections**

Tianyu He[1], Egidio Brocca-Cofano[1], Cuiling Xu[2], Jan Kristoff[2], Samantha Ross[2], Dongzhu Ma[3], Charles R. Rinaldo[4], Bernard J. C. Macatangay[4], Cristian Apetrei[3], Ivona Pandrea[1]

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328 **Dynamics of B Cell Subpopulations in Pathogenic and Nonpathogenic SIV Infections**

Egidio Brocca-Cofano[1], Basile Siewe[2], Dave Kurt[3], Xu Cuiling[1], Jan Kristoff[3], Dongzhu Ma[4], George S. Haret-Richter[1], David C. Montefiori[5], Alan Landy[2], Ivona Pandrea[1], Cristian Apetrei[4]

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Session P-D5 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Compartmentalization

329 **Transient Compartmentalization of SIV Variants in the Breast Milk of African Green Monkeys**

Carrie Ho

Human Vaccine Institute, Duke University Medical Center, Durham, NC, United States

330 **HIV Migrates Bi-Directionally Between Blood and Cerebrospinal Fluid and Between Blood and Semen**

Antoine Chaillon[1,2], Sara Gianella[1], Joel O. Wertheim[1], Sergei L. K. Pond[1], Douglas D. Richman[1,3], Sanjay R. Mehta[1,3], David M. Smith[1,3]

[1]Pathology, University of California San Diego, La Jolla, CA, United States, [2]INSERM UMR U966, Tours, France, [3]Veterans Affairs San Diego Healthcare System, San Diego, CA, United States

331 **Pol Versus Env Genetics in SHIV-Infected Macaques Highlights Importance of Phylogenetic Signal**

Chad Coomer[1], Elizabeth M. Anderson[1], Luke Smith[1], Wei Shao[1], Jonathan Spindler[1], John W. Mellors[2], John M. Coffin[3], Zandrea Ambrose[4], Mary F. Kearney[1]

[1]National Cancer Institute, NIH, Frederick, MD, United States, [2]Division of Infectious Disease, Department of Medicine, University of Pittsburgh, Pittsburgh, PA, United States, [3]Department of Molecular Biology and Microbiology, Tuffs University, Boston, MA, United States, [4]Division of Infectious Diseases, Department of Medicine, University of Pittsburgh, Pittsburgh, PA, United States

Session P-D6 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

New Themes in Host Control

332 **Effect of CD8 Depletion On CD4+ T-Cell Subsets in SIV Infection**

Timothy Hayes[1], Steven E. Bosinger[1], Ankita Chowdhury[1], Benton O. Lawson[1], Barbara Cervasi[2], Kiran Gill[2], Mirko Paiardini[1], Miles P. Davenport[3], Jacob D. Estes[4], Guido Silvestri[1]

[1]Yerkes, Microbiology and Immunology, Emory University, Atlanta, GA, United States, [2]Emory Vaccine Center, Emory University, Atlanta, GA, United States, [3]Centre for Vascular Research, University of New South Wales, Sydney, Australia, [4]Retroviral Immunopathology Section, Frederick National Laboratory for Cancer Research, Frederick, MD, United States

333 **Low Social Rank Prior To SIV or SHIV Infection Associates With Higher Viral Load in Chronic Infection**

Gretchen N. Neigh[1, 2], Timothy Hayes[2, 3], Ronald Trible[2, 3], Thomas H. Vanderford[2, 3], Diane G. Carnathan[2, 3], Constance S. Harrell[1], Kirk Easley[4], Mirko Paiardini[2, 3], Guido Silvestri[2, 3]

[1]Physiology, Emory University, Atlanta, GA, United States, [2]Yerkes National Primate Research Center, Atlanta, GA, United States, [3]Emory University, Atlanta, GA, United States, [4]Biostatistics, Emory University, Atlanta, GA, United States

334 **Modulation of Natural Killer Cell Activity by Simian Immunodeficiency Virus Peptides**

Jamie L. Schafer[1], Natasha Guha[1], Nancy A. Wilson[2], David T. Evans[2]

[1]Harvard University, Southborough, MA, United States, [2]University of Wisconsin, Madison, WI, United States

Session P-E1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Modulating Immune Activation

335 **Rosuvastatin Reduces Immune Activation and Inflammation in Treated HIV Infection**

Nicholas Funderburg[1], Brian Clagett[2], Ying Jiang[3], Sara M. Debanne[3], Norma Storer[4], Danielle Labbato[4], Steven Juchnowski[2], Brian Ferrari[2], Michael Lederman[2], Grace A. McComsey[4]

[1]Health and Rehabilitation Sciences, The Ohio State University, Columbus, OH, United States, [2]Case Western Reserve University/ Case Medical Center, Cleveland, OH, United States, [3]Epidemiology and Biostatistics, Case Western Reserve University, Cleveland, OH, United States, [4]University Hospitals Case Medical Center, Cleveland, OH, United States

336 **Effects of Prednisolone On CD4 Counts and HIV Disease Progression: A Two-Year Clinical Trial**

Christa Kasang[1], Samuel Kalluvya[2], Charles Majinge[3], Gilbert Kongola[1], Mathias Mlewa[3], Irene Massawe[3], R Kabyemera, K Magambo, H Klinker, E Koutsilieri, W Preiser, D Hofmann, J Hain, A Müller, Weissbrich, Albrecht Ulmer[1], Axel Rethwilm[1], August Stich[1], **Carsten Scheller**[1]

[1]Institute of Virology and Immunobiology, University of Wuerzburg, Wuerzburg, Germany, [2]Institute of Virology and Immunobiology, Bugando Medical Centre, Mwanza, United Republic of Tanzania, [3]Bugando Medical Centre, Mwanza, United Republic of Tanzania

337 **Sevelamer Does Not Decrease Plasma LPS or sCD14 But Does Decrease Soluble Tissue Factor and LDL**

Netanya G. Sandler[1], Xinyan Zhang[2], Ronald J. Bosch[2], Nicholas T. Funderburg[3], Janet K. Robinson[3], Daniel C. Douek[4], Cara C. Wilson[5], Steven G. Deeks[6], Michael M. Lederman[3], Rajesh T. Gandhi[7], for the A5296 Study Team

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338 **Reduction of sCD163, SP and PD1+ Th Cell Levels in a Phase 1B Trial of the NK1R Antagonist Aprepitant**

Pablo Tebas[1], Serguei Spitsin[2], Jeffrey Barrett[2], Florin Tuluc[2], Okan Elci[3], James Korelitz[3], Wayne Wagner[1], Deborah Kim[1], Renae Catalano[3], Steven D. Douglas[2]

[1]University of Pennsylvania, Philadelphia, PA, United States, [2]Children's Hospital of Philadelphia Research Institute, Philadelphia, PA, United States, [3]Westat, Rockville, MD, United States

339 **Rifaximin Has Marginal Impact On Immune Activation in Immune Non-Responders To ART - ACTG 5286**

Allan R. Tenorio[1], Cara C. Wilson[2], Ellen S. Chan[3], Ronald J. Bosch[4], Bernard J. Macatangay[5], Suria Yesmin[6], Sarah W. Read[7], David M. Margolis[8], Jeffrey M. Jacobson[9], Alan L. Landay[10]

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340 **Reduced Immune Activation During Tenofovir-Emtricitabine Therapy in HIV-Negative Individuals**

Jose R. Castillo-Mancilla[1], Amie Meditz[1], Sharon Seifert[2], Jia-Hua Zheng[2], Becky J. Kerr[2], Edward M. Gardner[3], Brent E. Palmer[4], Lane Bushman[2], Samantha MaWhinney[5], Peter L. Anderson[2]

[1]Infectious Diseases, University of Colorado, Aurora, CO, United States, [2]Pharmaceutical Sciences, University of Colorado, Aurora, CO, United States, [3]Infectious Diseases, Denver Health Hospital, Denver, CO, United States, [4]Allergy and Immunology, University of Colorado, Aurora, CO, United States, [5]Biostatistics and Informatics, University of Colorado, Aurora, CO, United States

341 **Mesalamine To Reduce Immune Activation During HIV Infection: A Randomized Controlled Trial**

Ma Somsouk, Richard M. Dunham, Michelle Cohen, Rebecca Albright, Teri Liegler, Yuaner Wu, Jeffrey N. Martin, Priscilla Y. Hsue, Steven G. Deeks, Joseph M. McCune, Peter W. Hunt

University of California San Francisco, San Francisco, CA, United States

342 **Decreased Levels of D-Dimer After Probiotic Supplementation in Patients Receiving ART**

Birgitte Stiksrud[1], Piotr Nowak[2], Dag Kvale[1], Anders Thalme[2], Stein-Erik Birkeland[3], Anders Dahm[1], Anne Ma Dyrhol-Riise[1], **Marius Troseid**[1]

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Session P-E2 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Therapeutic Vaccines and Immunotherapies

343 **Immune Function and Viral Load Post AGS-004 Administration To Chronic HIV Subjects Undergoing STI**

Mark DeBenedette[1], Irina Tcherepanova[1], Alicia Gamble[1], Joe Horatinovich[1], Jason Harris[1], Jean-Pierre Routy[2], Charles Nicolette[1], AGS-004-001 Study Team

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344 **Immunogenicity of AGS-004 Dendritic Cell Therapy in Patients Treated During Acute HIV Infection**

Cynthia L. Gay[1], Nancie Archin[1], Irina Tcherepanova[2], Esther Villiard[3], Charles Hicks[4], Mary Kearney[5], John Coffin[6], Mark DeBenedette[3], Joseph Eron[1], Charles Nicolette[3], David M. Margolis[1]

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345 **Immunogenicity and VL Rebound After ATI in Chronic HIV Infected Patients Receiving MVA-B**

Beatriz Mothe[1], Miriam Rosas[1], Montserrat Plana[2], Nuria Climent[2], Jose Luis Jimenez[3], Judith Pich[2], Mariano Esteban[4], Felipe García[5], Christian Brander[1]

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Gregorio Marañón, Madrid, Spain, [4]Centro Nacional de Biotecnología, Madrid, Spain, [5]Hospital Clinic-HIVACAT, IDIBAPS, University of Barcelona, Barcelona, Spain

346 **Dynamics of VL Rebound After cART Interruption in HIV Patients Receiving MVA-B Plus Disulfiram**

Beatriz Mothe[1], Sonsoles Sanchez-Palomino[2], Jose Luis Jimenez[3], Jose M. Gatell[2], Bonaventura Clotet[1], Mariano Esteban[4], Montserrat Plana[2], Juan Carlos Lopez Bernaldo de Quiros[3], Christian Brander[1], **Felipe García[2]**

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347 **Vaccination With Autologous Dendritic Cells Pulsed With Autologous HIV-Infected Apoptotic Cells**

Bernard J. Macatangay[1], Sharon A. Riddler[1], Nicole D. Wheeler[1], Mary J. Buffo[2], Aarika Yates[3], Luann Borowski[3], Theresa L. Whiteside[2], Charles R. Rinaldo[3]

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Session P-E3 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

New Technologies in Immunology

348 **Systems Biology, HIV Disease, and RNAs Big and Small**

Michael Katze

University of Washington, Seattle, WA, United States

349 **CoRSeq^{V3}: Novel Coreceptor Usage Prediction Algorithms for HIV-1 Subtypes B, C, D and CRF01_AE**

Kieran Cashin[1,2], Lachlan R. Gray[1,3], Katherine Harvey[1,2], Danielle Perez-Bercoff[4], Guinevere Q. Lee[5], Jasminka Sterjovski[1], Michael Roche[1], P. Richard Harrigan[5], Melissa J. Churchill[1,6], Paul R. Gorry[1,2]

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350 **Identification of Novel B*57:01 Restricted Peptides From HIV gp140 Using Immunopeptidomics**

Sri H. Ramarathinam[1], Nadine L. Dudek[1], Robert J. Center[2], Damian F. J. Purcell[2], Anthony W. Purcell[1]

[1]Department of Biochemistry and Molecular Biology, Monash University, Clayton, Australia, [2]Department of Microbiology and Immunology, University of Melbourne, Parkville, Australia

351 **New Summaries and Computational Tools at Los Alamos HIV Immunology Database**

Karina Yusim[1], Shihai Feng[1], Hyejin Yoon[1], KumKum Ganguly[1], Jennifer Macke[1], James Szinger[1], Anthony P. West[2], Pamela Bjorkman[2], Brian Foley[1], Bette T. Korber[1]

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Session P-E4 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall**

Monocytes, Dendritic Cells, NK Cells

352 **Identification of Pattern Recognition Receptor for HIV-1 in Human Dendritic Cells**

Sunnie M. Yoh[1], Monika Schneider[1], Stephen Soonthornvacharin[1], Kevin Olivieri[1], Sourav Bandyopadhyay[2], Elisa Decastro[3], Adolfo G. Sastre[3], Sumit K. Chanda[1]

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353 **Plasmacytoid Dendritic Cell Phagocytosis of IgG Anti-p24 Associates With Control of HIV Infection**

Christian Tjiam[1], James Taylor[1], Mazmah A. Morshidi[1], Jeffrey N. Martin[2], Steven G. Deeks[2], Dino Tan[3], Silvia Lee[1], Sonia Fernandez[1], **Martyn A. French[1]**

[1]School of Pathology and Laboratory Medicine, University of Western Australia, Perth, Australia, [2]School of Medicine, University California San Francisco, San Francisco, CA, United States, [3]Lung Institute of Western Australia, University of Western Australia, Perth, Australia

354 **Recruitment of Functionally Different NK Cells To the Rectal Mucosa in Vaccinated Macaques**

Namal P. M. Liyanage[1], Shari N. Gordon[1], Monica Vaccari[1], Poonam Pegu[1], Melvin Doster[1], David Venzon[1], James Tartaglia[2], Susan W. Barnett[3], Nelson Michael[4], Genoveffa Franchini[1]

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355 **HIV Myeloid-Derived Suppressor Cells Inhibit the Protective Response To Cytomegalovirus**

Ankita Garg[1], Stephen A. Spector[1,2]

[1]Pediatrics, University of California San Diego, La Jolla, CA, United States, [2]Rady Children's Hospital, San Diego, CA, United States

Session P-E5 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall**

Pre-Clinical Vaccine Studies

356 **Induction of Gut Anti-HIV Immune Response via Dendritic Cell Targeted Intranasal Vaccination**

Darren Ruane[1], Yoonkyung Do[2], Akash Greg[1], Haekyung Lee[1], Thomas Kraus[3], Jordan Poles[1], Lucas Brane[1], Christine Trumpfheller[4], Andres Salazar[5], Ralph Steinman[4], Saurabh Mehandru[1]

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357 **Conserved Element DNA Vaccine based On HIV-1 or SIV sequences Increases T-Cell Breadth**

Barbara K. Felber

NCI, Frederick, MD, United States

358 **DNA and Protein Co-Immunization Improves the Magnitude and Longevity of Humoral Immune Responses**

George N. Pavlakis

National Cancer Institute, Frederick, MD, United States

359 **The Adjuvant Used in an ALVAC/gp120 Regimen Alters Plasmablast Homing Markers in Macaque and Humans**

Luca Schifanella[1], Shari Gordon[1], Monica Vaccari[1], Georgia Tomaras[2], Mangala Rao[3], David Venzon[1], Susan Barnett[4], James Tartaglia[5], Silvia Ratto-Kim[6], Genoveffa Franchini[1]

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360 **ALVAC-SIV/gp120 Efficacy Is Not Improved by the Increase of Anti-Envelope B and T-Cell Responses**

Monica Vaccari[1], Shari N. Gordon[1], Brandon F. Keele[1], Georgia D. Tomaras[2], Mangala Rao[3], Mario Roederer[4], Donald M. Stablein[5], Sanjay Phogat[6], Susan W. Barnett[7], Genoveffa Franchini[1]

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361 **Altering the Prime Affects ALVAC-SIV/gp120 Immunogenicity and Efficacy**

Shari N. Gordon[1], Monica Vaccari[1], Georgia D. Tomaras[2], Mario Roederer[3], David Venzon[4], Dan H. Barouch[5], Barbara Felber[6], Nelson L. Michael[7], James Tartaglia[8], Genoveffa Franchini[1]

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362 **Immunization of Humanized BLT Mice Against HIV Influences Early Immune Responses and Viral Loads**

Timothy E. Dudek[1], Colby R. Maldini[1], Vladimir D. Vrbanac[2], Elizabeth F. Mellors[1], Damien Tully[1], Marcus Altfeld[1], David M. Knipe[3], Andrew M. Tager[2], Todd M. Allen[1]

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Session P-E6 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall**

Human Vaccine Trial Results

363 **Antibody Responses in Anogenital Secretions of RV305, a Late Boost Vaccination of RV144 Volunteers**

Siriwat Akapirat[1], Chitraporn Karnasuta[1], Viseth Ngauy[1], Robert J. O'Connell[1], Punnee Pitisuthithum[2], Supachai Rerks-Ngarm[3], Nelson L. Michael[4], Mark S. De Souza[1], Jerome H. Kim[4], Nicos Karasavvas[1]

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364 **Divergent HIV-Specific CD4 T-Cell Response Profiles in HIV Vaccine Trials**

Franco Pissani[1], Sebastien Maloveste[1], Bruce Shultz[1], Sorachai Nitayaphan[2], Prasert Thongcharoen[3], Punnee Pitisuttithum[4], Michael Eller[5], Silvia Ratto-Kim[5], Mary Marovich[6], Hendrik Streeck[1]

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365 **Immunogenicity and Reactogenicity of Cervarix® Versus Gardasil® in HIV-Infected Adults: An RCT**

Lars Toft[1], Merete Storgaard[1], Martin Müller[2], Peter Sehr[3], Jesper Bonde[4], Martin Tolstrup[1], Lars Østergaard[1], **Ole S. Søgaard**[1]

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366 **The Specificity of V3 Antibodies in RV144 Plasma Implicated in Reducing HIV Infection**

Susan Zolla-Pazner[1], Constance Williams[2], Morgane Rolland[3], Paul Edlefsen[4], Xiang-Peng Kong[5], Arthur Nadas[5], S. Tovanabutra[6], Supachai Rerks-Ngarm[7], Merlin Robb[6], Nelson Michael[6], Jerome Kim[6]

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Session P-E7 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall**

Immune Response To Infection

367 **HIV Cell Tropism Dependent Impact of CTL Escape Mutations in Gag On Viral Replicative Capacity**

Benedikt Grandel[1], Sara Wennige[1], Franziska Winter[1], Sven Breitschwerdt[1], Bernd Salzberger[1], Arne Schneidewind[2]

[1]Internal Medicine I, University of Regensburg, Regensburg, Germany, [2]Internal Medicine I, University of Bonn, Bonn, Germany

368LB **Epitope Targeting and the Antibody-Dependent Cellular Cytotoxicity Response Against HIV-1**

Priyamvada Acharya[1], William D. Tolbert[2, 3], Lei Yu[2, 4], James E. Robinson[5], Loic Martin[6], Peter D. Kwong[1], Yongjun Guan[2, 4], Anthony L. DeVico[2, 7], George K. Lewis[2, 4], Marzena Pazgier[2, 3]

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369 **Complex Impact of Reversion Mutations and CD8+ T Cell Escape Mutations On HIV-1 Fitness**

Hongshuo Song[1], Tanmoy Bhattacharya[2], Nilu Goonetilleke[3], Kevin Wiehe[1], Andrew McMichael[3], George Shaw[4], Beatrice Hahn[4], Alan Perelson[2], Barton Haynes[1], Feng Gao[1]

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370 **CD4+ and CD8+ T-Cells of HIV+ and HIV- Men Who Have Sex With Men Respond To a Broad Array of CMV Epitopes**

Huifen Li[1], Joseph B. Margolick[1], Jay H. Bream[1], Tricia L. Nilles[1], Susan Langan[1], Hanhvy T. Bui[1], Andrew W. Sylwester[2], Louis J. Picker[2], Sean X. Leng[1]

[1]The Johns Hopkins University, Baltimore, MD, United States, [2]Oregon Health & Science University, Beaverton, OR, United States

371 **Linkage Between Disease Status and a Naturally Arising Mutation in Functional Region of HIV-1 Nef**

Stanley C. Meribe[1], Zafrul Hasan[1], Hiroyuki Gatanaga[2], Toshiyuki Miura[3, 4], Ai Kawana-Tachikawa[3], Aikichi Iwamoto[3], Shinichi Oka[2], Takamasa Ueno[1]

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372 **Characterizing Acute HIV-1B CTL Escape by Full-Genome "Deep" Sequencing**

Christian L. Boutwell, Damien Tully, Rebecca Batorsky, Karen Power, Aaron Seese, Michael Sirignano, Marcus Altfeld, Todd M. Allen

Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, United States

373 **HIV-1 gp120-Specific Antibody Dependent Cell-Mediated Cytotoxicity in HIV-1 Elite Controllers**

Mariana M. Mata[1], Fareeha Mahmood[1], Elizabeth T. Golub[2], Ruth M. Greenblatt[3], Kathryn Anastos[4], Marek Nowicki[5], Mary Young[6], Helen Durkin[7], Seema N. Desai[1], Linda L. Baum[1]

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374 **CD8 T Cell Responses Emerging During Acute HIV Infection Drive Long-Term Control**

Hendrik Streeck[1], Jean-Pierre Routy[2], Heiko Jessen[3], Anthony Kelleher[4], Frederick Hecht[5], Rafick-Pierre Sekaly[6], Eric Rosenberg[7], Todd Allen[8], Mary Carrington[9], Marcus Altfeld[10]

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375LB **Modification of Antibody 10E8 To Improve HIV-1 Neutralization**

Gilad Ofek[1], Gabriel Lu[1], Baoshan Zhang[1], Amy Bao[1], Yongping Yang[1], McKee Krisha[1], Brett Zirkle[1], Jinghe Huang[2], Mark Connors[2], John R. Mascola[1], Peter D. Kwong[1]

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376 **Association of Gag-Specific CD28+CD95+ CD8+ T-Cell Responses in Lymph Nodes With Lower Viral Loads**

Hiroshi Ishii[1], Saori Matsuoka[1], Tetsuro Matano[1, 2]

[1]AIDS Research Center, National Institute of Infectious Diseases, Tokyo, Japan, [2]The Institute of Medical Science, The University of Tokyo, Tokyo, Japan

377 **Distinct Functional Properties of HIV-Specific Cytolytic CD4 T Cells Compared To Th1 or CD8 T Cells**

Susan Johnson[1], Richard Lu[1], Alexander Oster[1], Franco Pissani[1], Mary A. Marovich[2], Diane L. Bolton[1], **Hendrik Streeck**[1]

[1]US Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD, United States, [2]Division of AIDS, NIH/NIAID, Bethesda, MD, United States

378 **CD8+ T Cells From HLA-B*57 Elite Suppressors Inhibit Replication of HIV-1 Escape Mutants**

Christopher W. Pohlmeyer[1], Robert W. Buckheit[2, 3], Robert F. Siliciano[1, 4], Joel N. Blankson[1]

[1]School of Medicine, The Johns Hopkins Medical Institution, Baltimore, MD, United States, [2]National Cancer Institute, Frederick, MD, United States, [3]The Johns Hopkins Medical Institution, Baltimore, MD, United States, [4]Howard Hughes Medical Institute, Baltimore, MD, United States

Session P-F1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Mechanisms of HIV Latency

379LB **The Tat Inhibitor, Cortistatin A, Suppresses Transcription and Reactivation of HIV Latent Cells**

Guillaume Mousseau[1], Remi Fromentin[2], Nicolas Chomont[2], **Susana T. Valente**[1]

[1]The Scripps Research Institute, Jupiter, FL, United States, [2]Vaccine and Gene Therapy Institute, Port Saint Lucie, FL, United States

380 **Mechanisms by Which Negative Elongation Factor (NELF) Establishes and Maintains HIV Latency**

Gillian M. Schiralli Lester[1], Malini Natarajan[2], Andrew J. Henderson[1]

[1]Medicine, Infectious Disease, Boston University Medical Center, Boston, MA, United States, [2]Stowers Institute for Medical Research, Kansas City, MO, United States

381 **Differential Role of Bromodomain Proteins in HIV-1 Latency**

Daniela Boehm, Pao-Chen Li, Hendrik Sy, Melanie Ott

Gladstone Institute of Virology and Immunology, Gladstone Institute/University of California San Francisco, San Francisco, CA, United States

382 **The NCOR2-Nurr1-CoREST Axis Impairs HIV Reactivation in Latently Infected Microglial Cells**

David Alvarez, Biswajit Das, Yoelvis Garcia-Mesa, Curtis Dobrowolski, Jonathan Karn

Molecular Biology and Microbiology, Case Western Reserve University, Cleveland, OH, United States

383 **Repression of HIV Transcription in Memory CD4+ T Cells by Blimp-1**

Katarzyna Kaczmarek[1], Malini Natarajan[2], Zelda Euler[3], Galit Alter[3], Andrew J. Henderson[1]

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384 **HIV-1 Reactivation and Autophagy Inhibition Synergize To Cell Death via Amino Acid Deprivation**

Metodi V. Stankov[1], Diana Panayotova-Dimitrova[2], Georg M. N. Behrens[1]

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385 **JAK Inhibitors Tofacitinib and Ruxolitinib Block T-Cell Activation Mediated HIV Replication**

Franck P. Dupuy[1], Jessica Brehm[1], Christina Gavegnano[2, 3], Raymond F. Schinazi[2, 3], Rafick P. Sekaly[1]

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386LB **Human Genome shRNA Screen Identifies Cellular Factors Controlling Latency**

Shweta Hakre[1], Martin Kampmann[2], Nina N. Hosmane[3], Michael C. Bassik[4], Erik Verschueren[5], Emilie Battivelli[6], Robert F. Siliciano[7], Nevan J. Krogan[8], Jonathan S. Weissman[2], Eric Verdin[9]

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Session P-F2 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Dynamics of Persistent and Rebound HIV

387 **Incomplete Adherence To cART Is Associated With Higher Levels of Residual HIV-1 Viremia**

Jonathan Z. Li[1], Sebastien Gallien[2], Heather Ribaudo[3], Andrea Heisey[1], David R. Bangsberg[4], Daniel R. Kuritzkes[1]

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388 **Viral Dynamics of HIV-1 Rebound Viremia**

Benjamin Scheinfeld, **Katharine J. Bar**

Medicine, University of Pennsylvania, Philadelphia, PA, United States

389 **Transcripts Associated With the HIV Reservoir Correlate With the Pool Size of Long-Lived CD4 T Cells**

Maria J. Buzon[1, 2], Ouyang Zhengyu[1], Amy Shaw[1], Hong Sun[3], Forencia Pareyra[1, 4], Nadine Zangger[5], Xu Yu[1], Amalio Telenti[5], Eric S. Rosenberg[2], Mathias Lichterfeld[2]

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390 **Massive Expansion of HIV Infected Cells With Identical Proviruses in Patients On Suppressive ART**

Mary Kearney[1], Luke Smith[1], Johnathan Spindler[1], Charles Coomer[1], Guilaume J. Besson[2], Elizabeth M. Anderson[1], Wei Shao[3], John M. Coffin[4], John W. Mellors[5], Frank Maldarelli[1]

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391 **Effects of CCR5-Δ32 Heterozygosity On HIV-1 Reservoir Size and Immune Activation**

Charlene Wang[1,2], Mohamed Abdel-Mohsen[2,3], Matthew C. Strain[4,5], Steven M. Lada[4,5], Leslie Cockerham[3], Steven Yukl[3,6], Teri Liegler[3], Douglas D. Richman[4,5], Steven G. Deeks[3], Satish K. Pillai[2,3]

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392 **Seminal CMV Replication, Immune Activation, and Higher Proviral HIV DNA During Suppressive ART**

Sara Gianella[1], Marta Massanella[1], Douglas D. Richman[1,2], Susan J. Little[1], Celsa A. Spina[1,2], Eric S. Daar[3], Michael P. Dube[4], Richard H. Haubrich[1], Sheldon R. Morris[1], Davey M. Smith[1,5], and the CCTG 592 Team.

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393 **Persistent HIV in Plasma During cART Can Lead To Rebound Viremia After Treatment Interruption**

Junko Hattori[1], Wei Shao[2], Shawn Hill[1], Francesco R. Simonetti[1], Elizabeth M. Anderson[1], Catherine A. Rehm[3], Sara E. Jones[4], Richard T. Davey[3], Frank Maldarelli[1]

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Session P-F3 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Effect of ART Early in HIV Infection

394 **How To Characterize Post-Treatment Controllers in Patients Treated During Primary HIV Infection?**

Eva Wolf[1], Johannes Bogner[2], Knud Schewe[3], Véronique Avettand-Fenoel[4], Christine Koegl[1], Ramona Pauli[5], Jürgen Brust[6], Albrecht Ulmer[7], Lothar Schneider[8], Hans Jaeger[9], New Era Study Group

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395 **Loss of HIV Serological Markers Following Early Treatment of Acute HIV Infection**

Mark M. Manak[1], Sheila Peel[2], Jennifer Malia[2], Ashley Shutt[1], Siriwat Akapirat[3], Tippawan Pankam[4], James Fletcher[4], Merlin Robb[1], Jerome Kim[2], Jintanat Ananworanich[4]

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396 **Early Antiretroviral Therapy Prevents the Establishment of HIV-1 Infection in Humanized-BLT Mice**

Qingsheng LI[1], For Yue Tso[1], Guobin Kang[1], Wuxun Lu[1], Yue Li[1], Wenjin Fan[1], Chris J. Destache[2], Charles Wood[1]

[1]Nebraska Center for Virology & School of Biological Sciences, University of Nebraska-Lincoln, Lincoln, NE, United States, [2]Pharmacy Practice, Creighton University School of Pharmacy & Health Professions, Omaha, NE, United States

397LB **Lack of Detectable HIV DNA in a PrEP Study Participant Treated During "Hyperacute" HIV Infection**

Hiroyu Hatano[1], Oliver Bacon[1,2], Stephanie Cohen[1,2], Albert Liu[1,2], Susan Buchbinder[1,2], Nicolas Chomont[3], Mary Kearney[4], Janet Siliciano[5], Teri Liegler[1], Steven G. Deeks[1]

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398 **Early HAART in Primary HIV Infection Protects TCD4 Central Memory Cells and Can Induce HIV Remission**

Antoine Chéret[1,2], Charline Bacchus[3], Adeline Mélard[1], Georges Nembot[4], Catherine Blanc[3], Assia Samri[3], Véronique Avettand-Fenoël[1], Asier Saez-Cirion[5], Brigitte Autran[3], Christine Rouzioux[1], OPTIPRIM ANRS-147 Study Group

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Session P-F4 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Methods for Measuring Reservoirs

399LB **A Scalable RNA RT-PCR Based Assay To Quantify Latency Disruption in HIV-1 Infected Cells**

Jason M. Hataye, Joseph P. Casazza, David R. Ambrozak, Eli Boritz, Takuya Yamamoto, Daniel C. Douek, Richard A. Koup

Vaccine Research Center, National Institute of Allergy and Infectious Diseases, Bethesda, MD, United States

400 **HIV Antibody Characterization To Quantify Reservoir Size During Curative Interventions**

Peter D. Burbelo[1], Ahmad Bayat[2], Craig S. Rhodes[1], Rebecca Hoh[3], Jeffrey N. Martin[3], Gero Hütter[4], Joseph A. Kovacs[5], Steven G. Deeks[3]

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401 **High-Throughput Analysis of Full-Length Proviral HIV-1 Genomes From PBMCs**

Hiromi Imamichi[1], Yan Guo[2], Collen Ludka[2], Ellen E. Paxinos[2], H. Clifford Lane[1], Da Wei Huang[3], Richard A. Lempicki[3], Michael P. S. Brown[2]

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402 **Using Antibodies To Detect HIV Persistence in Treatment Intensification and Eradication Studies**

Sheila M. Keating[1,2], Christopher D. Pilcher[2], Gary Murphy[3], Alex Welte[4], Reshma Kassanjee[4], David Matten[4], Mila Lebedeva[1], Shelley N. Facente[2], Steve G. Deeks[5], Michael P. Busch[1,2], Consortium for Evaluation of Performance of HIV Incidence Assays (CEPHIA)

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403LB **HIV DNA in PHI Associates With T Cell Immunity and Predicts Disease Progression and Rebound Viraemia**

Jacob Hurst[1], James Williams[1], Elisabeth Hamlyn[2], Kersten Koelsch[3], Sarah Fidler[2], Abdel Babiker[4], Jonathan Weber[2], Tony Kelleher[5], Rodney Phillips[1], **John Frater[1]**, Spartac Trial Investigators

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404 **Next Generation Plasma HIV-1 RNA Single Copy Assays**

Anthony R. Cillo[1], David Vagratian[2], Margaret Bedison[2], Elizabeth Anderson[3], Mary Kearney[3], Elizabeth Fyne[2], Dianna Koontz[2], John Coffin[4], Michael Piatak[3], John Mellors[2]

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405 **Assessment and Quantification of Cell Associate Unspliced HIV-1 RNA Using RT-ddPCR**

Zixin Hu, Carlos Becerril, Nina H. Lin, Jonathan Li, Andrea Heisey, Athe M. Tsibris, Daniel R. Kuritzkes

Division of Infectious Diseases, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States

406 **Measuring HIV Latency Over Time: Reservoir Stability and Assessing Interventions**

Nancie M. Archin[1], Amanda M. Crooks[1], Rosalie Bateson[1], Anna B. Cope[2], Noelle P. Dahl[1], Joseph J. Eron[1], Cynthia L. Gay[1], JoAnn D. Kuruc[1], David M. Margolis[1, 3], **Ronald J. Bosch[4]**

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Session P-F5 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

What and Where Is the Reservoir?

407LB **The Role of HIV Integration Sites in Extensive Clonal Expansion of Infected Cells in Patients**

Frank Maldarelli[1], Xiaolin Wu[2], Mary Kearney[1], Ling Su[2], Wei Shao[3], Shawn Hill[1], Francesco Simonetti[1], Jon Spindler[1], John Coffin[4], **Stephen H. Hughes[1]**

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408 **Identification of a New Th17 Subset That Contributes To HIV-1 Persistence in ART-Treated Subjects**

Vanessa S. Wacleche[1, 2], Annie Gosselin[1], Patricia Monteiro[1], Aurélie Cleret-Buhot[1, 2], Sandrine DaFonseca[1, 2], Mohammad-Ali Jenabian[3], Jean-Pierre Routy[3], Petronela Ancuta[1, 2]

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409 **Identifying Defective and Identical Viral Genomes in HIV Reservoirs During Effective HIV Therapy**

Susanne von Stockenstrom[1], Lina Odevall[1], Elizabeth Sinclair[2], Rui A. Raposo[3], Douglas F. Nixon[3, 4], Hiroyu Hatano[2], Peter Hunt[2], Peter Bacchetti[5], Steven G. Deeks[2], Frederick M. Hecht[2], **Sarah Palmer[1, 6]**

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410 **Healthy HIV-Infected Subjects Harbor HIV in Alveolar Macrophages, Which Can Impair Lung Function**

Sushma K. Cribbs[1], David M. Guidot[1], Angela M. Caliendo[2], Lou Ann Brown[3], Jeffrey Lennox[4]

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411 **Quantitative and Phylogenetic Analyses of Persistent HIV in Blood and GALT During Long-Term cART**

Francesco R. Simonetti[1], Shawn Hill[1], Shao Wei[2], Robert Gorelick[3], Michael Piatak[3], Mark Voellinger[4], Stephen Wank[4], Gabriella Diaz[1], Joe Kovacs[5], Frank Maldarelli[1]

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412 **The Immune Checkpoint Blockers PD-1, LAG-3 and TIGIT Are Associated With HIV Persistence During ART**

Remi Fromentin[1], Sandrina DaFonseca[1], Wendy Bakeman[1], Gabriela Khoury[2], Elizabeth Sinclair[3], Frederick Hecht[3], Steven G. Deeks[3], Sharon R. Lewin[2, 4], Rafick P. Sekaly[1], Nicolas Chomont[1]

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413 **Distinct Patterns of TLR-Mediated HIV Reactivation in Latently-Infected Microglia vs Monocytes**

David Alvarez, Yoelvis Garcia-Mesa, Biswajit Das, Curtis Dobrowolski, Stephanie Milne, Roxana Rojas, Jonathan Karn

Molecular Biology and Microbiology, Case Western Reserve University, Cleveland, OH, United States

414 **CXCR3 and CCR5 Expression Are Associated With 2LTR Circles in Patients On Antiretroviral Therapy**

Gabriela Khoury[1], Jenny Anderson[1, 2], Rémi Fromentin[3], Nicolas Chomont[3], Elizabeth Sinclair[4], Wendy Hartogensis[5], Peter Bacchetti[5], Frederick M. Hecht[5], Steven G. Deeks[5], Sharon R. Lewin[1, 2]

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415 **CD4+ and CD8+ T Cell Activation Are Strongly Associated With HIV-1 DNA in Resting CD4+ T Cells**

Leslie Cockerham[1], Janet D. Siliciano[2], Elizbeth Sinclair[3], Una O'Doherty[4], Sarah Palmer[5], Steven A. Yukl[6], Matt C. Strain[7], Robert F. Siliciano[8], Douglas R. Richman[7], Steven G. Deeks[1]

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Session P-F6 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

What Can We Learn From Bone Marrow Transplantation?

416 **Targeting SIV Reservoirs via Autologous Hematopoietic Stem Cell Transplant in Rhesus Macaques**

Maud Mavigner[1], Benjamin Watkins[2, 3], Benton O. Lawson[1], Ann Chahroudi[1, 2], Leslie S. Kean[2, 3], Guido Silvestri[1]

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417 **Dynamics of HSPC Repopulation in Non-Human Primates Revealed by a Decade-Long Clonal Tracking**

Sanggu Kim[1], Namshin Kim[2], Angela Presson[1], Dong Sung An[1], Robert E. Donahue[3], Irvin S. Y. Chen[1]

[1]University of California, Los Angeles, Los Angeles, CA, United States, [2]Korean Bioinformatics Center, Daejeon, Republic of Korea, [3]National Heart, Lung and Blood Institute, Bethesda, MD, United States

418 **Impact of Systemic Cytotoxic Chemotherapy for Malignancies On HIV-1 Reservoir Persistence**

Timothy J. Henrich[1], Emily Hanhauser[2], Jonathan Z. Li[1], Andrea Heisey[2], Jeremy S. Abramson[3], Ayad Hamdan[4], Philippe Armand[5], Ann S. LaCasce[5], Daniel R. Kuritzkes[1]

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419 **Modeling Functional Cure of HIV in Nonhuman Primates Using Gene-Modified Hematopoietic Stem Cells**

Hans-Peter Kiem[1], Christopher W. Peterson[1], Patrick M. Younan[1], Shiu-Lok Hu[2], Patricia Polacino[2], Michael Holmes[3], Philip Gregory[3], Jianbin Wang[3]

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Session P-F7 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Effect of ART On Persistence

420 **Patterns of Persistent Viremia After 10 Years of Suppressive ART: ACTG A5276s**

Sharon A. Riddler[1], Evgenia Aga[2], Ronald Bosch[2], Joseph J. Eron[3], Rajesh Gandhi[4], Barbara Bastow[5], Margaret Bedison[1], David Vagratian[1], John W. Mellors[1], A5276s Protocol Team

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421LB **Comparison of Combination ART Regimens for Viral Suppression in SIV-Infected Rhesus Macaques**

G. Del Prete[1], R. Geleziunas[2], J. Hesselgesser[2], B. Li[2], J. Hattersley[2], B. Lu[2], J. Zheng[2], J. Smedley[3], M. Piatak, Jr.[1], **J. D. Lifson**[1]

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422 **Impact of RAL/MVC Intensification With or Without HIV-rAd5 Vaccination On HIV DNA: ERAMUNE 02 Study**

Chad Achenbach[1], Steven Deeks[2], Timothy Wilkin[3], Baiba Berzins[1], Joseph Casazza[4], Sidonie Lambert[5], Lambert Assoumou[6], Christine Katlama[5, 6], Brigitte Autran[5, 6], **Robert Murphy**[1], the ERAMUNE 02 Study Group

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423 **Impact of Three Different ART Regimens On the GALT: A Randomized Clinical Trial**

Sergio Serrano-Villar[1], Talia Sainz[2], Anthony Albanese[3], Tammy Yotter[3], Paolo Troia-Cancio[3], Steve Deeks[4], Elizabeth Sinclair[4], Darin Lartimore[3], Vera Go[3], David Asmuth[5]

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424 **HIV Reservoir Changes in Resting CD4 Subsets in the IL7 Plus ART Intensification Eramune-01 Study**

Manuela Pogliaghi[1, 2], Sidonie Lambert[3, 4], Lambert Assoumou[5], Rima Zoorob[1], Laura Papagno[1, 6], Francois Lecardonnel[6], Vincent Calvez[3, 4], Christine Katlama[5, 7], Brigitte Autran[1], The Eramune-01 Study Group

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425LB **Pre-ART HIV-1 RNA as well as On-Treatment CD8 Count and CD4/CD8 Ratio Predict Residual Viremia On ART**

Sharon A. Riddler[1], Evgenia Aga[2], Ronald Bosch[2], Barbara Bastow[3], Margaret Bedison[1], David Vagratian[1], Joseph J. Eron[4], Rajesh Gandhi[5], John W. Mellors[1], for the ACTG A5276s Protocol Team

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Session P-F8 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Immunology for Cure

426 **Eradication of HIV-1 Reservoirs With Antibody Mediated Killing**

Zelda Euler[1], Seav H. Ly[1], Matthew Hurton[1], Athe M. N. Tsibris[2, 3], Galit Alter[1]

[1]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, United States, [2]Division of Infectious Diseases, Brigham and Women's Hospital, Boston, MA, United States, [3]Harvard Medical School, Boston, MA, United States

427LB **Maraviroc Reverts Latent HIV-1 in ART Suppressed Patients Through NFkB Without Viral Load Increase**

Nadia Madrid-Elena[1], Beatriz Hernández-Novoa[1], Beatriz Sastre Turrión[1], Sergio Serrano-Villar[1], Ajantha Solomon[2], Carolina Gutierrez[1], Javier Zamora[3], Laura García-Bermejo[3], Sharon R Lewin[4], **Santiago Moreno**[1]

[1]Infectious Diseases, Hospital Ramón y Cajal, Madrid, Spain, [2]Burnet Institute, Melbourne, Australia, [3]Hospital Ramón y Cajal, Madrid, Spain, [4]Infectious Diseases, Monash University, Burnet Institute and Alfred Hospital, Melbourne, Australia

428 **Regulatory B cells Attenuate Anti-HIV CTL Responses After Reactivation of Latent Reservoirs**

Basile Siewe[1], Jennillee Wallace[1], Sonya Rygielski[1], Jack T. Stapleton[2], Jeffrey Martin[3], Steven G. Deeks[4], Alan Landay[1]

[1]Rush University Medical Center, Chicago, IL, United States, [2]Iowa City Veterans Affairs Medical Center and the University of Iowa, Iowa City, IA, United States, [3]Rush University Medical Center, San Francisco, CA, United States, [4]HIV/AIDS Division, San Francisco General Hospital, University of California, San Francisco, CA, United States

429 **Evaluation of HIV-1 Reservoir Characteristics in a Therapeutic HIV-1 Gag Vaccine Trial**

Jonathan Z. Li[1], Andrea Heisey[1], Hayat Ahmed[1], Michael M. Lederman[2], Hongying Wang[3], Lu Zheng[3], Robert T. Schooley[4], Daniel R. Kuritzkes[1], the ACTG A5197 Study Team

[1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States, [2]Case Western Reserve University, Cleveland, OH, United States, [3]Harvard School of Public Health, Boston, MA, United States, [4]University of California San Diego, La Jolla, CA, United States

430LB **Engineered TCR-Redirected Clearance of Gag-Positive Reservoir Cells From ART-Treated Subjects**

Hongbing Yang[1], Sandrine Buisson[2], Gemma Hancock[1], Rebecca Ashfield[1], Annelise Vuidepot[2], Tara M. Mahon[2], Peter E. Molloy[2], Namir Hassan[2], Bent K. Jakobsen[2], **Lucy Dorrell**[1]

[1]University of Oxford, Oxford, United Kingdom, [2]Immunocore Ltd, Abingdon, Oxon, United Kingdom

431 **Cross-Clade Inhibition of HIV On Primary Cells by CXCR4 or CCR5 Fused To the C34 Peptide From gp41 HR2**

George J. Leslie[1], Jianbin Wang[2], Max W. Richardson[3], Andrea P. O. Jordon[1], Philip D. Gregory[2], James L. Riley[3], Michael C. Holmes[2], James A. Hoxie[1]

[1]Medicine, University of Pennsylvania, Philadelphia, PA, United States, [2]Sangamo Bioscience, Inc, Richmond, CA, United States, [3]Microbiology, University of Pennsylvania, Philadelphia, PA, United States

Session P-F9 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Toward A Cure...

432LB **Ing-B a Potential PKC Activator for HIV Eradication Is Active in SIVmac251-Infected Macaques**

Amilcar Tanuri[1, 2], Lucio Gama[3], Renato Santana[1, 2], Mark Lewis[4], Andrea Savarino[5], Iart Shytaj[5], Janice E. Clements[3], **Luiz F. Pianowski**[6]

[1]Genetics, UFRJ, Rio de Janeiro, Brazil, [2]UFRJ, Rio de Janeiro, Brazil, [3]Johns Hopkins School of Medicine, Baltimore, MD, United States, [4]BioQual, Inc, Rockville, MD, United States, [5]Istituto Superiore di Sanità, Rome, Italy, [6]KyoLab, Valinhos, Brazil

434 **SAHA Dampens TCR-Mediated Reactivation of Latently Infected Cells**

Pejman Mohammadi[1, 2], Julia di Iulio[2, 3], Miguel Munoz[3], Niko Beerenwinkel[1, 2], Amalio Telenti[3], **Angela Ciuffi**[3]

[1]Department of Biosystems Science and Engineering, ETH Zurich, Basel, Switzerland, [2]Swiss Institute of Bioinformatics, Basel and Lausanne, Switzerland, [3]Lausanne University Hospital and University of Lausanne, Institute of Microbiology, Lausanne, Switzerland

435LB **HIV-1 Expression Within Resting CD4 T-Cells Following Multiple Doses of Vorinostat In Vivo**

Yang Kuo-Hsiung[1], Nancie M. Archin[2], Christopher H. Woelk[3], Matthew C. Strain[4], Douglas D. Richman[4], JoAnn D. Kuruc[2], Richard J. O. Barnard[5], Daria J. Hazuda[5], Joseph J. Eron[2], **David M. Margolis**[2]

[1]School of Pharmacy, UNC Chapel Hill, Chapel Hill, NC, United States, [2]School of Medicine, UNC Chapel Hill, Chapel Hill, NC, United States, [3]University of Southampton, Southampton, United Kingdom, [4]School of Medicine, UCSD and San Diego VAMC, San Diego, CA, United States, [5]Merck Research Laboratories, White Horse Junction, PA, United States

436 **Autophagy Induction by Histone Deacetylase Inhibitors Inhibits HIV-1 Infection in Macrophages**

Grant R. Campbell, Rachel S. Bruckman, Stephen A. Spector

University of California San Diego, La Jolla, CA, United States

437 **An In Vitro Compound Screen for Selective Apoptosis Induction in HIV-1 Infected Resting CD4+ T Cells**

Adam M. Spivak[1], Alberto Bosque[2], Vicente Planelles[2]

[1]Medicine, University of Utah School of Medicine, Salt Lake City, UT, United States, [2]Pathology, University of Utah School of Medicine, Salt Lake City, UT, United States

438LB **Panobinostat Induces HIV Transcription and Plasma Viremia in HIV Patients on Suppressive cART**

Thomas Rasmussen, and the CLEAR study group

Dept. of Infectious Diseases, Aarhus University Hospital, Aarhus, Denmark

439 **Failure of HIV-1 To Replicate in Human T Cells Expressing a Tat Mutant**

David Harrich, Hongping Jin, Lina Rustanti, Ann Apolloni, Haran Sivakumaran, Min-Hsuan Lin, Dongsheng Li, Ting Wei

Cell and Molecular Biology, QIMR Berghofer, Herston, QLD, Australia

440 **Hepatitis C Therapy Reduces CD4 T-Cell-Associated HIV-1 DNA in HIV-1/HCV Coinfected Patients**

Hong Sun[1, 2], Maria Buzon[1, 3], Amy Shaw[1], Randi Berg[4], Xu G. Yu[1], Sara Ferrando-Martinez[5, 6], Manuel Leal[5, 7], Ezequiel Ruiz-Mateos[5, 7], Mathias Lichterfeld[3]

[1]Ragon Institute of MGH, MIT, and Harvard, Boston, MA, United States, [2]Key Laboratory of AIDS Immunology, Department of Laboratory Medicine, First Affiliated Hospital of China Medical University, Shenyang, China, [3]Infectious Disease Division, Massachusetts General Hospital, Boston, MA, United States, [4]Infectious Disease Division, Aarhus University Hospital Skejby, Aarhus, Denmark, [5]Laboratory of Immunovirology, Biomedicine Institute of Seville, Division of Infectious Diseases, Microbiology and Preventive Medicine, Virgen del Rocío University Hospital, University of Seville, Seville, Spain, [6]Laboratorio InmunoBiología Molecular, Hospital General Universitario Gregorio Marañón, Madrid, Spain, [7]Consejo Superior de Investigaciones Scientificas, Madrid, Spain

441 **HIV-1 Nef Inhibits Autophagy in Macrophages Through Transcription Factor EB Sequestration**

Grant R. Campbell, Pratima Rawat, Rachel S. Bruckman, Stephen A. Spector

University of California San Diego, La Jolla, CA, United States

Session P-G1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

CNS Viral Escape and Neuroinflammation On ART

442 **HIV-1 RNA Detection in CSF in ART-Treated Subjects With Incomplete Viral Suppression in Plasma**

Sam Nightingale, the PARTITION Study Group

Institute of Infection and Global Health, University of Liverpool, Liverpool, United Kingdom

443 **CSF Viral Escape in Patients Without Neurological Disorders: Prevalence and Associated Factors**

Carmela Pinnetti[1], Patrizia Lorenzini[1], Federica Forbici[1], Adriana Ammassari[1], Raffaella Libertone[1], Maria Letizia Giancola[1], Maria Rosaria Capobianchi[1], Carlo Federico Perno[2], Andrea Antinori[1]

[1]National Institute for Infectious Disease, Rome, Italy, [2]University of Rome, Rome, Italy

444 **Early Monocyte Inflammation Among Treatment-Naïve Acute HIV-Infected Thai Subjects**

Lishomwa C. Ndhlovu[1], Mary Margaret Byron[1], Guangxiang Zhang[2], Duanghathai Sutthichom[3], Somprartthana Rattanamanee[3], Rapee Trichavaroj[4], Nittaya Phanuphak[3], Victor Valcour[5], Merlin Robb[6], Jintanat Ananworanich[7]

[1]Hawaii Center for AIDS, University of Hawaii, Honolulu, HI, United States, [2]University of Hawaii, Honolulu, HI, United States, [3]SEARCH, The Thai Red Cross AIDS Research Center, Bangkok, Thailand, [4]Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand, [5]University of California San Francisco, San Francisco, CA, United States, [6]US Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD, United States, [7]SEARCH, HIV-NAT, The Thai Red Cross AIDS Research Center, Bangkok, Thailand

445 **Cerebrospinal Fluid Viral Blips and Persistent Escape in HIV-Infected Patients On ART**

Arvid Eden[1], Lars-Magnus Andersson[1], Dietmar Fuchs[2], Lars Hagberg[1], Staffan Nilsson[3], Bo Svennerholm[1], Aylin Yilmaz[1], Henrik Zetterberg[1], Magnus Gisslen[1]

[1]University of Gothenburg, Gothenburg, Sweden, [2]Innsbruck Medical University, Innsbruck, Austria, [3]Chalmers University of Technology, Gothenburg, Sweden

446 **Mitochondrial DNA Is Associated With Inflammation and Neurocognitive Deficits in HIV Infection**

Josué Pérez-Santiago[1], Sanjay R. Mehta[1], Sara Gianella[1], Rachel D. Schrier[1], Mariana Cherner[1], Susanna R. Var[1], Tyler R. C. Day[1], Miguel Ramirez-Gaona[2], Davey M. Smith[1, 3], Scott L. Letendre[1]

[1]Medicine, University of California San Diego, La Jolla, CA, United States, [2]Bioinformatics, University of Alberta, Edmonton, AB, Canada, [3]Veterans Administration San Diego Healthcare System, San Diego, CA, United States

447 **CNS Outcomes of cART vs. cART plus Maraviroc and Raltegravir Intensification During Acute HIV**

Victor Valcour[1], Serena Spudich[2], Napaporn Sailasuta[3], Sukalaya Lerdlum[4], **James L. K. Fletcher**[5], Eugene D. M. B. Kroon[5], Peeriya Mangyu[5], Bonnie Slike[6], Jerome Kim[6], Jintanat Ananworanich[7], on behalf of the SEARCH 010/RV254 Study Group

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Session P-G2 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

HAND in Aging Populations

448 **The Effects of Age and Study Cohort On Brain Structure Among Men With HIV Disease**

James T. Becker[1], Lawrence A. Kingsley[2], Mikhail Popov[3], Nisha Shah[4], Andrew J. Levine[5], Eileen M. Martin[6], Eric N. Miller[7], Cynthia A. Munro[8], Ann Ragin[9], Ned Sacktor[10]

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449 **FMRI Reveals Asymptomatic Deficits Among HIV+ Older Adults On cART When Compared To HIV- Controls**

Manya Magnus[1], Rebecca Barasky[1], Halli Olsen[1], Xiong Jiang[2]

[1]Epidemiology and Biostatistics, George Washington University, Washington, DC, United States, [2]Georgetown University, Washington, DC, United States

450 **Longitudinal Progression of Cortical Atrophy in HIV-Patients On Stable Treatment**

Michael R. Nowak[1], Bradford Navia[2], Jaroslaw Harezlak[3], Constantin Yiannoutsos[3], Charles Guttmann[4], Elyse Singer[5], Thomas Campbell[6], Eric Daar[5], Giovanni Schifitto[7], David Tate[8]

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451 **FMRI Evidence for HIV-Induced Acceleration of Aging in Middle-Aged Women**

Xiong Jiang[1], Chenglong Liu[2], Matthew Leclair[2], Cuiwei Wang[2], Xiaohan Xu[2], Pilar Hamilton[2], Lakshmi Goparaju[2], Mary Young[2]

[1]Neuroscience, Georgetown University Medical Center, Washington, DC, United States, [2]Georgetown University Medical Center, Washington, DC, United States

452 **Factors Related To Brain Atrophy in a Cohort of HIV Infected Patients: ANRS CO3 Aquitaine Cohort**

Carole Dufouil[1], Laura Richert[1], Rodolphe Thiébaut[1], Mathias Bruyant[1], Frédéric Dauchy[2], Michèle Allard[3], Didier Neau[3], François Dabis[1], Fabrice Bonnet[3], Geneviève Chêne[1]

[1]HIV and associated disease team, INSERM Centre 897, Bordeaux, France, [2]Services de Maladies Infectieuses et Tropicales, Bordeaux Hospital, Bordeaux, France, [3]Bordeaux Hospital, Bordeaux, France

453 **Hyperphosphorylated Tau in Cerebrospinal Fluid: A Biomarker for Neurological Aging in HIV-1?**

Jan J. Krut[1], Magnus Gisslén[1], Lars Hagberg[1], Henrik Zetterberg[2], Richard W. Price[3], Staffan Nilsson[4], Paola Cinque[5]

[1]Infectious Diseases, Sahlgrenska Academy, Gothenburg, Sweden, [2]Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden, [3]Neurology, University of California San Francisco, San Fransisco, CA, United States, [4]Mathematical Sciences, Chalmers University of Technology, Gothenburg, Sweden, [5]Infectious Diseases, San Raffaele Hospital, Milan, Italy

Session P-G3 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Neuropathogenesis

454 **Efavirenz Produces a Differential Bioenergetic Response in Neurons and Glial Cells**

Haryes A. Funes[1], Nadezda Apostolova[1], Fernando Alegre[2], Miriam Polo[3], Ana Blas-Garcia[3], **Juan V. Esplugues**[1]

[1]Departamento de Farmacologia, Facultad de Medicina, Universitat de Valencia, Valencia, Spain, [2]Univeristy Hospital Dr. Peset, Valencia, Spain, [3]University Hospital Dr. Peset, Valencia, Spain

455 **Corneal Sensory Nerve Fiber Loss in SIV-Infected Macaques: Tracking HIV PNS Damage**

Jamie Dorsey[1], Lisa Mangus[1], Jonathan Oakley[2], **Joseph Mankowski**[1,3]

[1]Molecular and Comparative Pathobiology, Johns Hopkins University, Baltimore, MD, United States, [2]Voxeleron, Pleasanton, CA, United States, [3]Neurology, Johns Hopkins University, Baltimore, MD, United States

456 **HIV-Tat Protein in Inflammatory Infiltrates of CNS-IRIS and in CSF of Patients On ART**

Gloria von Geldern[1], Tory P. Johnson[1], Richa Tyagi[1], Ned Sacktor[2], Justin C. McArthur[3], Scott Letendre[4], Avindra Nath[1]

[1]NINDS, NIH, Bethesda, MD, United States, [2]Dept. of Neurology, Johns Hopkins University, Baltimore, MD, United States, [3]Dept. of Neurology, Johns Hopkins University, Baltimore, MD, United States, [4]Dept. of Neurology, Unversity of California, San Diego, San Diego, CA, United States

457 **Central Nervous System Demyelination in Pediatric SIV Infection**

Herman Kamboj[1], Kimberly Curtis[1], Heather Carryl[1], Hayford Agyemang[1], Koen Van Rompay[2], Kristina Abel[3], **Mark Burke**[1]

[1]Physiology & Biophysics, Howard University, Washington, DC, United States, [2]University of California Davis, Davis, CA, United States, [3]University of North Carolina at Chapel Hill, Chapel Hill, NC, United States

458 **Brain Iron Transport Is Associated With Neurocognitive Performance in HIV/AIDS**

Asha R. Kallianpur[1], James R. Connor[2], Christopher C. Coe[3], Benjamin B. Gelman[4]

[1]Genomic Medicine, Cleveland Clinic Foundation/Lerner Research Institute, Cleveland, OH, United States, [2]Neurosurgery, Penn State Milton S. Hershey Medical Center, Hershey, PA, United States, [3]Psychology, University of Wisconsin, Madison, WI, United States, [4]Pathology, University of Texas Medical Branch, Galveston, TX, United States

461 **Cognitive and Brain Microstructure Abnormalities in HIV-1 Infected Humanized Mice**

Prasanta K. Dash[1], Michael D. Boska[2], Sidra P. Akhter[1], Jaclyn S. Knibbe[1], Adrian A. Epstein[1], Robin R. High[1], Harris A. Gelbard[3], Larisa Y. Poluektova[1], Howard E. Gendelman[1], Santhi Gorantla[1]

[1]Pharmacology and Expt. Neuroscience, University of Nebraska Medical Center, Omaha, NE, United States, [2]Radiology, University of Nebraska Medical Center, Omaha, NE, United States, [3]University of Rochester Medical Center, NY, NY, United States

462 **SIV Dynamics in the CD8-Depleted vs Non-CD8-Depleted Rhesus Macaque Model for NeuroAIDS**

Susanna L. Lamers[1], David J. Nolan[2], Brittany D. Rife[3], Gary B. Fogel[4], Tricia Burdo[5], Kenneth C. Williams[5], Marco Salemi[3]

[1]Bioinfoexperts, LLC, Thibodaux, LA, United States, [2]Department of Pathology, Immunology, and Laboratory Medicine, University of Florida, Gainesville, FL, United States, [3]University of Florida, Gainesville, FL, United States, [4]Natural Selection, San Diego, CA, United States, [5]Boston College, Boston, MA, United States

463 **Vascular Endothelium and Neurological Performance During Primary HIV Infection**

Sebastian Urday[1], Kevin Robertson[2], Fang-yong Li[1], Felicia C. Chow[3], Julia Peterson[3], Elaine M. Nitta[3], Richard W. Price[3], Priscilla Y. Hsue[3], Serena Spudich[1]

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Session P-G4 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Host Genetics in HAND

464 **Heme Oxygenase-1 Polymorphism and Protein Deficiency Associated With Neurological Disease in HIV**

Alexander J. Gill[1], Suren S. Ambegaokar[1], Colleen E. Kovacsics[1], Stephanie A. Cross[1], Benjamin B. Gelman[2], Dennis L. Kolson[1]

[1]Department of Neurology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United States, [2]Department of Pathology, University of Texas Medical Branch, Galveston, TX, United States

465 **Mitochondrial DNA Haplogroups and Neurocognitive Impairment in the CHARTER Cohort**

Todd Hulgan[1], David Samuels[1], William Bush[1], Ronald Ellis[2], Scott Letendre[2], Peter Straub[1], Deborah Murdock[1], Donald Franklin[2], Igor Grant[2], Asha Kallianpur[3], for the CNS HIV Antiretroviral Therapy Research (CHARTER) Group

[1]Vanderbilt University, Nashville, TN, United States, [2]University of California San Diego, San Diego, CA, United States, [3]Cleveland Clinic Foundation/Lerner Research Institute, Cleveland, OH, United States

466 **MBL2 Promoter Polymorphism rs7096206 Predicts Brain Metabolite Anomalies in HIV-Infected Adults**

Kumud K. Singh, Qianqian Deng, Christine Fennema-Notestine, Florin Vaida, Ronald J. Ellis, Scott L. Letendre, Donald Franklin, Debralee Rosario, Robert K. Heaton, Igor Grant, and CHARTER Group

University of California San Diego, La Jolla, CA, United States

Session P-G5 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

PML and Other CNS Infections

467 **Pathogenesis of JC Virus Reactivation During Natalizumab Treatment**

Spyridon Chalkias[1], Xin Dang[1], Evelyn Bord[1], Marion Stein[2], Philip Kinkel[2], Jacob Sloan[2], Maria Houtchens[3], Guy Buckle[3], Carolina Ionete[4], Igor Koralnik[1]

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468 **Impaired *T. pallidum* Opsonic Antibody Function in HIV-Infected Patients With Neurosyphilis**

Christina Marra, Lauren Tantalo, Sharon Sahi, Emily Ho, Shelia Dunaway, Trudy Jones, Sheila Lukehart

University of Washington, Seattle, WA, United States

469 **Significance of Plasma JCV-DNA in HIV Progressive Multifocal Leukoencephalopathy (PML)**

Francesca Ferretti[1], Manuela Testa[1], Valeria Longo[1], Constantin Theodore Yiannoutsos[2], Beverly Sue Musick[2], Annamaria Pazzi[1], Antonio Boschini[3], Simona Bossolasco[1], Adriano Lazzarin[1], Paola Cinque[1]

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Session P-G6 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

CNS Viral Genetics

470 **CD4-Independent Infection in the CNS of R5 SHIV+ Macaques Is Associated With Severe Neuropathology**

Ana Rachel Leda[1,2], Ke Zhuang[1], Lily Tsai[1], Agegnehu Gettie[1], Heather Knight[3], Carole Harbison[3], Susan Westmoreland[3], Cecilia Cheng-Mayer[1]

[1]Aaron Diamond AIDS Research Center, New York, NY, United States, [2]Federal University of Sao Paulo, Sao Paulo, Brazil, [3]New England Primate Research Center, Southborough, MA, United States

471 **HIV-Associated Neurocognitive Disorder Is Associated With HIV-1 Dual Infection**

Gabriel A. Wagner[1], Antoine Chaillon[2], Donald R. Franklin[2], Gemma Caballero[3], Sergei L. Kosakovsky Pond[2], Robert K. Heaton[2], Douglas D. Richman[2,3], Davey M. Smith[2,3], CHARTER Group

[1]Infectious Diseases, University of California San Diego, La Jolla, CA, United States, [2]University of California San Diego, La Jolla, CA, United States, [3]Veterans Affairs San Diego Healthcare System, San Diego, CA, United States

472 **Single Genome Analysis Reveals Genetic Characteristics of Neuroadaptation Across HIV-1 Envelope**

Teresa H. Evering, Leslie St. Bernard, Charles Farmer, Martin Markowitz

The Aaron Diamond AIDS Research Center, New York, NY, United States

Session P-G7 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

ART Effects On HAND and CNS Reservoirs

473 **HIV-1 Replication in Central Nervous System Increases Over Time On Protease Inhibitor Only Therapy**

Christoph Stephan[1], Maximilian Donath[1], Timo Wolf[1], Annette Haberl[1], Markus Bickel[1], Siri Göpel[1], Pavel Khaykin[1], Annemarie Berger[2], Dimitria Bon[3], Reinhard Brodt[1]

[1]Infectious Diseases, Goethe-University Hospital, Frankfurt, Germany, [2]Medical Virology Institute, Goethe-University Hospital, Frankfurt, Germany, [3]Biomathematics, Goethe-University Hospital, Frankfurt, Germany

474 **Low Prevalence of Neurocognitive Impairment in a Swedish Cohort of HIV-1 Infected Individuals**

Åsa Mellgren[1,2]

[1]Department of Infectious Diseases, Sahlgrenska University Hospital, Gothenburg, Sweden, [2]Clinic of Infectious Diseases, Borås, Sweden

475 **Novel Method for More Reliably Estimating the Burden of Cognitive Impairment in HIV**

Tanja Su[1], **Judith Schouten**[2,3], Gert J. Geurtsen[2], Ferdinand W. Wit[3,4], Ineke G. Stolte[5], Peter Portegies[2,6], Matthan W. A. Caan[1], Peter Reiss[3,4], Charles B. Majoie[1], Ben A. Schmand[2,7], on behalf of the AGEhIV Cohort Study Group

[1]Radiology, Academic Medical Center, Amsterdam, Netherlands, [2]Neurology, Academic Medical Center, Amsterdam, Netherlands, [3]Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands, [4]Internal Medicine, Academic Medical Center, Amsterdam, Netherlands, [5]GGD Amsterdam, Amsterdam, Netherlands, [6]Neurology, Onze Lieve Vrouwe Gasthuis, Amsterdam, Netherlands, [7]Psychology, University of Amsterdam, Amsterdam, Netherlands

476 **Improvement of Depression and Anxiety After Discontinuation of Long-Term Efavirenz Treatment**

Khutso M. Mothapo[1], Arnt Schellekens[2], Reinout van Crevel[1], Karin Grintjes-Huisman[1], Monique Keuter[1], Peter Koopmans[1], Andre van der Ven[1]

[1]Internal Medicine and Nijmegen Institute for Infection, Inflammation and Immunity, Radboud University Medical Center, Nijmegen, Netherlands, [2]Psychiatry, Radboud University Medical Center, Nijmegen, Netherlands

477 **New Advanced EEG Technique To Monitor Early Brain Damage in Naïve HIV and Its Recovery During ART**

Massimo Andreoni[1], Claudio Babiloni[2,3], Paolo Maria Rossini[4], Paolo Onorati[3,5], Stefano Ferracuti[6], Francesco Di Campli[7], Antonio Aceti[8], **Elisabetta Teti**[8], Alfredo Pennica[8]

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478 **HIV-Replication Control Rates Needed To Prevent Neurocognitive Performance (NP) Decline**

Ignacio Pérez-Valero[1], Robert Heaton[2], Donald Franklin[3], Scott Letendre[2], Reena Deutsch[2], Bernard Gelman[4], David Simpson[5], Ann Collier[6], Igor Grant[2], and the CHARTER Group

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Deigo, CA, United States, [4]Hospital Universitario La Paz, Galveston, TX, United States, [5]Mount Sinai Hospital, New York, NY, United States, [6]University of Washington, Seattle, WA, United States

479 CSF Biomarker Profile in HIV Patients With and Without CSF Viral Escape

Ignacio Pérez-Valero[1], Scott Letendre[2], Robert Heaton[3], Ronald Ellis[3], Allen MCCutchan[3], David Simpson[4], Reena Deutsch[3], Igor Grant[3], And the CHARTER Group

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480 Accuracy of NEU Screen for Detecting Cognitive Impairment in Virologically Suppressed HIV Patients

Jose A. Muñoz-Moreno[1], Anna Prats[1], Núria Pérez-Álvarez[1], Inmaculada Nieto-Verdugo[1], Carmina R. Fumaz[1], Maria J. Ferrer[1], Maite Garolera[2], Bonaventura Clotet[1, 3]

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481 Determinants of Cognitive Impairment in HIV-Positive Men On cART and Uninfected Controls

Judith Schouten[1, 2], Tanja Su[3], Ferdinand W. Wit[2, 4], Neeltje A. Kootstra[5], Matthan W. A. Caan[3], Gert J. Geurtsen[1], Ben A. Schmand[1, 6], Charles B. Majoie[3], Peter Portegies[1, 7], Peter Reiss[2, 4], on behalf of the AGEhIV Cohort Study Group

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482 HIV Reactivation by the Histone Deacetylase Inhibitor Panobinostat: Effects On CNS

Thomas A. Rasmussen[1], Ole S. Søgaard[1], Holger J. Møller[2], Christel R. Brinkmann[1], Rikke Olesen[1], Alex L. Laursen[1], Lars Østergaard[1], Martin Tolstrup[1]

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Session P-G8 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

CNS Inflammation, Immune Activation, and HAND Biomarkers

484 Differences Between Cerebrospinal Fluid and Blood Biomarkers of Inflammation in HIV Infection

Julia Peterson[1], Sheila Keating[2], Dietmar Fuchs[3], Phillip Norris[2], Henrik Zetterberg[4], Barbara Shacklett[5], Serena Spudich[6], Magnus Gisslén[4], Richard W. Price[1]

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485 Plasma IP-10 and CSF MIP 1beta Contribute To Progressive Brain Injury in Chronic HIV Infection

Bradford N. Navia[1], Xi L. Luo[2], Peisi Y. Yan[2], Jaroslaw H. Harezlak[3], Giovanni S. Schifitto[4], Michael J. T. Taylor[5], Eric S. D. Daar[6], Thomas C. Campbell[7], Elyse S. Singer[8], Constantin T. Y. Yiannoutsos[3], Ronald C. Cohen[9]

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486LB Neuroinflammation in Asymptomatic HIV-Infected Subjects On Effective cART

Jaime H. Vera[1], Qi Guo[2], Illan Rabiner[3], Paul Matthews[4], Roger Gunn[3], Alan Winston[1]

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487 CSF Biomarkers Correlate With Magnetic Resonance Spectroscopy Metabolites During HIV Disease

Albert M. Anderson[1], Christine Fennema-Notestine[2], Anya Umlauf[2], David Clifford[3], Christina Marra[4], Benjamin Gelman[5], Justin McArthur[6], Allen McCutchan[2], Susan Morgello[7], Scott Letendre[2], for the CHARTER group

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488 Abdominal Obesity, Inflammation, Immune Activation and Neurocognitive Impairment

Fred R. Sattler[1], Jiaxiu He[2], Scott Letendre[3], Cara Wilson[4], Chelsea Sanders[5], Robert K. Heaton[6], Ronald Ellis[7], Donald Franklin[6], Igor Grant[6], J. Allen McCutchan[3], for the CHARTER Group

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489 Blood Cell Indices and Neurocognitive Impairment in the HAART Era: A CHARTER Study

Asha R. Kallianpur[1], Quan Wang[2], Peilin Jia[2], Justin C. McArthur[3], Susan Morgello[4], Ann C. Collier[5], Benjamin B. Gelman[6], David B. Clifford[7], J. Allen McCutchan[8], Igor Grant[9], the CHARTER Study Group

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490 CNS Immunoactivation in HIV Patients On ART With HIV-Associated Mild Neurocognitive Impairment

Arvid Eden[1], Donald R. Franklin[2], Dietmar Fuchs[3], Igor Grant[2], Scott Letendre[2], Thomas Marcotte[2], Staffan Nilsson[4], Richard W. Price[5], Henrik Zetterberg[1], Magnus Gisslen[1]

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491 CNS Inflammation During Treatment-Induced Viral Suppression

Julia Peterson[1], Sheila M. Keating[2], Viktor Dahl[3], Phillip J. Norris[2], Sarah Palmer[3, 4], Dietmar Fuchs[5], Henrik Zetterberg[6], Magnus Gisslén[6], Richard W. Price[1]

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492 CSF Viremia and Inflammatory Markers in Pts With NCI On TDF/FTC/EFV and After Switch To ABC/3TC/MVC

Juan M. Tiraboschi[1], Jose Muñoz-Moreno[2], MC Puertas[3], Carlos Alonso[4], Anna Prats-Paris[2], Elena Ferrer[1], Nerea Rozas[1], Marga Maso-Serra[1], Javier Martinez-Picado[3], Daniel Podzamczer[1]

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Session P-H1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Clinical Pharmacology of TB and HCV Coinfection

493 Rifapentine Once-Weekly Dosing Effect On Efavirenz, Emtricitabine and Tenofovir PKs

Christine Farenc[1], Severine Doroumian[1], Cathy Cantalloube[1], Laurent Perrin[2], Virginie Esposito[3], Isabelle Cierien-Puiseux[4], Xavier Boulenc[1], **Marilyn Maroni[4]**

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494 Relationship Between Efavirenz Trough & CYP2B6 Genotypes With Rifampin-Based TB Therapy in STRIDE

Anne Luetkemeyer[1], Susan L. Rosenkranz[2], Darlene Lu[3], Beatriz Grinsztejn[4], Jorge Sanchez[5], Michael Ssemmanda[6], Ian Sanne[7], Helen McIlleron[8], Diane Havlir[1], David Haas[9], ACTG A5221 & A5243 Study Teams

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495 Concentrations of Nevirapine or Efavirenz On and Off Anti-Tuberculosis Therapy (ANRS12214)

Nilesh Bhatt[1], Elisabeth Baudin[2], Bindiya Meggi[1], Carlota Silva[2], Valerie Furlan[3], Aurelie Barrail-Tran[3, 4], Maryline Bonnet[2], Anne-Marie Taburet[3]

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496 Pharmacokinetics of Raltegravir 400 vs 800 mg BID With Intermittent Rifampicin Dosed Thrice Weekly

Helen E. Reynolds[1], Deirdre Egan[1], Laura Else[1], Mas Chaponda[2], Ales Chrdle[2], David J. Back[1], **Saye H. Khoo[1]**

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497 Pharmacokinetics of Faldaprevir and Antiretrovirals in Patients With HIV/HCV Coinfection

Jürgen K. Rockstroh[1], Marc-Antoine Valantin[2], Josep Mallolas[3], Massimo Puoti[4], Juan Antonio Pineda[5], Patrick Ingiliz[6], Marina Núñez[7], Fenglei Huang[8], Richard Vinisko[8], Douglas Dieterich[9]

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498 Pharmacokinetic Interactions Between the HCV NS5A Inhibitor MK-8742 and Efavirenz

Wendy Yeh[1], William Marshall[1], Eric Mangin[1], Xiaobi Huang[1], Yali Zhu[1], Susanne Langley[1], Patricia Jumes[1], Stephen Youngberg[2], Joan Butterton[1]

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499 Effect of Faldaprevir On Atazanavir Pharmacokinetics in Patients With HIV/HCV Coinfection

Mark Nelson[1], Keikawus Arastéh[2], Mamta K. Jain[3], Vicente Soriano[4], José Valdez Madruga[5], Juvencio Furtado[6], Manuel Battegay[7], Fenglei Huang[8], Montserrat Manero[9], Douglas Dieterich[10]

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500 No Meaningful PK Interaction Between HCV Protease Inhibitor MK-5172 and Tenofovir or Raltegravir

Wendy W. Yeh[1], Iain P. Fraser[2], Luzelena Caro[3], Jennifer Talaty[3], Zifang Guo[4], Henry Davis[5], Stephen P. Youngberg[6], Joan R. Butterton[1]

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501 Effect of Faldaprevir On Raltegravir Pharmacokinetics in Healthy Volunteers

David Joseph[1], Peter Rose[2], Natalja Strelkowa[2], Armin Schultz[3], Jeanette Garcia[1], **Mabrouk Elgadi[4]**, Fenglei Huang[1]

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502 No Clinically Relevant Interactions Between Daclatasvir and Cyclosporine or Tacrolimus

Marc Bifano[1], Robert Adamczyk[1], Carey Hwang[1], Hamza Kandoussi[2], Alan Marion[3], **Richard J. Bertz[1]**

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Session P-H2 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Pharmacogenetics: Drug Disposition To Therapeutics

503 ABCC4 3348 T>C SNP Affects Tenofovir Urinary Output in HIV-Positive Patients

Andrea Calcagno, Jessica Cusato, Letizia Marinaro, Marco Simiele, Alice Trentalange, Chiara Montrucchio, Chiara Alcantarini, Antonio D'Avolio, Giovanni Di Perri, Stefano Bonora

Unit of Infectious Diseases, Department of Medical Sciences, University of Torino, Torino, Italy

504 Relative Genetic Contribution To the Pharmacokinetics of Commonly Prescribed Antiretrovirals

Marco S. Siccardi[1], Adeniyi Olagunju[1, 2], Marco Simiele[3], Antonio D'Avolio[3], Andrea Calcagno[3], Giovanni Di Perri[3], Stefano Bonora[3], Andrew Owen[1]

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505 Leveraging Genomics in HIV Treatment Decisions

Paul J. McLaren[1], Margalida Rotger[1], Manel Aouri[1], Huldrych Günthard[2], Catia Marzolini[3], Laurent Decosterd[1], Amalio Telenti[1]

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506 Contribution of CYP2A6, UGT2B7, and Other Non-CYP2B6 Polymorphisms To Plasma Efavirenz Exposure

David Haas[1], Awewura Kwara[2], Danielle M. Richardson[1], Paxton Baker[1], Ioannis Papageorgiou[3], Edward P. Acosta[4], Gene D. Morse[5], Michael Court[3], the AIDS Clinical Trials Group (ACTG)

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Session P-H3 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

ARV Pharmacokinetics, Drug Interactions, and Pharmacodynamics

507 **Rilpivirine With Darunavir/Ritonavir: Pharmacokinetics & Safety in HIV Therapy-Naïve Patients**

Akil G. A. Jackson[1], Laura J. Else[2], Christopher Higgs[1], Zeenat Karolia[1], Saye Khoo[2], David Back[2], Andrew Murungi[3], Emma Devitt[1], Anton Pozniak[1], Marta Boffito[1]

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508 **Rilpivirine Pharmacokinetics With/Without Darunavir/r in Adolescents and Young Adults**

Marc Foca[1], Ram Yogev[2], Andrew Wiznia[3], Rohan Hazra[4], Patrick Jean-Philipe[5], Bobbie Graham[6], Paula Britto[7], Vincent J. Carey[7], Jennifer King[8], Tim R. Cressey[9], for the IMPAACT P1058A team

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509 **The Cerebrospinal Fluid HIV Risk Score for Assessing Central Nervous System HIV Activity**

Edward R. Hammond[1], Rosa M. Crum[1], Glenn J. Treisman[1], Shruti H. Mehta[1], David B. Clifford[2], David M. Simpson[3], Benjamin B. Gelman[4], Ronald J. Ellis[5], Scott L. Letendre[5], Justin C. McArthur[1]

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510 **Efavirenz (EFV) 400 Versus 600 mg Daily: Results of the ENCORE1 Intensive PK Substudy**

Laura Dickinson[1], Rebekah Puls[2], on behalf of ENCORE1 Pharmacokinetics Substudy Group

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511 **Correlation Between Atazanavir Concentrations, Clinical Covariates and Side Effects**

Cristina J. P. Gervasoni, Paola Meraviglia, Simona Landonio, Valeria Cozzi, Agostino Riva, Nitin Charbe, Laurenzia Ferraris, Giuliano Rizzardini, Massimo Galli, Dario Cattaneo

Luigi Sacco University Hospital, Milan, Italy

512 **Tenofovir Diphosphate Concentration-Response Relationship for HIV Prevention in Vaginal Tissue**

Melanie R. Nicol[1], Cindi W. Emerson[2], Julie A. Nelson[3], Craig Sykes[1], Heather MA Prince[4], Kristine B. Patterson[4], Angela D. M. Kashuba[1]

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513 **A Pharmacokinetic Drug-Drug Interaction Study Between Raltegravir and Atorvastatin**

Maren Blonk[1], Michiel van Beek[2], Angela Colbers[1], Monique Roukens[1], Bas Schouwenberg[2], David Burger[1]

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514LB **PK Study of Depot Medroxyprogesterone Acetate in HIV+ Women On Lopinavir/Ritonavir: ACTG 5283**

Susan E. Cohn[1], **Amneris E. Luque**[2], Jeong-Gun Park[3], Yoninah Cramer[4], Francesca Aweeka[5], Adriana Weinberg[6], Elizabeth Livingston[7], Karin L. Klingman[8], Barbara Bastow[9], Heather Watts[10]

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515 **Multi-System Investigation of the Mechanisms for Raltegravir Association With Intestinal Tissue**

Darren Michael Moss[1], Paul Curley[1], Alison Shone[2], Marco Siccardi[1], Andrew Owen[1]

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516 **Tenofovir DF 150 mg Once Daily in HIV-Infected Adults With Moderate Renal Impairment**

Tim R. Cressey[1,2], Anchalee Avihingsanon[3,4], Guttiga Halue[5], Prattana Leenasirimakul[6], Pra-ornsuda Sukrakanchana[1], Nicole Ngo-Giang-Huong[1,7], Achara Eksaengsri[8], Gonzague Jourdain[1,7], Virat Klinbuayaem[9], Chureeratana Bowonwatanuwong[10]

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517 **Tenofovir Concentrations and Prophylactic Effect in a Macaque Model of Rectal SHIV Transmission**

Peter L. Anderson[1], David V. Glidden[2], Lane R. Bushman[1], Jia-Hua Zheng[1], L. Anthony Guida[1], Walid Heneine[3], J. Gerardo Garcia-Lerma[3]

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Session P-H4 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

New Clinical and Preclinical Formulations

518 **Optimisation of Intramuscular Sustained Release Nano-Formulations Using In Silico Modelling**

Rajith Kumar Reddy Rajoli[1], David Back[1], Steve Rannard[2], Andrew Owen[1], Marco Siccardi[1]

[1]Department of Clinical & Molecular Pharmacology, University of Liverpool, Liverpool, United Kingdom, [2]Department of Chemistry, University of Liverpool, Liverpool, United Kingdom

519 **Macrophage Targeted Nanomedicines for Mycobacterial Infections**

Benson Edagwa[1], Dongwei Guo[2], Pavan Puligujja[1], JoEllyn McMillan[1], Xinming Liu[1], Howard Gendelman[1], Prabagaran Narayanasamy[1]

[1]University of Nebraska Medical Center, Omaha, NE, United States, [2]Pharmaceutical Science, University of Nebraska Medical Center, Omaha, NE, United States

520 **Fluorescent Magnetic Nanoparticle as Anti-HIV Drug Carrier for Rodent Brain Targeting**

Upal Roy[1], Hong Ding[1], Sudheesh P. Kanthikeel[1], Elena M. Kaftanovskaya[2], Andrea Raymond[1], Karla Munoz-Caamano[1], Madhavan Nair[1]

[1]Immunology, Florida International University, Miami, FL, United States, [2]Department of Human and Molecular Genetics, Florida International University, Miami, FL, United States

521LB **A Novel Anti-HIV Particle Provides Sustained Plasma and Cell Drug Levels in Lymph Nodes in Primates**

Jennifer Freeling[1], Josefin Koehn, Cuiling Shu, **Rodney JY Ho**[2, 3]

[1]Pharmaceutics, University of Washington, Seattle, WA, United States, [2]Pharmaceutics, University of Washington, Seattle, WA, United States, [3]Clinical Pharmacology, Fred Hutchinson Cancer Research Center, Seattle, WA, United States

522 **NanoART Facilitated HIV-1 Clearance by a Mixed-Lineage Kinase 3 Inhibitor**

Gang Zhang[1], Prasanta K. Dash[1], Dongwei Guo[1], Jayme L. Wiederin[1], Pawel S. Ciborowski[1], Val S. Goodfellow[2], JoEllyn M. McMillan[1], Santhi Gorantla[1], Harris A. Gelbard[3], Howard E. Gendelman[1]

[1]Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, United States, [2]Califia Bio, San Diego, CA, United States, [3]University of Rochester Medical Center, Rochester, NY, United States

523 **A Multiple Dose Study of Raltegravir (RAL) Formulations**

Matthew L. Rizk, Rajesh Krishna, Valerie Schulz, Jolanda ten Bruggencate-Broeders, Patrick Larson, Larissa Wenning

Merck & Co., Inc., West Point, PA, United States

524 **In Vivo Effects of Solid Drug Nanoparticle and Conventional Efavirenz On Anxiogenesis in Rodents**

Paul Curley[1], Marco Giardiello[2], Neill Liptrott[1], Philip Martin[1], Tom McDonald[2], Marco Siccardi[1], Juliet McAdams[3], Steve Rannard[2], Tim Kirkham[3], Andrew Owen[1]

[1]Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, United Kingdom, [2]Chemistry, University of Liverpool, Liverpool, United Kingdom, [3]Institute of Psychology, Health and Society, University of Liverpool, Liverpool, United Kingdom

525 **Atazanavir/Cobicistat Fixed-Dose Combination Is Bioequivalent To the Separate Agents**

Xiaolu Tao[1], Heather Sevinsky[1], Reena Wang[1], Palanikumar Ravindran[2], Karen Sims[1], Xiaohui Xu[2], Navin Jariwala[1], Richard Bertz[1]

[1]Bristol-Myers Squibb, Pennington, NJ, United States, [2]Bristol-Myers Squibb, Princeton, NJ, United States

Session P-I1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Preclinical Studies of Novel ART Approaches: Entry

526 **Non-Integrating Lentivirus Delivered CCR5-ZFNs Can Inhibit HIV-1 Infection in Humanized Mice**

Guohua Yi, Jang-Gi Choi, Preeti Bharaj, Sojan Abraham, Manjunath Swamy, Premlata Shankar

Department of Biomedical Sciences, Center of Excellence in Infectious Disease, Texas Tech University Health Sciences Center, El Paso, TX, United States

527 **Role of Sulfhydryl in Causing Lytic Inactivation of HIV-1 by Env Targeting Peptide Triazole Thiols**

Lauren D. Bailey[1], Caitlin Duffy[1], Huiyuan Li[2], Ali Emileh[3], Arangassery R. Bastian[4], Irwin Chaiken[1]

[1]Biochemistry and Molecular Biology, Drexel University College of Medicine, Philadelphia, PA, United States, [2]West Virginia University, Morgantown, WV, United States, [3]Dartmouth College, Hanover, NH, United States, [4]Biomedical Engineering, Drexel University College of Medicine, Philadelphia, PA, United States

528 **eCD4-Ig Is a Highly Potent HIV-1 Entry Inhibitor**

Matthew Gardner[1], **Lisa Kattenhorn**[2], Jessica Chiang[3], Michael Farzan[1]

[1]Department of Infectious Diseases, The Scripps Research Institute, Jupiter, FL, United States, [2]Division of Comparative Pathology, Harvard Medical School, Southborough, MA, United States, [3]Department of Microbiology and Immunobiology, Harvard Medical School, Boston, MA, United States

529 **Computational Design of Novel Potent Inhibitors of HIV-1 Entry**

Marina Tuyishime, Simon Cocklin

Biochemistry, Drexel College of Medicine, Philadelphia, PA, United States

530 **Cenicriviroc Achieves High CCR5 Receptor Occupancy at Low Nanomolar Concentrations**

Emilie Jalbert[1], Mary Margaret Byron[1], Cecilia Shikuma[1], Helen Jenkins[2], Eric Lefebvre[2], **Jason D. Barbour**[1]

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Session P-I2 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Preclinical Studies of Novel ART Approaches: Post-Entry

531 **Identification of a Novel HIV-1 Inhibitor Targeting Vif-Dependent Degradation of Human APOBEC3G**

Erez Pery[1, 2], Andrew Jay Brazier[1], Ann Sheehy[3], Vikas Misra[1], Kottampatty S. Rajendran[1, 2], Marie K. Mankowski[4], Lynn Rasmussen[5], E. Lucile White[5], Roger G. Ptak[4], Dana Gabuzda[1, 6]

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532 **Drugging HIV Vif as a Rational Approach To Eradication**

Harold C. Smith, **Ryan P. Bennett**

OyaGen, Inc, Rochester, NY, United States

533 **A Novel Class of Multimerization Selective Inhibitors of HIV-1 Integrase**

Amit Sharma[1], Alison P. Slaughter[1], Nivedita Jena[1], Lei Feng[1], Jacques J. Kessl[1], Li Wu[2], James R. Fuchs[1], **Mamuka Kvaratskhelia**[1]

[1]College of Pharmacy, The Ohio State University, Columbus, OH, United States, [2]Center for Retrovirus Research, The Ohio State University, Columbus, OH, United States

534 **PF74 Inhibits Multiple HIV Capsid Functions Independent of Host Cyclophilin A and CPSF6**

Stephen R. Yant[1], Luong Tsai[1], Debi Jin[1], Rujuta A. Bam[1], Andrew Mulato[1], Magdeleine Hung[1], Chien-hung Chou[2], Randall Halcomb[2], Tomas Cihlar[1]

[1]Biology, Gilead Sciences, Foster City, CA, United States, [2]Medicinal Chemistry, Gilead Sciences, Foster City, CA, United States

536 **Recent Progress in Developing Potent and Broadly Active HIV-1 Maturation Inhibitors**

Emiko Urano[1], Sherimay D. Ablan[1], David Martin[2], Ritu Gaur[3], Paul W. Keller[4], Alasdair C. Steven[4], Theodore Nitz[2], Carl Wild[2], Eric O. Freed[1]

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Session P-J1 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

RCTs in Second-Line ART and Virologic Failure

537 **Mortality Among HIV+ Participants Randomized To Omit NRTIs vs. Add NRTIs in OPTIONS (ACTG A5241)**

Karen Tashima[1], Laura Smeaton[2], Karin Klingman[3], Adriana Andrade[4], Joseph Eron[5], Carl Fichtenbaum[6], Rajesh Gandhi[7], Victoria Johnson[8], Richard Haubrich[9]

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538 Partner-Based Intervention for Adherence To Second-Line ART: A Multinational Trial (ACTG A5234)

Robert Gross[1], Lu Zheng[2], Alberto La Rosa[3], Xin Sun[2], Susan Rosenkranz[2], Sandra Cardoso-Wagner[4], Francis Ssali[5], Robert Camp[6], Catherine Godfrey[7], Ann Collier[8], ACTG Team A5234

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539 Predictors of Late Virological Failure After Initial Successful Suppression On EFV-Based ART

Isaac Singini[1], Thomas Campbell[2], Laura Smeaton[3], Nagalingeswaran Kumarasamy[4], Karin Klingman[5], Sineenart Taejaroenkul[6], Timothy Flanigan[7], Alberto La Rosa[8], James Hakim[9], Michael Hughes[3], for the ACTG A5175/PEARLS Study Team

[1]Johns Hopkins Research Project, Blantyre, Malawi, [2]University of Colorado Denver, Aurora, CO, United States, [3]Harvard School of Public Health, Boston, MA, United States, [4]YRGCARE Medical Centre, Chennai, India, [5]NIH, NIAID, DAIDS, Bethesda, MD, United States, [6]Chiang Mai University, Chiang Mai, Thailand, [7]Miriam Hospital, Brown University, Providence, RI, United States, [8]Asociacion Civil Impacta Salud y Educacion, Lima, Peru, [9]University of Zimbabwe College of Health Sciences, Harare, Zimbabwe

540 Raltegravir Non-Inferior To Standard of Care in SECOND-LINE Therapy Over 96 Weeks

Janaki Amin, on behalf of the SECOND-LINE study team

The Kirby Institute, University of New South Wales, Sydney, Australia

541LB Randomized Comparison of Three Second Line ART Regimens in Africa: The 2 Lady/ANRS/EDCTP Study

Sinata Koulla-Shiro[1, 2], Laura Ciaffi[3], Vincent Le Moing[3], Cheikh Tidiane Ndour[4], Adrien Sawadogo[5], Sabrina Eymard-Duvernay[3], Avelin Aghokeng[6], Jacques Reynes[3], Alexandra Calmy[7], **Eric Delaporte[3]**, on behalf of the 2LADY study group

[1]Service Maladies Infectieuses, Central Hospital Yaounde, FMSB/UY1, Yaounde, Cameroon, [2]Site ANRS Cameroon, Yaounde, Cameroon, [3]UMI233, IRD, Montpellier, France, [4]Service Maladies Infectieuses, Hopital de Fann, CRCF, Dakar, Senegal, [5]CHU Sanou Souro, HDJ, Bobo Dioulasso, Burkina Faso, [6]UMI233/IRD, IMPM/CREMER, Yaounde, Cameroon, [7]Infectious Diseases, University Hospital Geneva, Geneva, Switzerland

Session P-J2 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

RCTs in First-Line ART in Treatment Naive Patients

542 First-Line Therapy With LPV/r vs NVP and 2 NRTIs in a Developing Country: W144 of a Randomized Trial

Nathan Clumeck[1], Claude Mwamba[2], Kabamba Kabeya[1], Serge Matanda[2], Dolores Vaira[3], Eric Kasamba[2], Coca Necsoi[1], David Kadiebwe[2], Chantal Milolo[2], Joe Ilunga[2], Lievin Kapend[2]

[1]Infectious diseases, CHU Saint-Pierre, Brussels, Belgium, [2]Lubumbashi Network & PNMLS, Lubumbashi, Democratic Republic of the Congo, [3]CHU Liège, Liège, Belgium

543 Dolutegravir Regimen Statistically Superior To Tenofovir/Emtricitabine/Efavirenz: 96-Wk Data

Sharon Walmsley[1], Juan Berenguer[2], Marie-Aude Khuong-Josses[3], Michael Kilby[4], Thomas Lutz[5], Daniel Podzamczer[6], Norman Roth[7], Catherine Granier[8], Brian Wynne[9], Keith Pappa[10]

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544LB A Randomized, Placebo-Controlled, Double-Blind Study of VM-1500 in HIV-Naïve Patients

Winai Ratanasuwan[1], Peerawong Werarak[1], Robert L. Murphy[2], Vadim Bichko[3]

[1]Preventive and Social Medicine, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand, [2]Northwestern University, Chicago, IL, United States, [3]ChemDiv, Inc, San Diego, CA, United States

545 The Oral Exam: A Simple Tool To Identify HIV-Infected Patients in Need of Antiretroviral Therapy

Ashita S. Batavia[1], Rode Secours[2], Patrice Espinosa[3], Marc A. Jean-Juste[2], Patrice Severe[2], Jean W. Pape[2], Daniel W. Fitzgerald[1]

[1]Department of Medicine, New York Presbyterian Hospital, New York, NY, United States, [2]The GHESKIO Center, Port-au-Prince, Haiti, [3]University of California San Francisco Medical Center, San Francisco, CA, United States

546 Efficacy of First-Line ARV Regimens: An Exploratory "Target Not Detected" Analysis

Kirsten L. White[1], Xuelian Wei[1], Lijie Zhong[1], Martin S. Rhee[1], Marshall W. Fordyce[1], Javier Szwarcberg[1], John Mellors[2], Michael D. Miller[1]

[1]Clinical Virology, Gilead Sciences, Inc, Foster City, CA, United States, [2]University of Pittsburgh, Pittsburgh, PA, United States

547 Randomized Comparison of Anthropometric Outcomes On EFV-Based Antiretroviral Therapies

Sineenart Taejaroenkul[1], Thomas Campbell[2], Laura Smeaton[3], Amita Gupta[4], Nagalingeswaran Kumarasamy[5], Karin Klingman[6], Isaac Singini[7], Javier R. Lama[8], Rosie Mngqibisa[9], **Michael Hughes[3]**, for ACTG A5175/PEARLS Study Team

[1]Chiang Mai University, Chiang Mai, Thailand, [2]University of Colorado Denver, Aurora, CO, United States, [3]Harvard School of Public Health, Boston, MA, United States, [4]Johns Hopkins University, Baltimore, MD, United States, [5]YRGCARE Medical Centre, Chennai, India, [6]NIH, NIAID, DAIDS, Bethesda, MD, United States, [7]Johns Hopkins Research Project, Blantyre, Malawi, [8]San Miguel CRS, Lima, Peru, [9]University of KwaZulu Natal, Durban, South Africa

548 NEGR1 Genetic Variants and Risk for Virological Failure With Genotypic Resistance in Botswana

Sophie Limou[1], Cheryl A. Winkler[1], Hermann Bussmann[2, 3], Vladimir Novitsky[2, 3], Sikhulile Moyo[3], Max Essex[2, 3], Richard G. Marlink[2, 3], C. William Wester[2, 4]

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Session P-J3 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

ART Simplification, Intensification, and Switch Studies

549LB Paradoxical Impact of Maraviroc/Raltegravir Added To HAART in Acute HIV Infection: ANRS 147 Trial

Antoine Chéret[1, 2], Georges Nembot[3], Adeline Mélard[1], Camille Lécuroux[4], Caroline Lascoux[5], Isabelle Ravaux[6], Jacques Reynes[7], Patrick Miailhes[8], Laurence Meyer[9], Christine Rouzioux[1]

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550LB **Randomised Controlled Trial of a PI Monotherapy Switch Strategy for Long-Term HIV Management**

Nicholas Paton[1,2], Wolfgang Stohr[2], Alejandro Arenas-Pinto[2], David Dunn[2], the PIVOT Trial Group

[1]National University of Singapore, Singapore, Singapore, [2]MRC Clinical Trials Unit at UCL, London, United Kingdom

551LB **Simplification of PI+RTV+FTC/TDF To E/C/F/TDF Maintains HIV Suppression and Is Well Tolerated**

Jose Arribas[1], Gilles Pialoux[2], Joseph Gathe[3], Giovanni Di Perri[4], Jacques Reynes[5], Pablo Tebas[6], Thai Nguyen[7], Ramin Ebrahimi[7], Kirsten White[7], David Piontkowsky[7]

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552LB **Effect of Selenium Supplementation On CD4 Depletion in Rwandan HIV Patients: A Randomized Trial**

Julius Kamwesiga[1], Vincent Mutabazi[2], Jean-Claude Tayari[2], Heather Fay[3], Dugald Seely[3], Cara Silva[3], Steve Kanters[4], Douglas J. McCready[5], Don Warren[3], **Edward Mills**[6]

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553LB **Switch From NNRTI plus FTC/TDF To E/C/F/TDF Maintains HIV Suppression and Is Well Tolerated**

Anton Pozniak[1], Martin Markowitz[2], Anthony Mills[3], Hans-Juergen Stellbrink[4], Antonio Antela[5], Pere Domingo[6], Pierre-Marie Girard[7], Keith Henry[8], Will Garner[9], Bill Guyer[9]

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Session P-K1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Viral Set Point and Elite Controllers

554 **Blunted Response To cART in Elite Controllers**

Faroudy Boufassa[1], Jerome Le Chenadec[2], Laurence Meyer[3], Dominique Costagliola[4], Peter W. Hunt[5], Florecia Pereyra[6], Steve Deeks[5], Gianfranco Pancino[7], Olivier Taulera[8], Mathias Lichterfeld[9], Pierre Delobel[10], Asier Saez-Cirion[7], Olivier Lambotte[11]

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555 **Viral Set Point After Cessation of Antiretroviral Therapy Initiated in Acute Primary HIV Infection**

Christine Durier[1], Cécile Goujard[2,3], Caroline Roussillon[4,5], Isabelle Fournier[1], Catherine Fagard[4,5], Isabelle Charreau[1], Gilles Pialoux[6,7], Bruno Hoen[8,9], Christine Rouzioux[10,11], Jean-Pierre Aboulker[1], ANRS 100 PRIMSTOP & ANRS 112 INTERPRIM study groups

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556 **HIV Elite Controllers Are Hospitalized More Often Than Persons With Medically Controlled HIV**

Trevor A. Crowell[1], Kelly A. Gebo[1], Joel N. Blankson[1], Baligh R. Yehia[2], Richard M. Rutstein[3], Stephen A. Berry[1]

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Session P-K2 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

ART Initiation, Monitoring, and Outcomes

557 **CD4 Cell Count Monitoring Frequency Among HIV+ Persons in New York City (NYC), 2007-2011**

Julie E. Myers[1,2], Qiang Xia[1], Lucia V. Torian[1], Mary K. Irvine[1], Blayne H. Cutler[1], Graham Harriman[1], Kent A. Sepkowitz[3], Colin W. Shepard[1]

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558 **Value of Viremia Copy Years in Deciding Optimal Timing of ART Initiation in Adults With HIV**

Ashley Olson[1], **Sarah Walker**[1], Amitabh Suthar[2], Caroline Sabin[3], Heiner Bucher[4], Inma Jarrin[5], Santiago Moreno[6], Santiago Perez-Hoyos[7], Kholoud Porter[1], Deborah Ford[1], CASCADE Collaboration in EuroCoord

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559 **Expansion of ART and Progressive Declines in All-Cause Mortality in British Columbia, Canada**

Christopher Cheung[1], Erin Ding[2], Julia Zhu[2], Benita Yip[2], Lillian Lourenco[2], Rolando Barrios[2], Julio Montaner[1,2], Robert S. Hogg[2,3], Viviane Lima[1,2], **David M. Moore**[1,2]

[1]University of British Columbia, Vancouver, BC, Canada, [2]BC Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada, [3]Simon Fraser University, Burnaby, BC, Canada

560 **Higher CD4 at ART Initiation Predicts Greater Long Term Likelihood of CD4 Normalization**

Frank J. Palella[1], Carl Armon[2], Joan S. Chmiel[3], John T. Brooks[4], Rachel Debes[2], Richard Novak[5], Bienvenido Yangco[6], Kathy Wood[2], Marcus Durham[7], Kate Buchacz[8]

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561 **Is CD4 Monitoring Needed Among Ugandan Clients Achieving Virologic Response To Treatment?**

Steven J. Reynolds[1,2], Joseph Sempa[3], Agnes N. Kiragga[3], Kevin Newell[4], Gertrude Nakigozi[5], Larry Chang[2], Ronald M. Galiwango[5], Ronald Gray[6], Thomas C. Quinn[2,7], David Serwadda[5,8]

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562 **Long Term Effects of Treatment Interruptions in Adults and Children**

Lindsay C. Thompson[1], Deborah Ford[1], James Hakim[2], Paula Munderi[3], Adeodata Kekitiinwa[4], Victor Musiime[5], Mutsawashe Bwakura-Dangarembizi[2], Charles F. Gilks[6], Diana M. Gibb[7], A. Sarah Walker[7]

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563 **Failure of Initial HAART in Caribbean, Central and South America**

Carina Cesar[1], Bryan E. Shepherd[2], Cathy A. Jenkins[3], Beatriz Grinsztejn[4], Marcelo Wolff[5], Jean W. Pape[6], Denis Padgett[7], Juan Sierra Madero[8], Eduardo Gotuzzo[9], Pedro E. Cahn[1], CCASANet

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564 **The HIV Treatment Cascade: Is There More To the Story?**

Baligh R. Yehia[1], Alisa J. Stephens[1], Allison L. Agwu[2], Stephen A. Berry[2], Joshua P. Metlay[3], Kelly A. Gebo[2]

[1]University of Pennsylvania, Philadelphia, PA, United States, [2]Johns Hopkins University, Baltimore, MD, United States, [3]Massachusetts General Hospital, Boston, MA, United States

565 **Cumulative Viral Load Predicts All-Cause and AIDS-Related Mortality After Initiation of ART**

Michael J. Mugavero[1], Andrew O. Westfall[2], M. John Gill[3], Michael Saag[1], Sophie Abgrall[4, 5], Gerd Fätkenheuer[6], Peter Reiss[7], Suzanne M. Ingle[8], Margaret T. May[8], Jonathan A. C. Sterne[8], on behalf of ART-CC

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Session P-K3 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

ART: Adherence and Retention

566 **Measures of ART Adherence Associated With Virological Failure in Rakai, Uganda**

Anthony Ndyanabo[1], Fred Makumbi[1, 2], Gertrude Nakigozi[1], David Serwadda[1, 2], Steven J. Reynolds[1, 3], **Larry Chang**[1, 4], Mary Grabowski[5], Maria Wawer[1, 5], Ronald Gray[1, 5], Xiangrong Kong[5]

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567 **Measures of Retention in HIV Care Differ in Their Associations With Clinical HIV Outcomes**

Baligh R. Yehia[1], Peter Rebeiro[2], Keri Althoff[2], Stephen Gange[2], Hasina Samji[3], Michael Horberg[4], Sonia Napravnik[5], Kelly Gebo[2]

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568 **Immune, Virologic and Adherence Measures as Time-Dependent Predictors of Loss To Follow-Up**

Seema T. Meloni[1], Charlotte Chang[1], Doug Hoi Cheung[1], Beth Chaplin[1], Holly Rawizza[2], Oluwatoyin Jolayemi[3], Bolanle Banigbe[3], Prosper Okonkwo[3], Phyllis Kanki[1]

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Session P-K4 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Second-Line ART

569 **Virologic Suppression With Second-Line Therapy: Does the Initial Regimen Matter?**

Kevin L. Ard[1], Lei Hua[2], Camlin Tierney[2], Eric S. Daar[3], Paul E. Sax[1]

[1]Brigham and Women's Hospital, Boston, MA, United States, [2]Harvard School of Public Health, Boston, MA, United States, [3]Harbor-UCLA Medical Center, Los Angeles, CA, United States

570 **Favorable Long-Term Outcomes of 2nd-Line ART Despite Drug-Resistant HIV-1 in Sub-Saharan Africa**

Tamara S. Boender[1], Kim C. E. Sigaloff[2], Raph L. Hamers[2], Cissy Kityo[3], Margaret Siwale[4], Mariette E. Botes[5], Kishor Mandaliya[6], Maureen Wellington[7], Suleiman Akanmu[8], Tobias F. Rinke de Wit[1]

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571 **Predictors of Time To Switch To Second Line ART After First Line Failure in Johannesburg South Africa**

Julia K. Rohr[1], Prudence Ive[2], Rebecca Berhanu[3], Kate Shearer[4], Mhairi Maskew[4], Lawrence Long[4], Ian Sanne[3, 4], Matthew P. Fox[1, 4]

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Session P-K5 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

HIV-2

572 **Dolutegravir in the French Early Access Program in Integrase HIV-2-Resistant Infected Patients**

Diane Descamps[1, 2], Gilles Peytavin[2, 3], Florence Damond[1, 2], Roland Tubiana[4], Pauline Campa[5], Marie-Aude Khuong[6], Claudine Duvivier[7, 8], Marina Karmochkine[9], Tuna Lukiana[10], Sophie Matheron[2, 11]

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573 **Long Term Outcomes of ART in HIV-2 Infection in Senegal, West Africa**

Selly Ba[1], Robert A. Smith[2], Dana N. Raugi[2], Macoumba Toure[1], Alassane Niang[3], Ibrahima Sall[3], Ousseynou Cisse[3], Moussa Seydi[1], Papa Salif Sow[1], **Geoffrey S. Gottlieb[2]**, University of Washington–Dakar HIV-2 Study Group

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574 **Raltegravir-Associated Mutations in HIV-2 Confer Cross-Resistance To Dolutegravir In Vitro**

Robert A. Smith[1], Dana Raugi[1], Charlotte Pan[1], Salif Sow[2], Moussa Seydi[3], James Mullins[4], Geoffrey Gottlieb[1], the University of Washington-Dakar HIV-2 Study Group

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575 **Predicting the Extinction of HIV-2 in Guinea-Bissau**

Helen Fryer[1], **Carla van Tienen[2, 3]**, Maarten Schim van der Loeff[4, 5], Matthew Cotten[6], Hilton Whittle[7, 8], Peter Aaby[9], Sarah Rowland-Jones[10], Thushan de Silva[10, 11]

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576 **HIV-2 X4 Tropism Is Associated With Lower CD4 Cell Count in Treatment-Experienced Patients**

Benoit Visseaux[1, 2], Charlotte Charpentier[1, 2], Caroline Rouard[1], Catherine Fagard[3], David Glohi[4], Roland Tubiana[5], Florence Damond[1, 2], Françoise Brun-Vézinet[1, 2], Sophie Matheron[2, 4], Diane Descamps[1, 2], the French HIV-2 ANRS Cohort CO5

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Session P-L1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Primary HIV Drug Resistance

577 **Current First-Line Regimens Are Effective in Patients With Single Transmitted TAM**

Claire M. F. Van Nispen tot Pannerden[1], Abdelilah El Barzouhi[2], Ard I. van Sighem[3], Jan M. Prins[4], Suzanne Jurriaans[5], Nicole K. Back[5], Kees Brinkman[6], Charles A. Boucher[7], Marchina E. Van der Ende[8], Martin Schutten[7]

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578 **Drug Resistance Mutations in Treatment-Naïve HIV-Infected Patients 2000-2013**

Nicolas A. Margot, Ross Martin, Michael D. Miller, Christian Callebaut

Clinical Virology, Gilead Sciences Inc., Foster City, CA, United States

579 **Transmitted HIV-1 Drug Resistance Among Men Who Have Sex With Men, 11 US Jurisdictions, 2008–2011**

M. Cheryl Bañez Ocfemia[1], Neeraja Saduvala[2], Alexandra M. Oster[1], David Kim[1], Richard Kline[1], Magan Pearson[1], Angela L. Hernandez[1], H. Irene Hall[1]

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580 **Primary Resistance To Integrase Strand-Transfer Inhibitors in Europe**

Maria Casadellà[1], Petra M. Ham[2], Marc Noguera-Julian[1], Christian Pou[1], Daniel Struck[3], Bonaventura Clotet[1, 4], Charles Boucher[5], Roger Paredes[1, 4], Annemarie M. J. Wensing[2], SPREAD programme

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581 **Antiretroviral Drug Resistance Among HIV-Infected Black Men Who Have Sex With Men in the US**

Iris Chen[1], Vanessa Cummings[1], Lei Wang[2], Matthew B. Connor[2], Mark A. Marzinke[1], Sheldon D. Fields[3], Darrell P. Wheeler[4], Kenneth H. Mayer[5, 6], Beryl A. Koblin[7], Susan H. Eshleman[1], for the HPTN 061 Study Team

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582 **Impact of Transmitted Drug Resistance On Susceptibility To First-Line HAART in France (2010-2012)**

Marie-Laure Chaix[1], Lambert Assoumou[2], Pierre Frange[1], Antoine Cheret[1], Laurence Morand-Joubert[3], Jean-Christophe Plantier[4], Marc Wirden[5], Florence Nicot[6], Diane Descamps[7], Laurence Meyer[8], the ANRS AC-11 Resistance Group, the ANRS PRIMO Cohort Study and the OPTIPRIM-ANRS 147 Study Group

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583 **Persistence of Transmitted HIV-1 Drug Resistance Mutations Associated With Fitness Costs**

Wan-Lin Y. Yang[1], Roger Kouyos[1], Jürg Böni[2], Sabine Yerly[3], Thomas Klimkait[4], Vincent Aubert[5], Christos Petropoulos[6], Mojgan Haddad[6], Sebastian Bonhoeffer[7], Huldrych F. Günthard[1], Swiss HIV Cohort Study (SHCS)

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Session P-L2 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Acquired HIV Drug Resistance

584 **High HIV Resistance and Mutation Accrual at Low Viral Loads Upon 2nd-Line Failure in Western Kenya**

Lameck Diero[1, 2], Allison DeLong[3], Leeann Schreier[4], Emmanuel Kemboi[2], Millicent Orido[2], Mary Rono[2], Marissa Reitsma[4], Wilfred Emonyi[2], Nathan Buziba[2], Joseph Hogan[3], **Rami Kantor[4]**

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585 **Drug Resistance After 2nd-Line Failure Can Be Managed Using WHO-Recommended Regimens in Nigeria**

Nicaise Ndembi[1], Rawlings W. Datir[1], Danjuma Sanda[1], David A. M. C. van de Vijver[2], Christopher Akolo[3], Alash'le G. Abimiku[3], William A. Blattner[3], Obinna Ogbanufe[4], Okey C. Nwanyanwu[4], Patrick Dakum[1]

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586 **Sociodemographic Determinants of HIV Drug Resistance in British Columbia, Canada**

Chanson J. Brumme[1], Melanie Rusch[2, 3], Keith Chan[1], Dmitry Shopin[1], Guillaume Colley[1], Zabrina L. Brumme[1, 4], Robert S. Hogg[1, 4], Julio S. G. Montaner[1, 5], P. Richard Harrigan[1, 5]

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587 **Week 144 Resistance Analyses of the Phase 3 EVG/COBI/FTC/TDF Studies**

Rima Kulkarni, Michael E. Abram, Martin S. Rhee, Marshall W. Fordyce, Javier Szwarcberg, Michael D. Miller, **Kirsten L. White**

Clinical Virology, Gilead Sciences, Inc., Foster City, CA, United States

588 **Emergent and Detectable Proviral DNA Drug Resistance in a Community Treatment Program**

Anne Derache[1], Hyoung Shik Shin[2], Elizabeth White[1], Dennis Israelski[1], Jeffrey D. Klausner[3], David Katzenstein[1], Peninsula AIDS Research Collaboration

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589 **Acquired Drug-Resistance Mutations and Mortality Among HIV Patients On First-Line ART**

Julia W. Wu[1], Hui Xing[2], Eric Tchetgen Tchetgen[1, 3], Lingjie Liao[2], Shahin Lockman[4, 5], Yuhua Ruan[2], Victor De Gruttola[3], Marc Lipsitch[1, 5], George R. Seage[1], Yiming Shao[2]

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590LB **PrEP Exposure and the Risk of Low-Frequency Drug Resistance**

Dara A. Lehman[1], Jared Baeten[2], Connor McCoy[3], Julie F. Weis[1], Dylan Peterson[1], Connie Celum[2], Nelly Mugo[4], Julie Overbaugh[1], Frederick Matsen[3], the Partners PrEP Study Team

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591 **Rilpivirine-Associated Resistance in HIV-1 DNA in Suppressed Patients Pretreated by NNRTIs**

Sebastien Gallien[1], Isabelle Charreau[2], Marie-Laure NERE[3], Nadia Mahjoub[3], Nathalie de Castro[1], Jean-Pierre Aboulker[4], Jean-Michel Molina[1], Constance Delaugerre[3]

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592 **Etravirine/Rilpivirine-Specific Mutations Selected by EFV and NVP in Kenyan Patients Failing ART**

Keith W. Crawford[1], Dorothy Njeru[2], Jonah Maswai[3], Milton Omondi[4], Jane Kinetto[3], Duncan Apollo[2], Appolonia Aoko[3], Raphael Langat[3], Lawrence Gitano[2], Jemutai Tarus[3], Tiffany E. Hamm[1]

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593 **Detection of NNRTI Resistance Mutations After Interrupting NNRTI-Based Regimens**

Valentina Cambiano[1], Hannah Castro[2], David Chadwick[3], Erasmus Smit[4], Anna M. Geretti[5], David Dunn[2], Andrew Phillips[1], on behalf of UK HIV Drug Resistance Database & UKCHIC study

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594 **HIV-1 Resistance Outcomes in Seroconverters From MTN 003 (VOICE)**

Urvi M. Parikh[1], Krista A. Eskay[1], Russell L. Hardesty[1], Cliff Kelly[2], Craig A. Magaret[3], Cindy Molitor[2], Zvavahera M. Chirenje[4], Jeanne Marrazzo[5], John W. Mellors[1], on behalf of the VOICE Study Team

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Session P-L3 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Mechanisms of HIV Drug Resistance

595 **Impact of Raltegravir/Elvitegravir Selected Mutations On Dolutegravir Cross-Resistance**

Wei Huang, Arne Frantzell, Jeannette M. Whitcomb, Christos J. Petropoulos

Monogram Biosciences, South San Francisco, CA, United States

596 **N348I in HIV-1 RT Confers Resistance To Etravirine and Rilpivirine But Restricts the Advent of E138K**

Veronica Zanichelli, Hong-Tao Xu, Susan Colby-Germinario, Maureen Oliveira, Yingshan Han, Yudong Quan, Mark Wainberg, Chen Liang

McGill AIDS Centre, Lady Davis Institute, Montreal, QC, Canada

597 **Analyses of Accessory Mutations in HIV-1 Protease Reveal Interdependent Mechanisms of Resistance**

Debra A. Ragland, Madhavi N.L. Nalam, Aysegül Ozen, Yufeng Cai, Hong Cao, Celia A. Schiffer

Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, Worcester, MA, United States

598LB **Two Distinct Mechanisms of Resistance To Allosteric HIV-1 Integrase Inhibitors**

Alison Slaughter[1], Kellie Jurado[2], Lei Feng[1], Nanjie Deng[3], Nivedita Jena[1], Jacques J. Kessl[1], James R. Fuchs[1], Ronald M. Levy[3], Alan Engelman[2], Mamuka Kvaratskhelia[1]

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599 **Impact of CD4 Mimetics-Resistant Mutations On Susceptibilities To Anti-Env nMAbs**

Shigeyoshi Harada[1], Samatchaya Boonchawalit[1, 2], Tetsuo Narumi[3], Hirokazu Tamamura[3], Shuzo Matsushita[2], Kazuhisa Yoshimura[1]

[1]AIDS Research Center, National Institute of Infectious Diseases, Shinjuku, Tokyo, Japan, [2]Kumamoto University, Kumamoto, Japan, [3]Tokyo Medical and Dental University, Tokyo, Japan

600 **M184I and M230I Minority Variants in ART-Naïve Patients Are Linked To APOBEC3G/F Activity**

Marc Noguera-Julian[1], Alessandro Cozzi-Lepri[2], Francesca di Giallonardo[3], Rob Schuurman[4], Martin Daümer[5], Sue Aitken[4], Huldryck F. Günthard[3], Françoise Brun-Vezinet[6], Roger Paredes[1], Karin J. Metzner[3], CHAIN Minority HIV-1 Variants Working Group

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601 **Characterising the Complex Mutational Pathways Associated With Maraviroc-Resistant HIV-1**

Xiaowei Jiang[1], Felix Feyertag[2], Conor Meehan[3], Simon Travers[4], Charles Craig[5, 6], Mike Westby[6], Marilyn Lewis[5, 6], David L. Robertson[2]

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Session P-L4 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

HIV Drug Resistance Variants

602 **Impact of Minority Drug-Resistant and X4 Variants in Naïve Patients Starting ART With <100 CD4+/mm³**

Maria Casadellà[1], Christian Manzardo[2], Susana Pérez-Álvarez[1], Daniel Podzamczer[3], Pere Domingo[4], Christian Pou[1], Marc Noguera-Julian[1], Josep M. Gatell[2], Josep M. Miró[2], Roger Paredes[1, 5]

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603 **Antiretroviral-Naïve and -Treated Patients Can Harbor Viruses in CSF More Resistant Than in Plasma**

Cathia Soulie[1], Diane Descamps[2], Maxime Grude[3], Véronique Schneider[4], Mary-Anne Trabaud[5], Laurence Morand-Joubert[6], Constance Delaugerre[7], Vincent Calvez[1], Philippe Flandre[3], Anne-Geneviève Marcelin[1], ANRS Resistance AC11 Group

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604 **Retention and Decay of HIV-1 Drug Resistance Mutations in Proviral DNA**

Justin De La Cruz[1], Saran Vardhanabhuti[2], Robert M. Rovner[1], Benjamin Pinsky[3], Ronald Bosch[2], David Katzenstein[1]

[1]Medicine, Infectious Diseases, Stanford University, Stanford, CA, United States, [2]Biostatistics, Harvard University, Cambridge, MA, United States, [3]Pathology, Stanford University, Stanford, CA, United States

605 **Prevalence of Minority Resistant Variants To ETR, DRV, and RAL at Baseline in the ANRS 139 TRIO Trial**

Charlotte Charpentier[1, 2], Lee Q. Guinevere[3], Christophe Rodriguez[4], Benoit Visseaux[1, 2], Catherine Fagard[5], Jean-Michel Molina[6], Christine Katlama[7], Yazdan Yazdanpanah[2, 8], Richard P. Harrigan[3], Diane Descamps[1, 2]

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Session P-L5 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Laboratory Detection of Drug Resistance and Tropism

606 **Pan Degenerate Amplification and Adaptation for Highly Sensitive Detection of ARV Drug Resistance**

Iain J. MacLeod[1, 2], Christopher F. Rowley[1, 3], M. Essex[1, 2]

[1]Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, MA, United States, [2]Botswana-Harvard AIDS Institute, Gaborone, Botswana, [3]Beth Israel Deaconess Medical Center, Boston, MA, United States

607 **Genotypic Tropism Testing of Proviral DNA To Guide Maraviroc Initiation in Aviremic Subjects**

Federico García[1], Eva Poveda[2], Maria Àngels Ribas[3], María Jesús Pérez-Elías[4], Onofre J Martínez-Madrid[5], Jordi Navarro[6], Antonio Ocampo[7], Félix Gutiérrez[8], Miguel García-Deltoro[9], **Roger Paredes**[10], PROTEST Study Group

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608 **Characterization of NNRTI Mutations in HIV-1 RT Using Single Molecule, Real-Time SMRT® Sequencing**

Anand Sethuraman[1], Michael P. S. Brown[2], Colleen Ludka[1], Yan Guo[1], Ellen E. Paxinos[1]

[1]Applications and Collaborations, Pacific Biosciences, Menlo Park, CA, United States, [2]Bioinformatics, Pacific Biosciences, Menlo Park, CA, United States

609 **Celera RUO Integrase Resistance Assay Performs Well Across Several Subtypes**

Carole L. Wallis[1], Raquel V. Viana[1], Elias Konstantine Halvas[2], John W. Mellors[2]

[1]Molecular Pathology, Lancet Laboratories, Johannesburg, South Africa, [2]Division of Infectious Diseases, University of Pittsburgh, Pittsburgh, PA, United States

610 **Feasibility and Clinical Utility of HIV-1 Genotype Testing in the Setting of Low-Level Viremia**

Maria Mercedes Santoro[1], Daniele Armenia[1], Claudia Alteri[1], Lavinia Fabeni[2], Domenico Di Pinto[1], Federica Forbici[2], Ada Bertoli[1, 3], Caterina Gori[2], Andrea Antinori[2], Carlo Federico Perno[2]

[1]University of Rome Tor Vergata, Rome, Italy, [2]L Spallanzani Hospital, Rome, Italy, [3]University Hospital Tor Vergata, Rome, Italy

611 **Tropism Testing by MiSeq Is Comparable To 454-Based Methods But Exhibits Contamination Issues**

Luke C. Swenson, Winnie Dong, Celia K. S. Chui, Conan K. Woods, Marjorie Robbins, Alejandro Gonzalez-Serna, Aram Karakas, Art Poon, Chanson J. Brumme, P Richard Harrigan

BC Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada

612 **A Proposed HIV Reference Sample Characterized by Three Next-Generation Sequencing Platforms**

Alejandro Gonzalez-Serna[1], Chanson J. Brumme[1], Winnie Dong[1], Eric Cai[1], Art F. Y. Poon[1], Kelly D. Huber[2], Nicolas Sluis-Cremer[3], Ellen E. Paxinos[4], Luke C. Swenson[1], Paul Richard Harrigan[1, 5]

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Session P-L6 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Cost Effectiveness Studies of ART and Drug Resistance Testing

613 **Antiretroviral Switch Strategies for Lowering Costs of Therapy: 48-Week Cost-Efficacy Analysis**

Josep M Llibre[1], Gloria Cardona[2], Jose R Santos[3], Angels Andreu[2], Xavier Bonafont[2], Bonaventura Clotet[1]

[1]HIV Unit, University Hospital Germans Trias i Pujol, Badalona, Spain, [2]Pharmacy, University Hospital Germans Trias i Pujol, Badalona, Spain, [3]University Hospital Germans Trias i Pujol, Badalona, Spain

614 **The Cost-Effectiveness of Genotype Testing for Primary Resistance in Brazil**

Paula M. Luz[1], Bethany L. Morris[2], Beatriz Grinsztejn[1], Kenneth A. Freedberg[2, 3], Valdilea G. Veloso[1], Rochelle P. Walensky[2, 4], Yoriko M. Nakamura[2], Paul E. Sax[5, 6], Claudio J. Struchiner[1], A. David Paltiel[7]

[1]Fundação Oswaldo Cruz, Instituto de Pesquisa Clinica Evandro Chagas, Rio de Janeiro, Brazil, [2]Massachusetts General Hospital, Medical Practice Evaluation Center, Boston, MA, United States, [3]Massachusetts General Hospital, Division

of General Medicine, Boston, MA, United States, [4]Massachusetts General Hospital, Division of Infectious Disease, Boston, MA, United States, [5]Harvard Medical School, Boston, MA, United States, [6]Brigham and Women's Hospital, Division of Infectious Disease, Boston, MA, United States, [7]Yale School of Public Health, New Haven, CT, United States

Session P-M1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

HIV Early Detection: Application of New Assays

615 **Application of the Geenius™ HIV1/2 Supplemental Assay for Detection of Recent HIV Infections**

Sheila M. Keating[1,2], Gary Murphy[3], Alex Welte[4], Reshma Kassanjee[4], David Matten[4], Shelley N. Facente[1], Mila Lebedeva[1], Michael P. Busch[1,2], Christopher D. Pilcher[5], Consortium for Evaluation of Performance of HIV Incidence Assays (CEPHIA)

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616 **Cost Effectiveness of Adding 4th-Generation Immunoassay Screening After a Negative Rapid HIV Test**

Angela B. Hutchinson[1], Stephanie Cohen[2], Emily Westheimer[3], Cynthia Gay[4], Elliott Marseille[5], Laura Hall[6], Lisa Hightow-Weidman[4], Benjamin Tsoi[3], Mark Pandori[7], Philip J. Peters[1]

[1]Centers for Disease Control and Prevention, Atlanta, GA, United States, [2]San Francisco Department of Public Health, San Francisco, CA, United States, [3]New York City Department of Health and Mental Hygiene, New York, NY, United States, [4]University of North Carolina at Chapel Hill, Chapel Hill, NC, United States, [5]Health Strategies International, Oakland, CA, United States, [6]ICF International, Atlanta, GA, United States, [7]San Francisco Department of Public Health Laboratory, San Francisco, CA, United States

617 **Performance of HIV Rapid Tests To Identify Seroconverters in MTN 003 (VOICE)**

Urvi M. Parikh[1], **Edward Livant[2]**, Cliff Kelly[3], Rashika Maharaj[4], Marshall W. Munjoma[5], Patrick Karugaba[6], Natasha Samsunder[7], Rosetta Lindiwe Nhlangulela[8], Jeanne Marrazzo[9], Zvavahera M. Chirenje[5], on behalf of the VOICE Study Team

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618 **Algorithms and Acute Infections: Innovations in Routine HIV Screening**

Kara I. Geren[1], Eric O. Moore[2], Robert E. Fromm[3], Dan Hobohm[4], Joy Jenkins[5], Heather L. Jordan[5], Frank LoVecchio[1], Nancy Lowman[5], Robert McGuire[6], Cheri K. Tomlinson[2]

[1]Emergency Medicine, Maricopa Integrated Health System, Phoenix, AZ, United States, [2]Grants Administration, Maricopa Integrated Health System, Phoenix, AZ, United States, [3]Administration, Maricopa Integrated Health System, Phoenix, AZ, United States, [4]Clinical Laboratory, Maricopa Integrated Health System, Phoenix, AZ, United States, [5]Adult Emergency Department, Maricopa Integrated Health System, Phoenix, AZ, United States, [6]Information Technology, Maricopa Integrated Health System, Phoenix, AZ, United States

619 **Evaluation of the Proposed US CDC Algorithm for Detection of Acute HIV Infection in Serial Samples**

Leigh Anne Eller[1], Mark Manak[1], Ashley Shutt[1], Rapee Trichavaroj[2], Joseph Oundo[3], Cornelia Lueer[4], Fatim Jallow[5], Jerome Kim[6], Merlin Robb[1], Sheila Peel[6]

[1]US Military HIV Research Program, Walter Reed Army Institute of Research/ Henry M. Jackson Foundation, Bethesda, MD, United States, [2]AFRIMS, Bangkok, Thailand, [3]Walter Reed Project, Kericho, Kenya, Kericho, Kenya, [4]Mbeya Medical Research Centre, Mbeya, Tanzania, United Republic of, [5]Makerere University Walter Reed Project, Kampala, Uganda, [6]US Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD, United States

Session P-M2 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

HIV Diagnostics

620 **Evaluation of the Hologic Aptima HIV-1 Quant Dx Assay With HIV-1 Subtypes**

Mark M. Manak[1], Holly Hack[1], Tracy Trsic[2], Sangeetha Nair[2], Andrew Worlock[2], Sheila A. Peel[3], Jennifer Malia[3], Linda Jagodzinski[3]

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621 **CAP/CTM V. 2.0 Using Dried Blood Spots Ineffective at Diagnosing Antiretroviral Treatment Failure**

Souleymane Sawadogo[1], Andreas Shiningavamwe[2], Joy Chang[3], Maher Andrew[1], Chunfu Yang[3], Esegiel Gaeb[2], Harold Kaura[2], Dennis Ellenberger[3], David Lowrance[1]

[1]CDC-Namibia, Windhoek, Namibia, [2]Namibia Institute of Pathology, Windhoek, Namibia, [3]DGHA/CGH/CDC, Atlanta, GA, United States

622 **Reliable and Accurate CD4 T Cell Count and Percent of the New Portable Flow Cytometer CyFlow MiniPOC**

Milena Nasi[1], Sara De Biasi[1], Elena Bianchini[1], Lara Gibellini[1], Marcello Pinti[1], Tiziana Scacchetti[2], Tommaso Trenti[2], Vanni Borghi[3], Cristina Mussini[3], Andrea Cossarizza[1]

[1]University of Modena and Reggio Emilia, Modena, Italy, [2]Department of Clinical Pathology, NOCSAE Baggiovara, Modena, Italy, [3]Infectious Diseases Clinics, Azienda Ospedaliero-Universitaria Policlinico of Modena, Modena, Italy

623LB **A Recombinant HIV-1 Gag Virus Panel for the Evaluation of p24-Antibodies and HIV Diagnostic Tests**

Beatrice N. Vetter, Vanessa Orlowski, Cyril Shah, Jürg Böni, Jörg Schüpbach

National Center for Retroviruses, Zurich University, Zurich, Switzerland

624 **Evaluation of Pima CD4 Point-Of-Care Device in Western Kenya for Potential Use in Field Settings**

Clement Zeh[1], Seth C. Inzaule[2], Fredrick Otieno[2], Boaz Oyaro[2], Richard Ndivo[2], Rose CE[3], Mitesh Desai[3], Robert Chen[3], Lisa A. Mills[1], Taraz Samandari[3]

[1]CDC, Kisumu, Kenya, [2]KEMRI/CDC, Kisumu, Kenya, [3]CDC, Atlanta, GA, United States

625 **Comparison of Central and Local HIV-1 RNA Quantification From Two International Clinical Trials**

Janaki Amin, Matthew Law, Anthony Kelleher, Rebekah Puls, David Cooper, Sean Emery

The Kirby Institute, University of New South Wales, Sydney, Australia

626 **HIV-1 Can Be Confirmed by Bio-Rad Geenius™ HIV 1/2 Confirmatory Assay Using Dried Blood Spots**

Carolina Fernández McPhee[1], Patricia Alvarez[1], Luis Prieto[2], Jacinta Obiang[3], Pedro Avedillo[4], Antonio Vargas[4], Pablo Rojo[5], José Tomás Ramos[2], África Holguín[1]

[1]Microbiology and Parasitology, Hospital Ramón y Cajal, Madrid, Spain, [2]Hospital de Getafe, Madrid, Spain, [3]Ministerio de Sanidad y Bienestar Social, Hospital Provincial de Bata, Bata, Equatorial Guinea, [4]Instituto de Salud Carlos III-Madrid, RICET, Centro Nacional de Medicina Tropical, Madrid, Spain, [5]Hospital Doce de Octubre, Madrid, Spain

627 **Standard Diagnostics Bioline HIV/Syphilis Duo Test: Multi-Site Laboratory Evaluation**

Claire C. Bristow[1], Yaw Adu-Sarkodie[2], Raphael O. Ondondo[3], Elizabeth Anne Bukusi[3], Claver Anoumou Dagnra[4], Khin Yi Oo[5], Jeffrey D. Klausner[6]

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Session P-N1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

HCV Testing and Epidemiology

628 **High Hepatitis C Infection Rate in Birth Cohort Testing of an Urban, Primary Care Clinic Population**

Alexander G. Geboy[1], Sandeep Mahajan[2], Allison P. Daly[1], Candice F. Sewell[2], Won K. Cho[2], Carmella A. Cole[2], Dawn A. Fishbein[2]

[1]MedStar Health Research Institute, Washington, DC, United States, [2]MedStar Washington Hospital Center, Washington, DC, United States

629 **Prevalence and Risk Factors of Hepatitis C Virus Infection in China's National Methadone Program**

Cynthia X. Shi[1,2], Aozhou Wu[3,4], Keming Rou[1], Enwu Liu[1], Yan Zhao[1], Xiaobin Cao[1], Changhe Wang[1], Wei Luo[1], Zunyou Wu[1]

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630 **The Burden of Hepatitis C Infection in Pennsylvania State Prisons and Implications for Treatment**

Madeline Mahowald[1], Sarah Larney[1,2], Nicholas Scharff[3], Curt Beckwith[1,4], Lynn E. Taylor[1,4], Nick Zaller[1,4], Timothy Flanigan[1,4]

[1]The Warren Alpert Medical School at Brown University, Providence, RI, United States, [2]National Drug and Alcohol Research Centre, Sydney, Australia, [3]Bureau of Health Care Services, Mechanicsburg, PA, United States, [4]Division of Infectious Diseases, The Miriam Hospital, Providence, RI, United States

631 **Impact of Rapid Hepatitis C Testing On Receipt of Hepatitis C Results in a Public STD Clinic**

Oluwaseun Falade-Nwulia[1,2], Shruti Mehta[3], Mark Sulkowski[1], Jackline Lasola[1], Khalil Ghanem[1], Patrick Chaulk[2], David Thomas[1]

[1]Division of Infectious Diseases, Johns Hopkins University, Baltimore, MD, United States, [2]Baltimore City Health Department, Baltimore, MD, United States, [3]Department of Epidemiology, Johns Hopkins University, Baltimore, MD, United States

632 **Hepatitis C Antigen Testing: A Reliable Alternative for Diagnosing Acute HCV Infection**

Simon George Shaw, Fiona Cresswell, Gary Homer, Mohammed Hassan-Ibrahim, Martin Fisher

HIV Medicine, Brighton and Sussex Univeristy Hospitals NHS Trust, Brighton, United Kingdom

673 **Hepatitis C Virus Incidence in the Amsterdam Cohort Study Among Men Who Have Sex With Men: 1984-2011**

Joost W. Vanhommerig[1,2], Ineke G. Stolte[1], Femke A. E. Lambers[1], Ronald B. Geskus[1,3], Thijs J. W. van de Laar[4], Martien W. Borgdorff[1,3], Sylvia M. Bruisten[1], Janke Schinkel[2], Maria Prins[1,5]

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Session P-N2 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

HCV Pre-Clinical Studies and Pharmacology

635 **Longitudinal Analysis of RAVs by PrimerID 454-Sequencing in the Boceprevir P-05063 Study**

Richard J. O. Barnard[1], Abha Chopra[2], Mark Watson[2], Don Cooper[2], Cassandra Jabara[3], Daria Hazuda[1], Stanley Lemon[3], Simon Mallal[2]

[1]Infectious Disease, Merck and Co, West Point, PA, United States, [2]Institute for Immunology & Infectious Diseases, Murdoch, Australia, [3]University of North Carolina, Chapel Hill, NC, United States

636 **ABT-493, a Potent HCV NS3/4A Protease Inhibitor With Broad Genotype Coverage**

Teresa Ng[1], Thomas Reisch[1], Tim Middleton[1], Keith McDaniel[1], Dale Kempf[1], Liangjun Lu[1], Guoqiang Wang[2], Lijuan Jiang[2], Yat Sun Or[2], Tami Pilot-Matias[1]

[1]AbbVie Inc., North Chicago, IL, United States, [2]Enanta Pharmaceuticals Inc., Watertown, MA, United States

637 **Use of Dried Blood Spots for Measuring Intracellular Ribavirin-Triphosphate**

Leah C. Jimmerson, Jia-Hua Zheng, Lane R. Bushman, Kyle P. Hammond, Peter L. Anderson, Jennifer J. Kiser

Pharmaceutical Sciences, University of Colorado, Denver, Aurora, CO, United States

638 **Ritonavir-Boosted Atazanavir, Lopinavir, & Darunavir Increase HCV NS5A Inhibitor MK-8742 Levels**

Wendy Y. Yeh[1], William Marshall[1], Joanne Ma[1], Eric Mangin[1], Xiaobi Huang[1], Patricia Jumes[1], Stephen Youngberg[2], Joan Butterton[1]

[1]Merck, Sharp and Dohme, Whitehouse Station, NJ, United States, [2]Celerion, Lincoln, NE, United States

639 **ABT-530, an HCV NS5A Inhibitor With Potent Pangenotypic Activity and High Barrier To Resistance**

Teresa Ng, Preethi Krishnan, Warren Kati, Thomas Reisch, Liangjun Lu, Tanya Dekhtyar, Akhter Molla, Christine Collins, Tami Pilot-Matias

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Session P-N3 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

HCV: Prognosis and Impact of Treatment Including Liver Transplantation

640 **FIB-4 Outperforms Liver Biopsy in the Assessment of Prognosis in HIV/HCV Coinfection**

Juan Berenguer[1], Francisco X. Zamora[2], Ana Carrero[1], Miguel Angel von Wichmann[3], José López-Aldeguer[4], María J. Téllez[5], José Sanz[6], Herminia Esteban[7], José M. Bellón[1], Juan González-García[2], and GESIDA 3603 Study Group

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641 **Sustained Virologic Response and the Risk of Liver Decompensation in HCV and HIV/HCV Patients**

Temitope O. Olufade[1], Li Wang[2], Scott Devine[1], Onur Baser[2], Vincent Lo Re[3]

[1]US Outcomes Research, Merck Sharpe & Dohme, North Wales, PA, United States, [2]STATinMED Research, Dallas, TX, United States, [3]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States

642LB **GWAS Reveals New Genetic Associations With Liver Fibrosis Progression**

Stephanie Dominguez[1,2], Sigrid Le Clerc[3], Damien Ulveling[3], Taoufik Labib[3], Maria Winnock[4], Ioannis Theodorou[5], Laurent Abel[6], Yves Levy[1,2], Dominique Salmon[7], Jean Francois Zagury[3]

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643 **Incident HCV Infections in the Swiss HIV Cohort Study: Natural History and Treatment Outcomes**

Gilles Wandeler[1,2], Janine Rohrbach[1], Karin Metzner[3], Jan Fehr[3], Marcel Stöckle[4], Matthias Cavassini[5], Juan Ambrosioni[6], Olivia Keiser[2], Hansjakob Furrer[1], Andri Rauch[1]

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644 **Is There Long-Term Evidence of Advanced Liver Fibrosis After Acute Hepatitis C in HIV Coinfection?**

Christoph Boesecke[1], Patrick Ingiliz[2], Mattias Mandorfer[3], Carolynne Schwarze-Zander[1], Florian Berger[4], Marc-Antoine Valantin[5], Jan-Christian Wasmuth[1], Thomas Reiberger[3], Stefan Mauss[4], Juergen K. Rockstroh[1], and the NEAT study group

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645 **Hepatic Decompensation in HIV/HBV/HCV Patients and the Impact of HBV Therapy**

Temitope O. Olufade[1], Li Wang[2], Scott Devine[1], Onur Baser[2], Vincent Lo Re[3]

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646 **Short-Term Risk of Decompensation Among HIV/HCV-Coinfected Patients With Significant Fibrosis**

Juan Macías[1], Manuel Márquez[2], Dolores Merino[3], Francisco Téllez[4], Antonio Rivero[5], Luis López Cortés[6], María Mancebo[1], Juan A. Pineda[1]

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647 **Differential Immune Marker Levels Linked To Liver Fibrosis in HIV/Hepatitis C (HCV) Coinfection**

Nasheed Moqueet[1], Cynthia Kanagaratham[2], Danuta Radzioch[2], Sahar Saeed[2], Marina B. Klein[1], Canadian Co-infection Cohort

[1]Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, QC, Canada, [2]McGill University, Montreal, QC, Canada

648 **Outcome of 215 HCV/HIV-Coinfected Liver Transplant Recipients: A Prospective Multicenter Study**

Jose M. Miro[1], Miguel Montejo[2], Marino Blanes[3], Abradelo Manuel[4], Santos del Campo[5], Lluis Castells[6], Antoni Rafecas[7], **Christian Manzardo**[1], Iñaki Perez[1], Antoni Rimola[1], and FIPSE investigators

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649 **Liver Fibrosis Progression Among Persons With Recently Acquired HCV Infection**

Adeel A. Butt[1,2], Peng Yan[3], Vincent Lo Re[4], Marina B. Klein[5], Matthew B. Goetz[6], David Leaf[6], Matthew S. Freiberg[1], Kenneth E. Sherman[7]

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650 **Predicting Risk of ESLD in HIV/HCV Patients for Individualized HCV Therapy Decisions**

Vincent Lo Re[1], Janet P. Tate[2], Adeel A. Butt[3], Marina B. Klein[4], Cynthia Gibert[5], David Rimland[6], Matthew B. Goetz[7], Jay R. Kostman[1], Amy C. Justice[2], Russell Localio[1]

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651 **Level of Alcohol Use and Advanced Hepatic Fibrosis in HIV-Infected and Uninfected Patients**

JP Tate[1], JK Lim[1], KJ Bryant[2], CL Gibert[3], D. Rimland[4], Mb Goetz[5], MB Klein[6], DA Fiellin[1], AC Justice[1], V. Lo Re[7]

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652 **Liver-Related Death in HIV/HCV Coinfected Individuals: Who Should Be Targeted for HCV Treatment?**

Daniel Grint[1], Lars Peters[2], Juergen K. Rockstroh[3], Aza Rakhmanova[4], Igor Karpov[5], Massimo Galli[6], Pere Domingo[7], Ole Kirk[2], Jens D. Lundgren[2], Amanda Mocroft[1]

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653 **Significant Decrease of Liver Fibrosis in HIV-HCV Coinfected Patients Treated for HCV Infection**

Marc Arthur Loko[1], Camille Gilbert[1], Karine Lacombe[2], Caroline Lascoux-Combe[2], Gilles Pialoux[2], Linda Wittkop[1], Christine Katlama[2], François Dabis[1], **Dominique Salmon**[2]

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Session P-N4 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

HCV Treatment: Real-World Experience

654LB **On-Treatment Viral Response To MK-5172/MK-8742 ± RBV for 12 Weeks in HCV/HIV-Coinfected Patients**

Mark Sulkowski[1], Josep Mallolas[2], Marc Bourliere[3], Jan Gerstoft[4], Oren Shibolet[5], Ronald Nahass[6], Edwin DeJesus[7], Melissa Shaughnessy[8], Peggy Hwang[8], Barbara Haber[8]

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655 **Slow HCV-RNA Decay and Early Resistance Predict the Risk of Failure To TVR/BOC Treatment**

Francesca Ceccherini-Silberstein[1], Valeria Cento[1], Velia Chiara Di Maio[1], Daniele Di Paolo[2], Sergio Babudieri[3], Antonio Di Biagio[4], Massimo Andreoni[5], Giustino Parruti[6], Giuliano Rizzardini[7], Carlo Federico Perno[1]

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656LB **Global Origin of HCV NS3 Substitution Q80K That Is Associated With Lower Simeprevir Susceptibility**

Art F. Poon[1], Richard H. Liang[1], Jeffrey B. Joy[1], Thuy Nguyen[1], Rosemary M. McCloskey[1], Mel Krajden[2], Julio S. G. Montaner[1], P. Richard Harrigan[1]

[1]BC Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada, [2]BC Centre for Disease Control, Vancouver, BC, Canada

658 **Protease Inhibitors To Treat Hepatitis C in the Swiss HIV Cohort Study: High Efficacy But Low Uptake**

Sebastian Haubitz[1], Verena Schaerer[2], Juan Ambrosioni[3], Matthias Cavassini[4], Marcel Stoeckle[5], Patrick Schmid[6], Laurent Decosterd[4], Karin Metzner[2], Jan Fehr[2], **Andri Rauch**[1]

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659LB **Boceprevir for Previously Treated HCV-HIV Coinfected Patients: The ANRS-HC27 BocepreVIH Trial**

Isabelle Poizot-Martin[1,2], Eric Bellissant[3,4], Philippe Colson[5,6], Alain Renault[3,4], Lionel Piroth[7], Caroline Solas[8,9], Marc Bourlière[10], Rodolphe Garraffo[11], Philippe Halfon[12], Jean-Michel Molina[13,14], and the ANRS HC27 BOCEPREVIH Study Group

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660 **Boceprevir/Telaprevir-Based Therapy in HIV-Infection: Interim Analysis of a Multicenter Cohort**

Karin Neukam[1,2], Daniela Munteanu[3,4], Antonio Rivero[5], Annette Haberl[6], Manuel Márquez[7], Patrick Ingiliz[8], Ignacio de los Santos-Gil[9], Thomas Lutz[10], Juergen K. Rockstroh[3], Juan A. Pineda[1]

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661 **Favorable Adverse Event Profile of Sofosbuvir/Ribavirin Versus Standard of Care for Hepatitis C**

Kerry Townsend[1], Shivakumar Narayanan[2], Amy Nelson[1], Adrian Majid[2], Luciano Kapelusznik[2], Robert R. Redfield[2], Shyamasundaran Kottilil[1], Rohit Talwani[2], Anuoluwapo Osinusi[1,2]

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662LB **IFN-Free 3 DAA Regimen in HCV Genotype 1-Infected Patients On Methadone or Buprenorphine**

Jacob Lalezari[1], J Greg Sullivan[2], Peter Varunok[3], Edward Galen[4], Kris V. Kowdley[5], Vinod Rustgi[6], Humberto Aguilar[7], Franco Felizarta[8], Daniel Cohen[9], Hui Tang[9]

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663 **Telaprevir Treatment of HIV/HCV G1 Patients With Severe Fibrosis: Efficacy Results To Week 16**

Andrea Gori[1], Manuela Doroana[2], Oksana Chernova[3], Jürgen Rockstroh[4], Denes Bánhegyi[5], Colm Bergin[6], Gabriella Verucchi[7], Andrew Hill[8], Blanca Hadacek[9], Mark Nelson[10]

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664LB **Telaprevir Increases Ribavirin Toxicity Through eGFR Decrease in HIV-HCV Coinfected Patients**

Laurent Cotte[1,2], Aurélie Barrail-Tran[3,4], Corine Vincent[5], Marc-Antoine Valantin[6,7], Isabelle Fournier[5], Karine Lacombe[8], Stéphane Chevaliez[9,10], Jean-Pierre Aboulker[5], Anne-Marie Taburet[3,4], Jean-Michel Molina[11,12]

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665LB **Safety and Efficacy of IFN-Free, Sofosbuvir/RBV Therapy in HIV/HCV Liver Transplanted Patients**

Ana Moreno[1], **María J. Pérez-Elías**[1], Rafael Bárcena[2], Carmen Quereda[1], Jose L. Casado[1], Fernando Dronda[1], Santos del Campo[2], Maria L. Mateos[3], Alberto Diaz[1], Santiago Moreno[1]

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666 **ss469415590 Variant Is a Better Predictor Than IL28B rs12979860 of PegIFN-α/RBV Therapy Failure**

Sandra Franco[1], Ester Aparicio[1], Mariona Parera[1], Bonaventura Clotet[1,2], Cristina Tural[1,2], Miguel Angel Martinez[1]

[1]IrsiCaixa, Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona, Badalona, Spain, [2]Fundació de la Lluita contra la SIDA, Badalona, Spain

667 **Pill Burden & Treatment Length Reduce Adherence To IFN-Free Hepatitis C Therapy in an Urban Cohort**

Tess Petersen[1], Lori A. Gordon[2], Kerry Townsend[3], Monica Calderon[4], Sreetha Sidharthan[1], Rachel Silk[4], Anu Osinusi[3,5], Henry Masur[1], Shyam Kottilil[3], Anita Kohli[1,4]

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668 **Telaprevir in Treatment-Experienced HIV-HCV G1 Coinfected Patients (ANRS HC26 TelapreVIH)**

Laurent Cotte[1,2], Corinne Vincent[3], Philippe Sogni[4,5], Isabelle Fournier[3], Hugues Aumaître[6], Pierre De Truchis[7], Isabelle Rosa[8], Stéphane Chevaliez[9], Jean-Pierre Aboulker[10], Jean-Michel Molina[4,11]

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Session P-N5 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

HCV: The Cascade

669 **The Treatment Cascade for People With Chronic Hepatitis C Virus Infection in the United States**

Baligh R. Yehia[1], Asher Schranz[2], Craig Umscheild[1], Vincent Lo Re[1]

[1]University of Pennsylvania, Philadelphia, PA, United States, [2]New York University, New York, NY, United States

670 **Initial Results of a Community-Based Rapid Hepatitis C Testing and Linkage To Care Program**

Christian B. Ramers[1], Robert Lewis[1], Letty Reyes[1], Alexander Kuo[2], David L. Wyles[3]

[1]Special Populations, Family Health Centers of San Diego, San Diego, CA, United States, [2]Hepatology and Liver Transplantation, University of California San Diego Health Sciences, San Diego, CA, United States, [3]Infectious Diseases, University of California San Diego Health Sciences, San Diego, CA, United States

671 **The CORE HCV Cascade a Decade Later: Looking Ahead To an IFN-Free Era**

Oluwatoyin M. Adeyemi, Stephon Effinger, Benjamin Go, Sonia Vibhakar, Maureen Gallagher, Deborah Wolen, Becky Goldberg, Mike Demetria, David Barker, Gregory Huhn

Ruth M Rothstein CORE Center, Cook County Health and Hospitals System, Chicago, IL, United States

672 **The Hepatitis C Cascade of Care Among HIV-Infected Patients Following Diagnosis of HCV Infection**

Edward R. Cachay[1], Lucas Hill[2], David Wyles[1], Francesca Torriani[1], Bradford Colwell[2], Craig Ballard[2], William Christopher Mathews[1]

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Session P-N6 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Acute HCV Infection: Pathogenesis

674 **Assessing HCV Acquisition Routes in HIV-Infected MSM Using Single Genome Sequencing-A Pilot Study**

Daniel S. Fierer[1], Andrew H. Talal[2], Kristen M. Marks[3], Wouter O. van Seggelen[1], Andrea D. Branch[4], Shirish Huprikar[1], Shuyi Wang[5], George M. Shaw[5], Hui Li[5]

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675 **Higher Risk of Sexually Acquired HCV Coinfection in MSM With Wide HIV Transmission Bottleneck**

Roger D. Kouyos[1], Andri Rauch[2], Dominique Braun[1], Sabine Yerly[3], Jürg Böni[4], Thomas Klimkait[5], Vincent Aubert[6], Bruno Ledergerber[1], Hulrdrych Günthard[1], The Swiss HIV Cohort Study (SHCS)

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676 **Seminal HCV RNA Level May Mirror Dynamics of Plasma HCV RNA in HIV-Positive Men With Acute HCV**

Daniel Bradshaw[1], Francois Lamoury[1], Beth Catlett[2], Tanya L. Applegate[1], John Mcallister[2], Gregory J. Dore[1], Gail Matthews[1], Mark Danta[3]

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677 **HCV Viral Load Kinetics During Acute Hepatitis C in HIV-Infected Patients: A Model-Based Analysis**

Romain Ragonnet[1], Christoph Boesecke[2], Marguerite Guiguet[3], Karine Lacombe[4, 5], Jeremie Guedj[1], Jürgen K. Rockstroh[2], **Yazdan Yazdanpanah[1, 6]**, Sylvie Deuffic-Burban[1, 7]

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Session P-N7 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

HCV Infection and Cellular and Humoral Immune Responses

678 **Impaired CD8+ T Cell IL-7 Activity in HCV Infection: Implications for HIV-HCV Co-Infection**

Stephanie C. Burke[1, 2], Lorna Carrasco-Medina[2], Curtis L. Cooper[2, 3], Angela M. Crawley[1, 2]

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679 **HCV and GBV-C NS5A Proteins Inhibit TCR-Mediated Activation of Human CD4+ T Cells**

Nirjal Bhattarai, Bennett E. Thompsaon, James H. McLinden, Jinhua Xiang, **Jack T. Stapleton**

University of Iowa and Iowa City VA, Iowa City, IA, United States

680 **Impact of HCV Coinfection On T-Cell Dynamics in Long-Term HIV Suppressors Under cART**

Olivia Zaegel[1], Sylvie Bregigeon[1], Carla E. Cano[1], Véronique Obry-Roguet[1], Corinne Nicolino-Brunet[2], Catherine Tamalet[3, 4], Françoise Dignat-George[2], **Isabelle Poizot-Martin[1, 5]**

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681 **CD3+CD56+ Natural Killer-Like T Cells in HIV(+) Patients With Acute Hepatitis C**

Pavlos Kokordelis[1, 2], Benjamin Krämer[1, 2], Christoph Boesecke[1, 2], Esther Voigt[3], Patrick Ingiliz[4], Andreas Glässner[1, 2], Ulrich Spengler[1, 2], Jürgen K. Rockstroh[1, 2], Jacob Nattermann[1]

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682 **The Effect of Hepatitis C (HCV) Clearance On Macrophage Activation in HIV/HCV Coinfection**

Kara W. Chew[1], Lei Hua[2], Debika Bhattacharya[1], Adeel A. Butt[3], Martha Lewis[1], Raymond T. Chung[4], Janet W. Andersen[2], Judith S. Currier[1]

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683 **HIV Patients Develop High Levels of Broadly Neutralizing Antibodies Against Hepatitis C Virus**

Quentin Lepiller[1, 2], Catherine Fauvelle[2], Laura Heydmann[2], Christiane Moog[2], David Rey[3], Olivier Lambotte[4], Nicolas Meyer[5, 6], Heidi Barth[2, 7], Françoise Stoll-Keller[1, 2], **Samira Fafi-Kremer[1, 2]**

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684 **Activation and Senescence Markers in HCV-Infected Patients On PegIFN/RBV/Telaprevir Tritherapy**

Isabelle Pellegrin[1], Céline Cognet[1], Pascale Trimoulet[2], Juliette Foucher[3], Julien Vergniol[3], Wassil Merrouche[3], Jean-Luc Taupin[4], Linda Wittkop[5], Jean-François Moreau[4], Victor de Ledinghen[3]

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Session P-N8 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

HCV-Related Outcomes: Cardiac and Non-Liver

685 **HCV Viremia and the Risk of Acute Myocardial Infarction at Various Lipid Levels**

Adeel A. Butt[1, 2], Kara W. Chew[3], Kathleen Corey[4], Raymond T. Chung[4], Javed Butler[5], Kenneth E. Sherman[6], Matthew S. Freiberg[1], Sebhat Erqou[7]

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Cincinnati, OH, United States, [7]Weill Cornell Medical Center, New York, NY, United States

686 Association of Coinfection With HBV, HCV, or Both On Survival Among HIV-Infected Adults

Tanyaporn Wansom[1], Catherine G. Sutcliffe[2], Shruti H. Mehta[2], Carleigh L. Benton[1], Richard C. Moore[1], David T. Thomas[1], Mark S. Sulkowski[1]

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687 Incidence Rates and Risk Factors for Severe Bacterial Infections in HIV/HCV-Coinfected Patients

Kathleen C. Rollet[1], John Gill[2], Curtis Cooper[3], Mark Hull[4], Joseph Cox[5], Bryan Conway[6], Neora Pick[7], Marie-Louise Vachon[8], Marina B. Klein[1]

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688 Association of HIV and HCV Coinfection With Cardiovascular Disease Outcomes Among US Veterans

Sebhat E. Erqou[1], Arpan Mohanty[2], Adeel A. Butt[3]

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689 Performance of the Framingham Risk Score in Hepatitis C-infected Persons

Kara W. Chew[1], Debika Bhattacharya[1], Kathleen McGinnis[2], Judith S. Currier[1], Adeel A. Butt[3]

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690 HCV Accelerates Non-Liver Mortality in HIV-Infected Patients: A Nationwide Cohort Study

Vincent Mallet[1,2], Sophie Thiébaut[3], Yazdan Yazdanpanah[4,5], Stanislas Pol[1,2], Michael Schwarzinger[3,5]

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Session P-N9 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

HBV and HDV

691 The Role of HBV Quasispecies Diversity & Other Factors in Residual HBV Viremia On TDF-Based cART

Jennifer Audsley[1,2], **Anchalee Avihingsanon[3]**, Gail Matthews[4], Margaret Littlejohn[5], Stephen Bent[6], Lilly Yuen[5], Fabio Luciani[7], Stephen Locarnini[5], Sharon Lewin[1,2], Joe Sasadeusz[2]

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692 Therapeutic Management and Evolution of Chronic Hepatitis B: Does HIV Coinfection Still Matter?

Lionel Piroth[1], Stanislas Pol[2], Patrick Miailhes[3], Karine Lacombe[4], Amanda Lopes[5], Françoise Borsa-Lebas[6], Dominique Salmon[7], Eric Rosenthal[8], Fabrice Carrat[9], Patrice Cacoub[10]

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693 Increased Hepatitis B Virus Coinfection Screening Following a Change in Zambian HIV Guidelines

Kalo Musukuma[1], Arianna Zanolini[1,2], Lloyd Mulenga[1,3], Carolyn Bolton-Moore[1,4], Samuel Zuercher[5], **Izukanji Sikazwe[1]**, Aggrey Mweemba[3], Gilles Wandeler[6], Benjamin H. Chi[1,4], Michael J. Vinikoor[1,2]

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694 HBsAg Genetic Elements Critical for Immune Escape Drive HBV Reactivation Upon Immunosuppression

Romina Salpini[1], Claudia Alteri[1], Maria-Concetta Bellocchi[1], Emanuela Balestra[1], Claudio Mastroianni[2], Aldo Marrone[3], Massimo Andreoni[1], Mario Angelico[1], Carlo-Federico Perno[1], **Valentina Svicher[1]**

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695 Isolated Hepatitis B Core Antibody Is Associated With Advanced Hepatic Fibrosis

Debika Bhattacharya[1], Chi-hong Tseng[1], Jan Tate[2,3], Vincent Lo Re[4,5], Cynthia Gibert[6,7], Joseph K. Lim[2,3], Maria Rodriguez-Barradas[8,9], David Rimland[10,11], Amy C. Justice[2,3], Matthew B. Goetz[12,13]

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696 Isolated Hepatitis B Core Antibody and Hepatic Fibrosis in HIV/HCV-Coinfected Women

Audrey L. French[1,2], Anna Hotton[3], Mary Young[4], Marek Nowicki[5], Michael Augenbraun[6], Kathryn Anastos[7], Marion Peters[8]

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697 Effectiveness of Taiwan Nationwide HBV Vaccination in Persons at Risk for HIV Infection

Hsin-Yun Sun[1], Chia-Jui Yang[2], Nan-Yao Lee[3], Shiou-Haur Liang[4], Chien-Ching Hung[1]

[1]National Taiwan University Hospital, Taipei, Taiwan, [2]Far Eastern Memorial Hospital, New Taipei City, Taiwan, [3]National Cheng Kung University Hospital, Tainan, Taiwan, [4]E-Da Hospital, Kaohsiung, Taiwan

698 Hepatitis B Virus Mother-To-Child-Transmission Among HIV-Infected Pregnant Women in Kenya

Timothy D. Minniear[1,2], Alex Morwabe[3], Sonali Girde[1,4], Fredrick Harrison[3], Frank Angira[3], Boaz Oyaro[5], Lisa A. Mills[1,3], Clement Zeh[1,3], **Philip J. Peters[1]**

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699 **Vaccine Escape Mutants and Suboptimal Hepatitis B Virus Response in HIV HBV Coinfected Patients**

Anders Boyd[1], Raoul Moh[2], Paul Dény[3], Mariama Issoufou[3], Christine Danel[2], Xavier Anglaret[2], Serge Eholié[2], Pierre-Marie Girard[4], Fabien Zoulim[3], Karine Lacombe[4]

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700 **Long-Term Benefit of Tenofovir On Hepatitis Delta**

Rocio Sierra-Enguita, Zulema Plaza, Eugenia Vispo, Pablo Barreiro, Pablo Labarga, José Vicente Fernández-Montero, Carmen De Mendoza, Vicente Soriano

Infectious Diseases, Hospital Carlos III, Madrid, Spain

Session P-N10 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

HEV

633 **Chronic Hepatitis E Virus Infection Is Uncommon in HIV-Infected Patients**

Antonio Rivero-Juárez[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]

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634 **High Frequency of HEV Seropositivity in HIV-Infected Patients in Southern Spain**

J. A. Pineda, M. Parra, C. Cifuentes, K. Neukam, J. C. Palomares, E. Pérez-Navarro, L. M. Real, N. Merchante, F. Lozano, J. Macías

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Session P-O1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Lymphoma/Liver/Gammopathy

701 **Monoclonal Gammopathy and HIV-1 Infection: Evolution With Highly Active Antiretroviral Therapy**

Marie-Laure Casanova[1], **Alain Makinson**[2]

[1]Infectious Diseases, CHU Gui de Chauliac, Montpellier, France, [2]Infectious Diseases, University Hospital Montpellier, Montpellier, France

702 **Predicting Survival of HIV-Infected Patients With Liver Cancer: The SHILCA Score and Staging Model**

Nicolas Merchante[1], Ting-Yi Chen[2], Eugenia Vispo[3], Mamta Jain[2], Emma Page[4], Pablo Barreiro[3], Mark Nelson[4], Judith Aberg[5], Juan A. Pineda[1], Jorge Marrero[2], Norbert Bräu[6, 7]

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703 **Different Immunologic and Virologic Contexts for HIV-Associated Lymphoma in the CNICS Cohort**

Satish Gopal[1], Monita Patel[1], Chad Achenbach[2], Elizabeth Yanik[1], Stephen Cole[1], Sonia Napravnik[1], Kristy Richards[1], Joseph Eron[1], for the CNICS Investigators

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Session P-O2 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Cancer: Natural History and Epidemiology

704 **Risk of Cancer Among HIV Patients Compared To the Background Population: Impact of Smoking and HIV**

Marie Helleberg[1], Jan Gerstoft[1], Shoaib Afzal[2], Gitte Kronborg[3], Carsten S. Larsen[4], Stig E. Bojesen[2], Court Pedersen[5], Börge G. Nordestgaard[2], Niels Obel[1]

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705 **Cancer Stage at Diagnosis in HIV-Infected Individuals and Transplant Recipients**

Meredith S. Shiels[1], Glenn Copeland[2], Marc Goodman[3], Charles F. Lynch[4], Karen Pawlish[5], Ruth M. Pfeiffer[1], Jon J. Snyder[6], Eric A. Engels[1]

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706 **Cancer Incidence in a Nationwide HIV/AIDS Patient Cohort in Taiwan in 1998-2009**

Yi-Ming A. Chen[1], Marcelo Chen[2], Ian Jen[3], Matthew G. Law[4], Kishor Bhatia[5], Gerald B. Sharp[6]

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707 **Excess Burden of Cancer Among HIV-Infected Persons in the United States**

Hilary A. Robbins[1], Meredith S. Shiels[1], Ruth M. Pfeiffer[1], Jianmin Li[2], H. Irene Hall[2], Eric A. Engels[1]

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Session P-O4 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Kaposi Sarcoma, PEL, and KSHV

708 **The Effect of Protease Inhibitor Use On Kaposi Sarcoma Incidence in a cART-Experienced Cohort**

Elizabeth Chiao, Marc Kowalkowski

Baylor College of Medicine, Houston, TX, United States

709 **Guidelines On Kaposi's Sarcoma Treatment: Results From Two Cochrane Systematic Reviews**

Esther E. Freeman[1], Charles Okwundu[2], Oluwatoyin Gbabe[3], Miriam Laker[4], Philippa Easterbrook[5], Toby Maurer[6], Jeffrey Martin[4]

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710 **Randomized Trial of Protease Inhibitor-Based Antiretroviral Therapy for Kaposi Sarcoma in Africa**

Jeffrey Martin[1], Miriam Laker-Oketta[1, 2], Victoria Walusansa[3], Jackson Orem[3], John Bennett[1], Adrienne Mocello[1], Toby Maurer[1], Peter Hunt[1], Andrew Kambugu[2], Edward Mbidde[2, 4]

[1]University of California San Francisco, San Francisco, CA, United States, [2]Infectious Diseases Institute, Kampala, Uganda, [3]Uganda Cancer Institute, Kampala, Uganda, [4]Uganda Virus Research Institute, Entebbe, Uganda

711 **Kaposi Sarcoma in the Era of Combination Antiretroviral Therapy**

Natascha Wyss, Matthias Egger, Julia Bohlius, Malignancy Working Group for COHERE in EuroCoord

Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

712 **Vitamin D Insufficiency in AIDS-Associated Kaposi Sarcoma in Zimbabwe**

Kristine M. Erlandson[1], Ivy Gudza[2], Suzanne Fiorillo[1], Buxton Ndemera[2], Robert T. Schooley[3], Lovemore Gwanzura[4], Margaret Borok[2], Thomas B. Campbell[1]

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713 **Primary Effusion Lymphoma and HIV Infection: 51 Patients From a Single Institution**

Stephanie Guillet[1], **Laurence Gerard**[1, 2], Veronique Meignin[3], Felix Agbalika[4], Wendy Cuccuini[5], Lionel Galicier[1, 2], Eric Oksenhendler[1, 2]

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714 **Indoleamine 2, 3-Dioxygenase (IDO) Activity as a Determinant of Kaposi Sarcoma in Africa**

Helen Byakwaga[1, 2], Peter W. Hunt[1], Miriam Laker-Oketta[1, 3], David V. Glidden[1], Yong Huang[1], Mwebesa Mwebesa[2], Victoria Walusansa[4], David R. Bangsberg[5], Edward Mbidde[3], Jeffrey N. Martin[1]

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Session P-O5 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Cervical Cancer, HPV, and HPV Vaccine

715 **Epidemiology and Dynamics of HPV Infection in Romanian Women Infected With HIV in Early Childhood**

Sanjay R. Mehta[1], Lumi Ene[2], Cristina Voinea[2], Claudia Stefanescu[2], Diana Sima[2], Dan Duiculescu[2, 3]

[1]Medicine, University of California San Diego, La Jolla, CA, United States, [2]"Dr. Victor Babes" Hospital for Infectious and Tropical Diseases, Bucharest, Romania, [3]Titu Maiorescu University, Bucharest, Romania

716 **Baseline Data of a Phase 3 Trial of the Quadrivalent HPV Vaccine in HIV+ Males and Females: ACTG 5298**

Ross Cranston[1], Ming Yang[2], Pawel Paczuski[2], Michelle Cespedes[3], Elizabeth Chiao[4], Jennifer Webster-Cyriaque[5], Catherine Godfrey[6], Timothy Wilkin[7]

[1]University of Pittsburgh, Pittsburgh, PA, United States, [2]Harvard University, Cambridge, MA, United States, [3]New York University School of Medicine, New York, NY, United States, [4]Houston VA Medical Center, Houston, TX, United States, [5]University of North Carolina at Chapel Hill, Chapel Hill, NC, United States, [6]DAIDS, NIAID, NIH, Bethesda, MD, United States, [7]Weill Cornell Medical College, New York, NY, United States

717 **Cervical Abnormalities in HIV-Infected South African Women With High Screening and Referral Rates**

Ingrid T. Katz[1, 2], Alexi A. Wright[2, 3], Tamaryn L. Crankshaw[4, 5], Janet Giddy[4, 6], Sean Mould[4, 7], Lisa M. Butler[2, 8]

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Session P-O6 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Anal Cancer and HPV

718 **Prevalence of Anal Dysplasia in HIV-Infected Women From Johannesburg, South Africa**

Bridgette Goeieman[1, 2], Cynthia Firnhaber[1, 2], Pamela Michelow[1, 3], Avril Swarts[1], Jennifer S. Smith[4], Timothy Wilkin[5]

[1]University of Witwatersrand, Johannesburg, South Africa, [2]Right to Care, Johannesburg, South Africa, [3]National Health Laboratory Services, Johannesburg, South Africa, [4]University of North Carolina, Chapel Hill, NC, United States, [5]Weill Cornell Medical College, New York, NY, United States

719 **Mucosal and Systemic Immune Responses in HIV/HPV Co-Infected Males**

Laura Comi[1], **Camilla Tincati**[1], Giusi Maria Bellistri[1], Alessandro Pandolfo[1], Javier Sanchez Martinez[1], Veronica Rainone[2], Marco Rovati[3], Daria Trabattoni[2], Antonella d'Arminio Monforte[1], Giulia Marchetti[1]

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720 **Natural History of HIV-Related Anal Dysplasia: A Multi-State Modeling Analysis**

Wollelaw W. Agmas[1], Edward R. Cachay[1], Christopher Jackson[2], Wm. Christopher Mathews[1]

[1]Internal Medicine, University of California San Diego, La Jolla, CA, United States, [2]Public Health, Medical Research Council Biostatistics Unit, Cambridge, United Kingdom

721 **Antiretroviral Therapy as Protector Factor of Anal Dysplasia in HIV-Infected MSM**

Carmen Hidalgo Tenorio[1], Concepcion Gil Anguita[1], Jessica Ramirez Taboada[1], Juan Gabriel Martínez Cara[2], Javier Esquivias[3], Pablo Palma[4], Mar Rivero[1], Rosario Javier Martinez[1], Miguel Angel Lopez Ruz[1], Juan Pasquau Liaño[1]

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722 **HPV16-Specific T-Cell Responses and Spontaneous Regression of Anal Intraepithelial Neoplasia**

Winnie W. Y. Tong[1], Kelsee Shepherd[1], Fengyi Jin[2], John Zaunders[1, 2], Richard J. Hillman[1], Andrew E. Grulich[2], Anthony Kelleher[1, 2], Andrew Carr[1]

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Session P-P1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Heart Failure, Cardiac Steatosis, and HIV

723 **Elevated NT-proBNP Levels Predict Mortality in HIV-Infected Women**

Matthew R. Gingo[1], Kidane Ghebrehawariat[1], Jong-Hyeon Jeong[1], Yanxia Chu[1], Quanwei Yang[1], Lorrie Lucht[1], David Hanna[2], Jason Lazaar[3], Mark Gladwin[1], Yingze Zhang[4], Alison Morris[1]

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724 **Cardiac Steatosis Increased in HIV: Related To Gender, Visceral Fat and ARV Exposure**

Julia B. Purdy[1], Chia-Ying Liu[2], Sabrina Mangat[3], Horacio Duarte[4], Diana Thiara[5], Nancyanne Schmidt[6], Jamie Hur[7], Christopher T. Sibley[2], David A. Bluemke[2], Colleen Hadigan[3]

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725 **ST2 and GDF-15 Are Associated With Structural Heart Disease and Mortality in HIV**

Eric Secemsky[1], Rebecca Scherzer[2], Elaine Nitta[2], Alan Wu[2], David Lange[2], Steven Deeks[2], Jeffrey Martin[2], James Snider[2], Peter Ganz[2], Priscilla Hsue[2]

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726 **Depression and HIV Are Risk Factors for Incident Heart Failure Among Veterans**

Jessica R. White[1], Chung-Chou H. Chang[1, 2], Adeel A. Butt[2, 3], Hilary A. Tindle[2], Maria C. Rodriguez Barradas[4, 5], David Rimland[6, 7], David Leaf[8, 9], Matthew Budoff[10, 11], Amy C. Justice[12, 13], Matthew S. Freiberg[2, 3]

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Session P-P2 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Immune Activation, Immunodeficiency, and CVD

727 **Impact of Low CD4 Count and HIV Persistence On Endothelial Function in Patients With Low Plasma RNA**

Amanda Schnell Heringer[1], Hiroyu Hatano[2], Peter W. Hunt[2], Yuaner Wu[1], Yifei Ma[3], Rebecca Scherzer[4, 5], Jeffrey N. Martin[2, 6], Peter Ganz[1], Steven G. Deeks[2], Priscilla Y. Hsue[1]

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728 **Carotid Distensibility and Immune Activation in HIV-Infected Patients Without Coronary Calcium**

Chris T. Longenecker[1, 2], Ying Jiang[1], Sara Debanne[1], Grace A. McComsey[1, 2]

[1]Case Western Reserve University, Cleveland, OH, United States, [2]University Hospitals Case Medical Center, Cleveland, OH, United States

729 **Microvascular Disease in Controllers Is Mediated by HIV DNA and Immune Dysfunction**

Hiroyu Hatano[1], Yifei Ma[2], Rebecca Scherzer[1, 3], Yuaner Wu[1], Elaine Nitta[1], Kara Harvill[1], Elizabeth Sinclair[1], Michael P. Busch[4, 5], Steven G. Deeks[1], Priscilla Y. Hsue[1]

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730 **Monocyte But Not Cellular Activation Is Associated With Coronary Atherosclerosis in the MACS**

Eric S. Daar[1], Wendy S. Post[2], Annie T. Darilay[2], Peter W. Hunt[3], Todd T. Brown[2], Rebeccah McKibben[2], Beth Jamieson[4], Mathew J. Budoff[1], Mallory D. Witt[1]

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Session P-P3 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Alcohol, Smoking, and Atherosclerosis

731 **The J-Curve in HIV: Better Cardiovascular-Disease-Free Survival With Moderate Alcohol Intake**

Gilles Wandeler[1, 2], David Kraus[1], Jan Fehr[3], Anna Conen[4], Alexandra Calmy[5], Christina Orasch[6], Manuel Battegay[7], Patrick Schmid[4], Enos Bernasconi[8], **Hansjakob Furrer**[2], Swiss HIV Cohort Study

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732 **Soluble CD14 and D-Dimer Are Associated With Smoking and Heavy Alcohol Use in HIV-Infected Adults**

Patricia A. Cioe[1], Jason Baker[2], John Hammer[3], Erna M. Kojic[4], Nur Onen[5], Pragna Patel[6], Christopher W. Kahler[7]

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733 **Antiviral Therapy and Smoking Associated With Coronary Vessel Thickening in HIV-Infected Youth**

Aylin Unsal[1], Khaled Z. Abd-Elmoniem[2], Sarah Eshera[2], Julia B. Purdy[3], Rohan Hazra[4], Colleen Hadigan[1], Ahmed M. Gharib[2]

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Session P-P4 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Risk Factors and Incidence: MI and Stroke

734 **HIV Infection and the Risk of Cardiovascular Disease in Women**

Julie A. Womack[1], Chung-Chou H. Chang[2, 3], Kaku A. Armah[3], Kathleen McGinnis[4], Matthew B. Goetz[5, 6], Cynthia L. Gibert[7, 8], Sheldon T. Brown[9, 10], Alberta L. Warner[5], Amy C. Justice[4, 11], Matthew S. Freiberg[12, 13], for the VACS Project Team

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735 **Depression Predicts Incident Myocardial Infarction in HIV+ Veterans: Veterans Aging Cohort Study**

Tasneem Khambaty[1], Jesse C. Stewart[1], Samir K. Gupta[2], Chung-Chou H. Chang.[3], Adeel A. Butt[3], Cynthia L. Gilbert[4], Hilary A. Tindle[3], Heidi Crane[5], Roger Bedimo[6], Matthew S. Freiberg[3], on behalf of the VACS project team

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736 **HIV Infection, Cardiovascular Risk Factor Profile, and Risk for Acute Myocardial Infarction**

Anne-Lise Paisible[1], Joyce Chang[2], Kaku Armah[3], Matthew B. Goetz[4], Adeel A. Butt[5, 6], Maria C. Rodriguez-Barradas[7, 8], David Rimland[9, 10], Sheldon T. Brown[11, 12], Amy C. Justice[13, 14], Matthew S. Freiberg[1], the VACS Project Team

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737 **No Difference in Incidence of Myocardial Infarction for HIV+ and HIV- Individuals in Recent Years**

Daniel B. Klein[1], Wendy A. Leyden[2], Chun R. Chao[3], Michael A. Horberg[4], William J. Towner[5], Leo B. Hurley[2], Charles P. Quesenberry[2], Michael J. Silverberg[2]

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738 **MACE Incidence Among HIV- and Non-HIV-Infected Patients in a Clinical Care Cohort**

Virginia A. Triant, Susan Regan, Steven Grinspoon

Massachusetts General Hospital, Boston, MA, United States

739 **Lower CD4 Count and Higher Viral Load Are Associated With Increased Risk of Myocardial Infarction**

Daniel R. Drozd[1], Robin M. Nance[1], Joseph A. C. Delaney[1], Greer A. Burkholder[2], William C. Mathews[3], Richard D. Moore[4], Joseph J. Eron[5], Peter W. Hunt[6], Mari M. Kitahata[1], Heidi M. Crane[1], Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) Cohort

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740 **Long-Term Effects of Nitrite Inhalants On Cardiovascular and Renal Outcomes in the MACS Cohort**

Alex Holman, Anupriya Dutta, **Dana Gabuzda**

Dana-Farber Cancer Institute, Boston, MA, United States

741 **HIV Infection and Immunodeficiency as Risk Factors for Ischemic Stroke**

Julia L. Marcus[1], Wendy A. Leyden[1], Chun R. Chao[2], Felicia C. Chow[3], Michael A. Horberg[4], Leo B. Hurley[1], Daniel B. Klein[5], Charles P. Quesenberry[1], William J. Towner[6], Michael J. Silverberg[1]

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Session P-P5 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Antiretroviral Therapy, Lipids, and CVD

742 **Antiretroviral Therapy Is Associated With Significant Changes in Plasma Lipidome**

Janine M. Trevillyan[1, 2], Gerard Wong[3], Rebekah Puls[4], Kathy Petoumenos[4], Sean Emery[4], Natalie Mellett[3], Peter J. Meikle[3], Jennifer F. Hoy[1, 2]

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743 **Rosuvastatin Lowers Cystatin C in HIV-Infected Subjects On Antioretroviral Therapy: SATURN-HIV**

Chris T. Longenecker[1, 2], Corrilynn O. Hileman[1, 3], Norma J. Storer[1, 2], Dani E. Labatto[1, 2], Grace A. McComsey[1, 2]

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744 **Abacavir Induces Leukocyte Accumulation Through the Interaction of ATP and $P2X_7$ Receptors**

Carmen de Pablo[1, 2], Samuel Orden[1], Cesar Ruiz-Navarro[1], Maria Angeles Martinez-Cuesta[1], Juan V. Esplugues[1, 3], **Angeles Alvarez**[1, 4]

[1]Pharmacology, University of Valencia and CIBERehd, Valencia, Spain, [2]Fundación Juan Esplugues, Valencia, Spain, [3]FISABIO-Fundación Hospital Universitario Dr. Peset, Valencia, Spain, [4]Fundación General Universidad de Valencia, Valencia, Spain

745 **LDL Particles and Lipoprotein-Phospholipase A2 in Naive HIV+ Patients Randomized To DRV/r vs ATV/r**

Maria Saumoy[1], Jordi Ordoñez-Llanos[2], Esteban Martinez[3], Elena Ferrer[1], Gracia Mateo[4], Esteban Ribera[5], Eugenia Negredo[6], Iñaki Perez[3], Daniel Podzamczer[1]

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746 **Darunavir or Atazanavir vs Raltegravir Lipid Changes Are Unlinked To Ritonavir Exposure: ACTG 5257**

Ighovwerha Ofotokun[1], Heather Ribaudo[2], Lumine Na[2], Grace McComsey[3], Susan E. Cohn[4], Catherine Godfrey[5], Manish Sagar[2], Frances Aweeka[6], Jeffrey Lennox[1], Judith Currier[7]

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747LB **Is There Continued Evidence for an Association Between Abacavir and Myocardial Infarction Risk?**

Caroline Sabin[1], Peter Reiss[2], Lene Ryom[3], Stephane de Wit[4], Ole Kirk[3], Rainer Weber[5], Christian Pradier[6], Matthew Law[7], Andrew Phillips[1], Jens Lundgren[3], DAD Study Group

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748 **Lipidomic Profiling in HIV: Implications for Risk-Prediction Models**

Gerard Wong[1], **Janine M. Trevillyan**[2, 3], Benoit Fatou[1], Michelle Cinel[1], Jacqui Weir[1], Jennifer F. Hoy[2, 3], Peter J. Meikle[1], Peter J. Meikle[1]

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749LB **Effect of Switch From Abacavir To Tenofovir DF On Platelet Function Markers: A SWIFT Trial Substudy**

Jane A. O'Halloran[1], Eimear Dunne[2], Willard Tinago[1], Stephanie Denieffe[1], Dermot Kenny[2], Patrick W. G. Mallon[1]

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Session P-P6 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Statins and ARV Effects in HIV

750 **Rosuvastatin Lowers Oxidative LDL in HIV-Infected Persons On Antiretroviral Therapy: SATURN-HIV**

Corrilynn O. Hileman[1,2], Richard D. Semba[3], Randi Turner[3], Danielle E. Labbato[1,4], Norma J. Storer[1,4], Grace A. McComsey[1,4]

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751LB **After 52 Weeks, Pitavastatin Is Superior To Pravastatin for LDL-C Lowering in Patients With HIV**

Craig A. Sponseller[1], Judith Aberg[2], INTREPID Team

[1]Medical Affairs, Kowa Pharmaceuticals America, Inc., Montgomery, AL, United States, [2]Chief, Division of Infectious Diseases, ICAHN School of Medicine at Mount Sinai, New York, NY, United States

752 **Endothelial Progenitor Cells Increase in Older HIV-Infected Patients Receiving Telmisartan**

Jordan E. Lake, Theodoros Kelesidis, Diana H. Liao, Judith S. Currier, Otto O. Yang

University of California Los Angeles, Los Angeles, CA, United States

Session P-Q1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Biomarkers and Non-AIDS Events

753 **Incidence of CD4/CD8 Ratio Normalization and Its Role in the Onset of Non-AIDS-Related Events**

Cristina Mussini[1], Patrizia Lorenzini[2], Alessandro Cozzi-Lepri[3], Giuseppe Lapadula[4], Giulia Marchetti[5], Emanuele Nicastri[2], Antonella Cingolani[6], Miriam Lichtner[7], Andrea Antinori[2], Antonella d'Arminio Monforte[5], for the Icona Foundation Study Group

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754 **Longitudinal Changes in Free Testosterone Among Older HIV-Infected and HIV-Uninfected Men**

Laurence Slama[1,2], Lisa P. Jacobson[3], Xiuhong Li[3], Frank J. Palella[2], Joseph B. Margolick[4], Lawrence Kingsley[5], Dorothy Wiley[6], Gilles Pialoux[1], Adrian Dobs[7], Todd T. Brown[7]

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755 **Inflammatory Biomarkers in Chronic HIV Disease Predominantly Associate With Monocyte Activation**

Eleanor M. P. Wilson[1], Amrit Singh[1], Kathy Huppler Hullsiek[2], Keith Henry[2,3], Ken Lichetenstein[4], Pragna Patel[5], John T. Brooks[5], Irini Sereti[1], Jason V. Baker[2,3]

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756 **Extrinsic Pathway Coagulation Factors Are Associated With Mortality During Treated HIV Disease**

Jason V. Baker[1], Kathleen Brummel-Ziedins[2], Jacqueline Neuhaus[3], James D. Neaton[3], Russell P. Tracy[2], INSIGHT SMART and ESPRIT Study Groups

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757 **Correlates of Inflammatory Markers After One Year of Suppressive Antiretroviral Treatment (ART)**

Supriya Krishnan[1], Ronald J. Bosch[1], Benigno Rodriguez[2], Peter W. Hunt[3], Cara Wilson[4], Steven G. Deeks[3], Michael M. Lederman[2], Alan L. Landay[5], Allan R. Tenorio[6]

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758 **Pro12Ala Polymorphism Is Associated With Metabolic Disturbance in HIV/HCV Coinfected Patients**

Pilar García-Broncano[1], Juan Berenguer[2,3], Amanda Fernández-Rodríguez[1], Daniel Pineda-Tenor[1], María A Jiménez-Sousa[1], Mónica García-Álvarez[1], Teresa Aldámiz-Echevarria[2,3], Juan Carlos López[2], Dariela Micheloud[4], Salvador Resino[5]

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759 **Predictors of Incident Hypertension in HIV-Positive Adults Over 24 Months On ART in South Africa**

Alana T. Brennan[1,2], Matthew P. Fox[1,2], Mhairi Maskew[2], Ian Sanne[1,2], Prudence Ive[3], Julia Rohr[1,2], Lawrence Long[2], Sydney Rosen[1,2]

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Session P-Q2 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Frailty: Physical Function and Telomeres

762 **Frailty, Inflammation and Mortality Among Aging HIV-Infected and At-Risk Injection Drug Users**

Damani A. Piggott, Ravi Varadhan, Shruti H. Mehta, Todd T. Brown, Sean X. Leng, Gregory D. Kirk

Johns Hopkins University, Baltimore, MD, United States

763 **Brisk Walking Improves Inflammatory Markers in cART-Treated Patients**

Valeria Longo[1], Matteo Bonato[2], Simona Bossolasco[1], Laura Galli[1], Andrea Caumo[2], Gaspare Pavei[3], Adriano Lazzarin[1], Giampiero Merati[3], Antonio La Torre[2], Paola Cinque[1]

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764 **Cell-Mediated CMV Responses in HIV-Infected Persons With Impaired Physical Function**

Kristine M. Erlandson, Amanda A. Allshouse, Rick Rapaport, Brent E. Palmer, Cara C. Wilson, Samantha MaWhinney, Thomas B. Campbell

University of Colorado Anschutz Medical Campus, Aurora, CO, United States

765 **Presence of the Immune Risk Phenotype and Telomere Shortening Among HIV Treated Patients**

Patricia Ndumbi, Julian Falutz, Jason Szabo, Orin Rosengren, Christos M. Tsoukas

Immune Deficiency Treatment Centre, McGill University Health Centre, Montreal, QC, Canada

766 **Geriatric Syndromes Are Common Among Older HIV-Infected Adults**

Meredith Greene[1,2], Victor Valcour[1,3], Yinghui Miao[2,4], Ken Covinsky[1,2], Joy Madamba[5], Monica Mattes[6], Harry Lampiris[2,7], Jeffrey Martin[8], Steven Deeks[5]

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767 **Physical Function Impairment On Quality of Life Among Persons Aging With HIV Infection**

Kristine M. Erlandson, Amanda A. Allshouse, Catherine M. Jankowski, Samantha MaWhinney, Wendy M. Kohrt, Thomas B. Campbell

University of Colorado Anschutz Medical Campus, Aurora, CO, United States

Session P-Q3 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Diabetes and Insulin Resistance

768 **IL-6, hsCRP, and the Development of Type 2 Diabetes Among HIV Positive Patients Taking ART**

Claude L. Béténé A Dooko

School of Public Health, University of Minnesota, St Paul, MN, United States

769 **HbA1c Is A Poor Predictor of Fasting Glycemia in HIV-Infected Men With Low CD4 Count, High MCV and MCH**

Laurence Slama[1,2], Frank J. Palella[2], Alison G. Abraham[3], Xiuhong Li[3], Corinne Vigouroux[4,5], Gilles Pialoux[1], Lawrence Kingsley[6], Jordan E. Lake[7], Todd T. Brown[8]

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770 **Triglycerides/HDL Ratio and Risk of Developing Diabetes Mellitus During Antiretroviral Therapy**

Nicola Squillace[1], Patrizia Lorenzini[2], Giuseppe Lapadula[1], Alessandro Cozzi-Lepri[3], Stefano Rusconi[4], Massimo Puoti[5], Antonella Castagna[6], Andrea Antinori[2], Andrea Gori[1], Antonella d'Arminio Monforte[7], for the Icona Foundation Study Group

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771 **Measuring Physical Activity and its Impact On Insulin Resistance in MACS Men**

Anne K. Monroe[1], Todd T. Brown[1], Christopher Cox[2], Dorothy Wiley[3], Frank Palella[4], Lawrence Kingsley[5], Michael Plankey[6]

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772 **Impact of Randomized Antiretroviral Therapy (ART) Initiation On Glucose Metabolism: ACTG A5224s**

Kristine M. Erlandson[1], Douglas Kitch[2], Paul E. Sax[3], Eric S. Daar[4], Camlin Tierney[2], Kathleen M. Melbourne[5], Belinda Ha[6], Grace A. McComsey[7]

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Session P-Q4 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Lung Disease and HIV

773 **HIV Infection Increases Risk of Acute Exacerbations of COPD**

Allison A. Lambert, Gregory D. Kirk, Jacquie Astemborski, Shruti H. Mehta, M. Bradley Drummond

Johns Hopkins University, Baltimore, MD, United States

774 **Association of HIV Infection and Immune Activation With Decline in Lung Function**

Kristina Crothers[1], Carla V. Rodriguez[1], Cherry Wongtrakool[2], Guy Soo Hoo[3], Joon Kim[4], Sheldon T. Brown[4], David Rimland[2], Maria C. Rodriguez-Barradas[5], Matthew B. Goetz[3], Amy C. Justice[6]

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775 **HIV Infection and Related Biomarkers Are Independent Risk Factors for Radiographic Emphysema**

Engi F. Attia[1], Matthew B. Goetz[2], Maria C. Rodriguez-Barradas[3], David Rimland[4], Sheldon T. Brown[5], Guy Soo Hoo[2], Joon Kim[5], Cherry Wongtrakool[4], Kathleen Akgun[6], Kristina Crothers[1]

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776 **Factors Associated With Chronic Obstructive Pulmonary Disease in a High Risk HIV-Infected Cohort**

Alain Makinson[1], Maurice Hayot[2], Sabrina Eymard-Duvernay[3], François Raffi[4], Laurence Thirard[5], Fabrice Bonnet[6], Pierre Tattevin[7], Sophie Abgrall[8,9], Jacques Reynes[1], Vincent Le Moing[1], ANRS EP48 HIV CHEST Study Team

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Session P-Q5 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Bone Disease: Osteopenia, Fracture Risk, and Osteoarthritis

777 Minimal Change in Bone Density and No Association With HIV Factors Over 12 Months in HIV-Infected Men

Amanda Samarawickrama[1], Sophie Jose[2], Caroline Sabin[2], Karen Walker-Bone[3], Martin Fisher[4], Yvonne Gilleece[5]

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778 New Fracture Risk and FRAX 10-Year Probability of Fracture in HIV-Infected Adults

Linda A. Battalora[1], Kate Buchacz[2], Carl Armon[3], Edgar T. Overton[4], John Hammer[5], Pragna Patel[2], Joan Chmiel[6], Kathy Wood[3], John T. Brooks[2], Benjamin Young[7]

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779LB Bone Density Changes After Antiretroviral Initiation With Protease Inhibitors or Raltegravir

Todd Brown[1], Carlee Moser[2], Judith Currier[3], Heather Ribaudo[2], Jennifer Rothenberg[4], Michael Dube[5], Robert Murphy[6], James Stein[7], Grace McComsey[8]

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780 Hand Osteoarthritis, a Joint Disorder Frequent and More Severe in HIV-1 Patients: METAFIB-OA Study

Anne-Laurence Tomi[1], Jeremy Sellam[2], Karine Lacombe[3], Manuela Sebire[4], Caroline Rey-Jouvin[2], Anne-Laurence Miquel[5], Emmanuel Maheu[1], Francis Berenbaum[1], Pierre-Marie Girard[3], **Jean-Luc Meynard**[6]

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781 Low Bone Mineral Density Is Associated With Increased Risk of Incident Fracture in HIV+ Adults

Linda A. Battalora[1], Kate Buchacz[2], Carl Armon[3], Edgar T. Overton[4], John Hammer[5], Pragna Patel[2], Joan S. Chmiel[6], Tim Bush[2], John T. Brooks[2], Benjamin Young[7]

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782 A Randomized Open Label Study for Comparing Two Doses of Zoledronic Acid in HIV Infected Patients

Eugènia Negredo[1], Anna Bonjoch[1], Nuria Pérez-Álvarez[1, 2], Arrelly Ornellas[1, 3], Jordi Puig[1], Cristina Herrero[1], Patricia Echeverria[1], Bonaventura Clotet[1, 4]

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783 Mechanism of Bone Disease in HIV and HCV: Impact of Tenofovir Exposure and Severity of Liver Disease

James Cutrell[1], Naim M. Maalouf[2], Song Zhang[3], Henning Drechsler[1], Ang Gao[4], Pablo Tebas[5], Roger Bedimo[1]

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784 Low Bone Mineral Density (BMD) Among Ugandan HIV-Infected Patients On Failing First-Line ART

Bonnie Wandera[1, 2], Fred Ssemitala[3], Agnes Kiragga[2], Jayne Ellis[4], Cissy Kityo[5], Robert Colebunders[6], Nicholas Paton[7], Andrew Kambugu[2], Philippa Easterbrook[1]

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Session P-Q6 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Hepatic Fibrosis and Other Hepatic Complications

785 Abacavir and Didanosine Enhance Susceptibility To Acetaminophen-Induced Hepatotoxicity

Ana Blas-García[1, 2], Víctor M. Víctor[2, 3], Alberto Martí-Rodrigo[1], Lara Milián-Medina[1, 2], Nadezda Apostolova[3, 4], **Juan V. Esplugues**[1, 2]

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786 Liver Fibrosis Is Not Uncommon in HIV-Infected Patients Without Viral or Alcoholic Hepatitis

Anchalee Avihingsanon[1, 2], Salyavit Jitmitraparp[3], Vorapot Sapsirisavat[1], Tanakorn Apornpong[1], Tawan Mengthisong[1], Stephen Kerr[1, 4], Gail V. Matthews[4], Sharon R. Lewin[5, 6], Kiat Ruxrungtham[1, 7], and the HIV-NAT 006 study team.

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787 Association Between Dideoxynucleoside Analogues (d-Drugs) and End-Stage Liver Disease (ESLD)

Lene Ryom[1], Caroline A. Sabin[2], Peter Reiss[3], Wafaa El-Sadr[4], Antonella D. A. Monforte[5], Stephane De Wit[6], Matthew Law[7], Ole Kirk[1], Andrew N. Phillips[2], Jens D. Lundgren[1], on behalf of the D:A:D Study Group

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788 Microbial Translocation, Immune Activation, Apoptosis and Liver Fibrosis in the MASH Cohort

Marianna K. Baum[1], Kenneth E. Sherman[2], Sabrina S. Martinez[1], Pedro Greer[3], Tiffanie Stewart[1], Christina Jacobs[1], Sonya Luisi[1], Kimberly Dizon[1], Adriana Campa[1]

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789 **Cumulative Exposure To Ritonavir-Boosted Atazanavir Is Associated With Cholelithiasis**

Takeshi Nishijima[1,2], Hiroyuki Gatanaga[1,2], Takuro Shimbo[3], Yohei Hamada[1], Junko Tanuma[1], Kunihisa Tsukada[1], Katsuji Teruya[1], Yoshimi Kikuchi[1], Shinichi Oka[1]

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790 **Prevalence of Liver Fibrosis Based On Non-Invasive Markers Among HIV-Infected Patients in Zambia**

Michael J. Vinikoor[1,2], Kalo Musukuma[1], Gilles Wandeler[3], Arianna Zanolini[1,2], Aggrey Mweemba[4], Carolyn Bolton-Moore[1,5], Izukanji Sikazwe[1], Benjamin H. Chi[1,5], Lloyd Mulenga[1,4]

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791 **Significance of Alcohol Abuse Diagnosis vs Other Risk Factors for Advanced Liver Fibrosis by FIB-4**

H. Nina Kim[1], Heidi M. Crane[1], Carla V. Rodriguez[1], Stephen Van Rompaey[1], W. Christopher Mathews[2], Michael Mugavero[3], Kenneth H. Mayer[4], Katerina Christopoulos[5], Sonia Napravnik[6], Mari M. Kitahata[1]

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Session P-Q7 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Renal Disease: ART, Genetic Factors, and Long Term Outcomes

792 **Predictors of Progression, Stabilisation, or Improvement of eGFR After Chronic Renal Impairment**

Lene Ryom[1], Amanda Mocroft[2], Ole Kirk[1], Peter Reiss[3], Michael Ross[4], Olivier Moranne[5], Philippe Morlat[6], Colette Smith[2], Christoph A. Fux[7], Jens D. Lundgren[1], on Behalf of the D:A:D Study Group

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793 **Spectrum of HIV-Associated Kidney Disease in the Era of Combination Antiretroviral Therapy**

John Booth[1], **Lisa Hamzah**[2], Sophie Jose[1], Stephen Mcadoo[3], Emil Kumar[3], Catherine Horsfield[4], Patrick O'Donnell[4], Rachael Jones[5], Caroline Sabin[1], Frank A. Post[2]

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794 **Renal and Metabolic Safety of Initial HIV-1 Therapy in Resource-Limited Settings**

Francine Touzard Romo[1], Laura M. Smeaton[2], Thomas B. Campbell[3], Cynthia Riviere[4], Rosie Mngqibisa[5], Khuanchai Supparatpinyo[6], Johnstone Kumwenda[7], Nagalingeswaran Kumarasamy[8], James G. Hakim[9], Timothy Flanigan[10]

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795 **Risk Factors for Atazanavir (ATV)-Associated Urolithiasis: A Case-Control Study**

Barbara De Sousa[1], Diane Ponscarme[1], Nathanael Lapidus[2], Michel Daudon[3], Laurence Weiss[4], Christophe Rioux[5], Erwan Fourn[6], Christine Katlama[7], Jean-Michel Molina[1], **Matthieu Lafaurie**[1]

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796 **Single Nucleotide Polymorphisms in UGT1A1 Associate With Atazanavir-Related Nephrolithiasis**

Takeshi Nishijima, Kiyoto Tsuchiya, Akane Joya, Yohei Hamada, Junko Tanuma, Kunihisa Tsukada, Katsuji Teruya, Yoshimi Kikuchi, Shinichi Oka, Hiroyuki Gatanaga

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797 **Atazanavir and Tenofovir Attenuate the Benefit of Antiretroviral Therapy On Cystatin C: ACTG A5224**

Chris T. Longenecker[1,2], Douglas Fitch[3], Paul Sax[4,5], Eric Daar[6,7], Camlin Tierney[3], Grace A. McComsey[1,2]

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798 **A Chronic Kidney Disease Risk Score To Determine Tenofovir Safety Among HIV+ Male Veterans**

Rebecca Scherzer[1], Monica Gandhi[1], Michelle Estrella[2], Phyllis Tien[1], Steven Deeks[1], Carl Grunfeld[1], Carmen Peralta[1], Michael Shlipak[1]

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799 **Genetic Variants of ABCC2 and ABCC10 Are Associated With TFV-Induced Proximal Tubular Dysfunction**

Anchalee Avihingsanon[1,2], Baralee Punyawudho[3], Kearkiat Praditpornsilpa[4], Yingyos Avihingsanon[4], Wirach Maek-a-nantawat[1], Jiratchaya Sophonphan[1], Sasiwimol Ubolyam[2], Stephen Kerr[1,5], David Burger[6], Kiat Ruxrungtham[1,7], and HIV-NAT 114 study team

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800 **End-Stage Kidney Disease and Kidney Transplantation in HIV-Positive Patients**

Esther N. Gathogo[1], Sophie Jose[2], John Booth[2], Stephen P. McAdoo[3], Emil A. Kumar[3], Michael Rayment[4], Clifford Leen[5], Deborah Williams[6], Caroline Sabin[2], Frank Post[1]

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Session P-Q8 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Obesity: ART and Animal Models

801 **Maraviroc, a CCR5 Antagonist, Alters Gut Microbiota Composition in a Mouse Model of Obesity**

Patricia Pérez-Matute[1], Laura Pérez-Martínez[1], **José R. Blanco**[2], Jose A. Oteo[2]

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802 **Low Pre-ART CD4+ T Cells, Female Sex, and Atazanavir Use Increase Obesity Risk After Starting ART**

Benjamin Atkinson[1], **Supriya Krishnan[2]**, Ann C. Collier[1,3]

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803 **Obesity or Hypertension at ART Initiation and Outcomes Amongst HIV Patients in South Africa**

Alana T. Brennan[1,2], Matthew P. Fox[1,2], Mhairi Maskew[2], Ian Sanne[1,2], Prudence Ive[3], Julia Rohr[1,2], Lawrence Long[2], Sydney Rosen[1,2]

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Session P-Q9 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Genetic Factors and ART Outcomes

804 **Specific Binding Characteristics of HLA Alleles Associate With Nevirapine Hypersensitivity**

Rebecca Pavlos[1], Craig Rive[1], Elizabeth McKinnon[1], David Ostrov[2], Bjoern Peters[3], Jing Yuan[4], Silvana Gaudieri[1,5], David Haas[6], Simon Mallal[1,6], **Elizabeth J. Phillips[1,6]**

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805 **Large-Scale Gene-Centric Exploration of Risk for NRTI/NNRTI-Associated Toxicities in Botswana**

C. William Wester[1,2], **Sophie Limou[3]**, Hermann Bussmann[2,4], Vladimir Novitsky[2,4], Sikhulile Moyo[4], Max Essex[2,4], Richard G. Marlink[2,4], Cheryl A. Winkler[3]

[1]Vanderbilt Institute for Global Health (VIGH), Vanderbilt University School of Medicine, Division of Infectious Diseases, Nashville, TN, United States, [2]Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, MA, United States, [3]Center for Cancer Research, Basic Science Program, Frederick National Laboratory, Leidos BioMedical Research for the National Cancer Institute, Frederick, MD, United States, [4]Botswana-Harvard School of Public Health AIDS Initiative Partnership for HIV Research and Education (BHP), Gaborone, Botswana

Session P-Q10 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

ART and Suicidality

760 **Suicide Rates Decrease Among HAART Initiators From 1996 To 2012 in British Columbia, Canada**

Silvia Guillemi[1,2], Erin Ding[1], Jasmine Gurm[1], Julia Zhu[1], Verena Strehlau[1,3], Julio S. G. Montaner[1,2], Robert S. Hogg[1,4]

[1]BC Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada, [2]University of British Columbia, Faculty of Medicine, Vancouver, BC, Canada, [3]University of British Columbia, Department of Psychiatry, Vancouver, BC, Canada, [4]Simon Fraser University, Faculty of Health Sciences, Burnaby, BC, Canada

761 **Disproportionality Analysis of Antiretrovirals With Suicidality Using FDA AERS Data**

Andrew Napoli[1], John Coumbis[2], Jennifer Wood[2], Amit Soitkar[2], Daniel Seekins[1]

[1]Bristol-Myers Squibb, Plainsboro, NJ, United States, [2]Bristol-Myers Squibb, Hopewell, NJ, United States

Session P-R1 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Epidemiology and Transmission of TB

806 **High Clonality of *M. tuberculosis* Strains Among MDR-TB Patients in Gauteng, South Africa**

Dorothy A. Fallows[1], Nicole Kushner[1], Amanda Axcell[2], Lynsey Stewart-Isherwood[3], Pamela Deniso[3], Francesca Conradie[3], Gerrit Coetzee[2], Hendrik Koornhof[2], Nazir Ismail[2], Gilla Kaplan[1]

[1]PHRI, NJMS-Rutgers University, Newark, NJ, United States, [2]Centre for Tuberculosis, Johannesburg, South Africa, [3]Department of Clinical Medicine, University of the Witwatersrand, Johannesburg, South Africa

807 **Identifying Location of Recent TB Transmission in Rural Uganda: A Multidisciplinary Approach**

Gabriel Chamie[1], Bonnie Wandera[2], Carina Marquez[1], Midori Kato-Maeda[3], Moses R. Kamya[4], Diane V. Havlir[1], Edwin D. Charlebois[5]

[1]Division of HIV/AIDS, San Francisco General Hospital, University of California San Francisco, San Francisco, CA, United States, [2]Makerere University-University of California San Francisco Research Collaboration, Kampala, Uganda, [3]Division of Pulmonary & Critical Care Medicine, San Francisco General Hospital, University of California San Francisco, San Francisco, CA, United States, [4]Department of Medicine, School of Medicine, Makerere University College of Health Sciences, Kampala, Uganda, [5]Center for AIDS Prevention Studies, University of California San Francisco, San Francisco, CA, United States

808 **Timing of TB Episodes After the End of Isoniazid Preventive Therapy: Reinfection or Reactivation?**

Sabine Hermans[1], Alison Grant[2], Violet Chihota[3], James Lewis[1], Gavin Churchyard[3], Katherine Fielding[1]

[1]Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom, [2]Clinical Research, London School of Hygiene and Tropical Medicine, London, United Kingdom, [3]Aurum Institute for Health Research, Johannesburg, South Africa

809 **HIV and Tuberculosis in Kenya, 2012-2013: Results From a National Survey**

Agneta Mbithi[1], Anthony Gichangi[2], Herman Wyenga[2,3], John Williamson[2], Tom Oluoch[2], Katherine Robinson[2], Timothy Kellogg[4], Andrea A. Kim[2], William Maina[1], Kevin M. De Cock[2]

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Session P-R2 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

TB Screening and Diagnosis

810 **Screening for Tuberculosis in HIV-Infected Nigerian Children With a Urinary Antigen Assay**

Holly E. Rawizza[1,2], Stephen Oguche[3], Godwin Imade[4], Oche Agbaji[4], David Olaleye[5], Georgina Odaibo[5], Kike Osinusi[5], Isaac Adewole[5], Prosper Okonkwo[6], Phyllis Kanki[2]

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811LB **Massive Diagnostic Yield of HIV-Associated Tuberculosis Using Rapid Urine Assays in South Africa**

Stephen D. Lawn[1], Andrew Kerkhoff[2], Rosie Burton[3], Charlotte Schutz[3], Gavin van Wyk[3], Monica Vogt[4], Pearl Pahlana[5], Mark Nicol[6], Graeme Meintjes[3]

[1]Department of Clinical Research, London School of Hygiene & Tropical Medicine, London, United Kingdom, [2]University of Cape Town, Cape Town, South Africa, [3]Department of Medicine, University of Cape Town, Cape Town, South Africa, [4]Department of Clinical Research, University of Cape Town, Cape Town, South Africa, [5]Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa, [6]Division of Medical Microbiology, University of Cape Town, Cape Town, South Africa

812 **Symptom-Based Screening for Tuberculosis Among Pregnant Women Living With HIV in Kenya**

Surbhi Modi[1], Joseph S. Cavanaugh[2], Ray W. Shiraishi[1], Barbara Burmen[3], Heather Alexander[1], Kimberly McCarthy[2], Hellen Muttai[4], Kevin P. Cain[5]

[1]Division of Global HIV/AIDS, Centers for Disease Control and Prevention, Atlanta, GA, United States, [2]Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Atlanta, GA, United States, [3]Kenya Medical Research Institute/Centers for Disease Control and Prevention Public Health Collaboration, Kisumu, Kenya, [4]Division of Global HIV/AIDS, Centers for Disease Control and Prevention, Kisumu, Kenya, [5]Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Kisumu, Kenya

813 **Highly Multiplexed Detection of Antibodies in Whole Blood During Tuberculosis Infection**

Charles Greef[1], Greg Husar[1], Christen Gray[2], David Danks[3], Pamela Nabeta[2], Mark Perkins[2], **Michael Lochhead**[1]

[1]MBio Diagnostics, Inc, Boulder, CO, United States, [2]FIND, Geneva, Switzerland, [3]Carnegie Mellon University, Pittsburgh, PA, United States

814 **Performance of the World Health Organization Algorithm for Tuberculosis Screening in Kenya**

Surbhi Modi[1], Joseph S. Cavanaugh[2], Ray W. Shiraishi[1], Barbara Burmen[3], Heather Alexander[1], Kimberly McCarthy[2], Hellen Muttai[4], Kevin Cain[5]

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815 **Diagnosing Extra Pulmonary Tuberculosis Using Xpert MTB/RIF: A Laboratory Algorithm**

Lesley E. Scott[1], Natalie Beylis[2], Mark Nicol[3], Tintswalo Nkuna[1], Sebaka Molapo[1], Leigh Berrie[1], Adriano Duse[2], Wendy S. Stevens[1]

[1]Molecular Medicine and Haematology, University of the Witwatersrand, Johannesburg, South Africa, [2]Division of Clinical Microbiology and Infectious Diseases, University of the Witwatersrand, Johannesburg, South Africa, [3]Division of Medical Microbiology, Clinical Laboratory Sciences and Institute for Infectious Disease, University of Cape Town, Cape Town, South Africa

Session P-R3 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Latent TB Screening and Treatment

816 **Rifapentine Safety and PK With Novel Dosing Strategies To Increase Drug Exposures for TB: ACTG A5311**

Kelly E. Dooley[1], Rada Savic[2], Jeong-Gun Park[3], Yoninah Cramer[3], Richard Hafner[4], Jennifer Janik[5], Mark A. Marzinke[1], Marc Weiner[6], Susan Dorman[1], David W. Haas[7], and the A5311 Study Team

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817 **Three Months of Weekly Rifapentine + INH for *M. tuberculosis* Infection in HIV-Infected Persons**

Timothy Sterling[1], Connie Benson[2], Nigel Scott[3], Jose Miro[4], Guilherme Calvet[5], Richard Chaisson[6], Alberto La Rosa[7], Rosa Infante[7], Michael Chen[3], Elsa Villarino[3], TBTC / ACTG

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818 **Effect of HIV On Latent TB Screening of Pregnant Women in Pune, India**

Jyoti S. Mathad[1], Ramesh Bhosale[2], Savita Kanade[3], Prasad Deshpande[3], Vandana Kulkarni[3], Neetal Nevrekar[3], Vidya Mave[3], Nishi Suryavanshi[3], Nikhil Gupte[4], Amita Gupta[4]

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Session P-R4 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Inflammatory and Immune Activation Markers in TB

819 **Baseline Inflammatory and Immune Activation Markers Predictive of TB After ART Initiation**

Mark Tenforde[1], Nikhil Gupte[1], David Dowdy[2], David Asmuth[3], Ashwin Balagopal[1], Richard Pollard[3], James Hakim[4], Richard Semba[5], Thomas Campbell[6], Amita Gupta[1], for the ACTG A5175 (PEARLS) and NWCS 319 Study Group

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820 **MAIT Cells Are Highly Enriched in the Bronchoalveolar Lavage Fluid of Patients With TB**

Emily B. Wong[1,2], Zuri Sullivan[1], Marielle C. Gold[3,4], Umesh G. Lalloo[5], Anish Ambaram[5], Prinita Baijnath[5], Leon Naidoo[6], Thumbi Ndung'u[1,7], William R. Bishai[1,8], David M. Lewinsohn[3,4]

[1]KwaZulu Natal Research Institute for Tuberculosis and HIV, Durban, South Africa, [2]Division of Infectious Diseases, Massachusetts General Hospital, Boston, MA, United States, [3]Division of Pulmonary and Critical Care Medicine, Oregon Health & Science University, Portland, OR, United States, [4]Portland Veterans Administration Medical Center, Portland, OR, United States, [5]Department Pulmonology and Critical Care, Nelson R. Mandela School of Medicine, Durban, South Africa, [6]Department of Pulmonolgy and Critical Care, Nelson R. Mandela School of Medicine, Durban, South Africa, [7]HIV Pathogenesis Programme, University of KwaZulu Natal, South Africa, [8]Division of Infectious Diseases, Johns Hopkins School of Medicine, Baltimore, MD, United States

821 **Vitamin D and TMEM16J Host Variants Associated With TB or Death in HIV-Infected and -Exposed Infants**

Amita Gupta[1], Jennifer Jubulis[2], Bret Zeldow[3], Grace Montepiedra[3], Barbara Detrick[4], Avy Violari[5], Shabir A. Madhi[6], Charles Mitchell[7], Stephen A. Spector[8], for the IMPAACT NWCS113 and P1041 Study Team

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822 **Latent and Active TB Infection Increase Harmful Immune Activation in Those Co-Infected With HIV**

Zuri A. Sullivan[1], Emily B. Wong[1], Thumbi Ndung'u[1], Victoria O. Kasprowicz[1], William R. Bishai[2]

[1]KwaZulu-Natal Research Institute for Tuberculosis and HIV, Durban, South Africa, [2]School of Medicine, Johns Hopkins University, Baltimore, MD, United States

823 **Ex Vivo Fitness of MTB Correlates With Lysozyme Sensitivity in the East-African Indian Lineage**

Claire Pardieu[1], Nicola Casali[1], Simon Clark[2], Ann Rawkins[2], Richard Hooper[3], Preya Velji[4], Ximena Gonzalo[4], Jane R. Deayton[5], Francis A. Drobniewski[4]

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824 **Polyfunctionality of TB-Specific CD4+ T-Cells in HIV-TB Co-Infection in Latent and Pulmonary TB**

Puja Van Epps[1,2], Sankar Sridaran[1], Htin Aung[1], Michael R. Betts[3], Zahra Toosi[1], David H. Canaday[1,2]

[1]Department of Medicine, Division of Infectious Diseases and HIV Medicine, Case Western Reserve University, Cleveland, OH, United States, [2]Geriatric Research Education & Clinical Center (GRECC), Louis Stokes Cleveland VA Medical Center, Cleveland, OH, United States, [3]Department of Microbiology, University of Pennsylvania, Philadelphia, PA, United States

Session P-R5 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Impact of ART On TB Risk and Disease

825 **Increased Risk of TB and Persistent Immune Deficit With Delayed ART: A Randomized Trial From Haiti**

Sean E. Collins[1], Marc Antoine Jean Juste[2], Patrice Severe[2], Serena P. Koenig[3], Rode Secours[2], Oksana Ocheretina[1], Daphne Bernard[2], Allison Dunning[4], Sandra M. Hurtado Rúa[4], Jean W. Pape[1,2]

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826 **Viral Suppression in HIV-Infected Pregnant Women With and Without TB, South Africa**

Jennifer Hoffmann[1], Silvia Cohn[1], Fildah Mashabela[2], Reginah Msandiwa[2], Richard Chaisson[1], Neil Martinson[2], Tshepiso Study Team

[1]The Johns Hopkins University, Baltimore, MD, United States, [2]Perinatal HIV Research Unit, Soweto, South Africa

827 **Depleted DHEA-S Reserves Are Associated With Early Mortality After ART Initiation in HIV/TB**

Shruthi Ravimohan[1,2], Neo Tamuhla[2], Andrew P. Steenhoff[2,3], Rona Letlhogile[2], Kebatshabile Nfanyana[2], Tumelo Rantleru[2], Michael Adu[4], Drew Weissman[2,4], Gregory P. Bisson[2,4]

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829 **Impacts of National ART Initiation Policy Change On Integrated TB HIV Practice in Zomba, Malawi**

Kevin D. Bezanson[1], **Adrienne K. Chan**[1], Monique van Lettow[2], Jean Bourgeois[2], Edson Mwinjiwa[2], Harry Mbewe[3], Martin Kachingwe[2], Donald Cole[4], Sumeet Sodhi[1]

[1]Dignitas International, Toronto, ON, Canada, [2]Dignitas International, Zomba, Malawi, [3]Zomba Central Hosptial, Zomba, Malawi, [4]Dalla Lana School of Public Health, Toronto, ON, Canada

830 **Does Long-Term ART Reduce TB Rates To Background Population Levels? Data From a National HIV Cohort**

Rishi K. Gupta[1,2], Marc Lipman[1], Alison Brown[2], Brian Rice[2], Anton Pozniak[3], Dominik Zenner[2], Lucy Thomas[2], Ibrahim Abubakar[1,2], Valerie Delpech[2]

[1]University College London, London, United Kingdom, [2]Public Health England, London, United Kingdom, [3]Chelsea and Westminster NHS Foundation Trust Hospital, London, United Kingdom

831 **Development of Tuberculosis in HIV-Infected Patients Receiving Successful TARGA**

Esteban Martin-Echevarria[1], Sergio Serrano Villar[2], Talía Sainz[2], **Ana Moreno**[2], Jose Luis Casado[2], Fernando Dronda[2], Maria Jesus Perez Elias[2], Enrique Navas[2], Manuel Rodriguez Zapata[1], Santiago Moreno[2]

[1]Hospital Universitario Guadalajara, Guadalajara, Spain, [2]Hospital Universitario Ramón y Cajal, Madrid, Spain

832 **Timeliness of ART Initiation Among HIV-Infected Patients With TB in Sub-Saharan Africa**

Suzue Saito[1,2], Wafaa El-Sadr[1,2], Yael Hirsch-Moverman[1], Faiz A. Khan[1], Veronicah Mugisha[1], Zulmira de Silva[1], Batya Elul[1,2], Andrea Howard[1,2]

[1]ICAP, Columbia University, New York, NY, United States, [2]Department of Epidemiology, Columbia University, New York, NY, United States

833 **Antiretroviral Therapy Initiation and Tuberculosis (TB) Risk in the United States (US) and Canada**

April Pettit[1], Adell Mendes[2], Sonia Napravnik[3], Aimee Freeman[2], Bryan Shepherd[1], David Dowdy[2], Anita Rachlis[4], Richard Moore[2], Timothy Sterling[1], for the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD)

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Session P-R6 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Cryptococcal Disease

834 **Prevalence of Cryptococcal Antigen Positivity Among AIDS Patients, United States From 1986-2012**

Jennie L. McKenney[1], Sean Bauman[2], Brandon Neary[3], Roger Detels[1], Audrey French[4], Joseph Margolick[5], Jeffrey D. Klausner[6]

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835 **High Prevalence of Undiagnosed *Cryptococcus* at HIV Diagnosis Across the CD4 Spectrum in Durban**

Paul K. Drain[1], Julia M. Kleene[2], Elena Losina[1], Sharon M. Coleman[3], Janey Giddy[4], Douglas Ross[5], Jeffrey Katz[6], Rochelle P. Walensky[1], Kenneth A. Freedberg[1], Ingrid V. Bassett[1]

[1]Massachusetts General Hospital; Harvard Medical School, Boston, MA, United States, [2]Stony Brook School of Medicine, Stony Brook, NY, United States, [3]Boston University School of Public Health, Boston, MA, United States, [4]McCord Hospital, Durban, South Africa, [5]St. Mary's Hospital, Durban, South Africa, [6]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States

836 **Monocyte Dysfunction Is Associated With 14-Day Mortality in Cryptococcal Meninigits**

James Scriven[1], Lisa Graham[1], Charlotte Schutz[1], Robert Wilkinson[1], Britta Urban[2], Graeme Meintjes[1], David Lalloo[2]

[1]Institute of Infectious Diseases and Molecular Medicine, Univeristy of Cape Town, Cape Town, South Africa, [2]Liverpool School of Tropical Medicine, Liverpool, United Kingdom

837 **Serum Biomarkers Following Induction Therapy for Cryptococcal Meningitis Predict Survival**

Joshua Rhein[1], James Scriven[2], Kathy Huppler Hullsiek[3], Maximilian von Hohenberg[3], David B. Meya[4], Conrad Muzoora[5], Graeme Meintjes[6], David R. Boulware[3], COAT Trial Team

[1]University of Minnesota, Kampala, Uganda, [2]Liverpool School of Tropical Medicine, Cape Town, South Africa, [3]University of Minnesota, Minneapolis, MN, United States, [4]Infectious Disease Institute, Kampala, Uganda, [5]Mbarara University of Science and Technology, Mbarara, Uganda, [6]University of Cape Town, Cape Town, South Africa

838 **Cryptococcal Antigenemia in Severely Immunocompromised HIV Patients in Rural Tanzania**

Matthias C. Müller[1], Alex J. Ntamatungiro[2], Namvua Kimera[2], Hansjakob Furrer[3], Manuel Battegay[4], Marcel Tanner[1], Christoph Hatz[1], David R. Boulware[5], Tracy R. Glass[1], Emilio Letang[1]

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Session P-R7 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM Exhibit Hall D

OIs Other Than TB and Cryptococcal Disease

839 **HSV-2 Serostatus Is Not Associated With Inflammatory or Metabolic Markers in ART-Treated HIV**

Darrell Tan[1], Janet Raboud[2], Leah Szadkowski[3], Tae Joon Yi[4], Brett Shannon[4], Rupert Kaul[4], W. Conrad Liles[5], Sharon Walmsley[3]

[1]St. Michael's Hospital, Toronto, ON, Canada, [2]Toronto General Research Institute, Toronto, ON, Canada, [3]University Health Network, Toronto, ON, Canada, [4]University of Toronto, Toronto, ON, Canada, [5]University of Washington, Seattle, WA, United States

840 **Latent, Acute, or Neuro-Syphilis Does Not Increase HIV-1 Replication in Central Nervous System**

Maximilian Donath[1], Timo Wolf[2], Annette Haberl[2], Markus Bickel[2], Siri Göpel[2], Annemarie Berger[3], Dimitria Bon[4], Claudia Brandt[5], Christoph Stephan[2]

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841 **Early Impact of cART On the Risk of Herpes Zoster: Results From the FHDH-ANRS CO4**

Sophie Grabar[1,2], Pierre Tattevin[3], Hana Selinger-Leneman[1], Arnaud de la Blanchardière[4], Christian Rabaud[5], David Rey[6], Vincent Daneluzzi[7], Samuel Ferret[8], Dominique Costagliola[1], Odile Launay[9]

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842 **Antigen-Presenting Cells Ingest Malaria Parasites and Cause an Increase in HIV-1 Replication**

Marika Orlov[1], Florin Vaida[1], Kathryn Williamson[2], Qianqian Deng[1], David Smith[1], Patrick Duffy[3], Robert Schooley[1]

[1]School of Medicine, University of California San Diego, La Jolla, CA, United States, [2]Seattle Biomedical Research Institute, Seattle, WA, United States, [3]NIAID, NIH, Rockville, MD, United States

843 **Incidence of AIDS-Defining Opportunistic Illnesses (ADOIs) Among Patients in North America**

Kate A. Buchacz[1], Bryan Lau[2], Yuezhou Jing[2], Stephen J. Gange[2], John T. Brooks[1]

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Session P-S1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM Exhibit Hall D

Reproductive Hormones in Women: Impact On Risk and Barrier Dysfunction

844 **Depot-Medroxyprogesterone Acetate Does Not Increase Genital SHIV Shedding in Macaques**

Jessica Radzio[1], Krisztina Hanley[2], Debra Hanson[1], James Mitchell[1], Leecresia Jenkins[1], Shanon Ellis[1], Frank Deyounks[1], Walid Heneine[1], J. Gerardo Garcia-Lerma[1]

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845 **Dysregulation of Estradiol Signaling Contributes To Mucosal Barrier Dysfunction HIV+ Women**

Sumathi Sankaran-Walters[1], Anne Fenton[1], Chris Gaulke[1], Lauren Nagy[1], Irina Grishina[1], Jason Flamm[2], Thomas Prindiville[3], Satya Dandekar[1]

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846 **Hormonal Contraceptives Increase Innate Immune Effector Molecules in Cervicovaginal Secretions**

Brandon L. Guthrie[1], Robert Y. Choi[2], Alison C. Roxby[2], Rose Bosire[3], Barbara Lohman-Payne[1,2], Taha Hirbod[4], Carey Farquhar[1,2], Kristina Broliden[4]

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847 **Injectable Contraception and HIV Acquisition in the VOICE Study (MTN-003)**

Lisa M. Noguchi[1,2], Barbra Richardson[3], Z. Mike Chirenje[4], Gita Ramjee[5], Gonasagrie Nair[6], Thesla Palanee[7], Pearl Selepe[8], Ravindre Panchia[9], Kailazarid Gomez[10], Jeanne Marrazzo[11], on behalf of the VOICE Study Team

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Session P-S2 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM Exhibit Hall D

HIV in Women: Pregnancy, Progression, Pap, and Bones

848 **Rapid Disease Progression in HIV-1 Subtype C Infected South African Women**

Nigel J. Garrett[1], Lise Werner[1], Koleka Mlisana[1,2], Lyle McKinnon[1], Francois van Loggerenberg[1,3], Thumbi Ndung'u[4], Clive Gray[5], Lynn Morris[6], Carolyn Williamson[5], Salim Abdool Karim[1,7]

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849 **Pregnancy Intentions Among HIV-Infected Women Seeking Antenatal Care in Cape Town, South Africa**

Tammy Phillips[1], Allison Zerbe[2], James McIntyre[3], Greg Petro[4], Elaine Abrams[2], Landon Myer[1]

[1]Division of Epidemiology & Biostatistics, University of Cape Town, Cape Town, South Africa, [2]ICAP, Columbia University, New York, NY, United States, [3]Anova Health Institute, Johannesburg, South Africa, [4]Division of Obstetrics & Gynaecology, University of Cape Town, Cape Town, South Africa

850 **Effect of Antiretroviral Regimens On Bone Mineral Density of HIV Infected Lactating Ugandan Women**

Carolyne Onyango-Makumbi[1], Mike Mubiru[1], Prossy Ethel Namuli[1], Jane Ssebaggala[1], Joyce Matovu Namale[1], Mary Glenn Fowler[1,2]

[1]Makerere University - Johns Hopkins University Research Collaboration, Kampala, Uganda, [2]Johns Hopkins University, Baltimore, MD, United States

851 **Visual Inspection With Acetic Acid Is Good for Follow-Up After Cryotherapy in HIV-Infected Women**

Elkanah O. Omenge[1], Peter M. Itsura[1], Tao Liu[2], Hillary Mabeya[1], Astrid Christoffersen-Deb[3], Sierra Washington[4], Susan Cu-Uvin[5]

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Session P-S3 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM Exhibit Hall D

Immune Mediators and Immune Activation in Women

852 **HIV Inhibition and Variation in Anti-Microbial Peptides Associated With Intercourse**

J. D. Fortenberry[1], Mary A. M. Rogers[2], Krystle Fordyce[2], Steven R. King[2], David M. Aronoff[3], Sari M. Van Anders[2]

[1]Pediatrics, Indiana University School of Medicine, Indianapolis, IN, United States, [2]University of Michigan, Ann Arbor, MI, United States, [3]Vanderbilt University, Nashville, TN, United States

853 **Sex-Related Inflammatory Marker Changes Pre- and Post-ART Initiation**

Jyoti S. Mathad[1], Nikhil Gupte[2], Ashwin Balagopal[2], David Asmuth[3], James Hakim[4], Nagalingeswaran Kumarasamy[5], Thomas Campbell[6], Judith S. Currier[7], Susan E. Cohn[8], Amita Gupta[2], for the NWCS319 and ACTG 5175 PEARLS Study Teams

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854 **Influence of RAL vs Boosted ATZ-based Regimens On Cervical Immune Reconstitution and Activation**

Amie L. Meditz[1], Claire Palmer[2], Julie Predhommme[3], Kristina Searls[1], Becky Kerr[3], Patricia Caraway[4], Edward M. Gardner[4], Samantha MaWhinney[2], **Peter L. Anderson**[3]

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Session P-S4 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Immune Response To Vaccination in HIV+ Women

855 **AMC 054: Safety and Immunogenicity of the Quadrivalent HPV Vaccine in Indian HIV-Infected Women**

Joel Palefsky[1], Selvamuthu Poongulali[2], Shelly Lensing[3], Jeannette Lee[3], Maria Da Costa[1], Arumugham Jeeva[2], Syed Iqbal[2], Nagalingeswaran Kumarasamy[2]

[1]University of California San Francisco, San Francisco, CA, United States, [2]YRGCARE Medical Centre, Chennai, India, [3]University of Arkansas for Medical Sciences, Little Rock, CA, United States

856 **B and T Cell Immune Responses To pH1N1 Monovalent Vaccine in HIV+ Pregnant Women in IMPAACT P1086**

Adriana Weinberg[1], Petronella Muresan[2], Kelly Richardson[1], Terrence Fenton[2], Teresa Dominguez[1], Anthony Bloom[3], Mark Abzug[4], Myron Levin[1], Sharon Nachman[5]

[1]Pediatric Infectious Diseases, University of Colorado Denver, Aurora, CO, United States, [2]Harvard School of Public Health, Boston, MA, United States, [3]Frontier Science & Technology Research Foundation, Amherst, NY, United States, [4]The Children's Hospital, Aurora, CO, United States, [5]State University of New York at Stony Brook, Stony Brook, NY, United States

Session P-T1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Clinical Outcomes of HIV-Exposed Uninfected Infants

857 **Maternal CD4 and Infectious Risk for Uninfected Infants Born To HIV+ Mothers in a European Country**

Clement Taron-Brocard[1], Jerome Le Chenadec[1], Albert Faye[2, 3], Catherine Dollfus[4], Laurent Mandelbrot[1, 5], Vincent Gajdos[6, 7], Anais Perilhou[1], Jean-Marc Labaune[8], Stephane Blanche[9, 10], Josiane Warszawski[1, 11], and the ANRS French Perinatal Cohort (ANRS CO1/CO11)

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858 **Effect of Breastfeeding On Mortality and Morbidity in HIV-Exposed Un-Infected Children in Uganda**

Carina Marquez[1], Jaffer Okiring[2], Gabriel Chamie[1], Jane Achan[2, 3], Theodore Ruel[1], Abel Kakuru[2], Moses R. Kamya[2, 3], Edwin D. Charlebois[1], Grant Dorsey[1], Diane V. Havlir[1]

[1]University of California, San Francisco, San Francisco, CA, United States, [2]Infectious Diseases Research Collaboration, Kampala, Uganda, [3]Makerere University College of Health Sciences, Kampala, Uganda

859 **Growth Differences in Infants Born To Perinatally vs. Non-Perinatally HIV-Infected Women**

Jennifer Jao[1], Allison Agwu[2], Grace Mhango[3], Annie Kim[4], Kaye Park[5], Roberto Posada[6], Elaine J. Abrams[7], Nancy Hutton[8], Rhoda S. Sperling[9]

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860LB **Four Year Cotrimoxazole Prophylaxis Prevents Malaria in HIV-Exposed Children: A Randomized Trial**

Jaco Homsy[1], Grant Dorsey[2], Emmanuel Arinaitwe[3], Humphrey Wanzira[3], Abel Kakuru[3], Victor Bigira[3], Mary Muhindo[3], Moses R. Kamya[4], Taylor G. Sandison[5], Jordan W. Tappero[6]

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861 **No Evidence of Neurodevelopmental Delay in HEU Infants Exposed To cART In Utero and Breastfeeding**

Mary Ngoma[1], Jessica Harper[2], Jennifer Hunter[2], Paige Church[2], Helene Cote[3], Chisomo Selemani[1], Mulla Chandwe[1], Arianne Albert[3], Marylou Smith[2], **Michael Silverman**[2]

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Session P-T2 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Neonatal Sequelae of In Utero ART Exposure

862 **In Utero Exposure To Zidovudine and Neonatal Heart Abnormalities in the ANRS-EPF/PRIMEVA Studies**

Jeanne Sibiude[1, 2], Jérome Le Chenadec[2], Damien Bonnet[3, 4], Roland Tubiana[5, 6], Laurent Mandelbrot[1, 7], Sandrine Delmas[2], Camille Runel Beliard[8], Babak Khoshnood[9], Josiane Warszawski[10, 11], Stéphane Blanche[12, 13], for the ANRS-French Perinatal Cohort/PRIMEVA

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863LB **Congenital Anomalies and In Utero Antiretroviral Exposure in HIV-Exposed Uninfected Children**

Paige L. Williams[1], Cenk Yildirim[2], Marilyn Crain[3], Rohan Hazra[4], Russell B. VanDyke[5], Kenneth Rich[6], Jennifer S. Read[7], Emma Stuard[8], Mobeen Rathore[9], D. Heather Watts[10], for the Pediatric HIV/AIDS Cohort Study

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of Pediatric Infectious Diseases, University of Alabama at Birmingham, Birmingham, AL, United States, [4]Maternal and Pediatric Infectious Disease Branch, National Institute of Child Health and Human Development, Bethesda, MD, United States, [5]Department of Pediatrics, Tulane University School of Medicine, New Orleans, LA, United States, [6]Department of Pediatrics, University of Illinois at Chicago, Chicago, IL, United States, [7]Department of Pediatrics, George Washington University School of Medicine, Washington, DC, United States, [8]Department of Pediatric Infectious Disease, Bronx-Lebanon Hospital, Bronx, NY, United States, [9]University of Florida at Jacksonville, Jacksonville, FL, United States, [10]Office of the U.S. Global AIDS Coordinator, U.S. Department of State, Washington, DC, United States

865 Abnormal Fatty-Acid Oxidation in HIV-Exposed Uninfected Neonates in the United States

Brian Kirmse[1], Tzy-Jyun Yao[2], Sean Hofherr[1], Paige Williams[2], Deborah Kacanek[2], Rohan Hazra[3], William Borkowsky[4], Russell Van Dyke[5], Marshall Summar[1]

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866 Comparative Genotoxic Signatures in Cord Blood Cells From Neonates Exposed To AZT or TDF In Utero

Alexandre Vivanti[1], Wendy Cuccuini[2, 3], Sonia Luce[1], Tayebeh Soheili[1], Laurent Mandelbrot[4, 5], Josiane Warszawski[5], Jean Soulier[3, 6], Marina Cavazzana[1, 7], Isabelle André-Schmutz[1], Stéphane Blanche[8, 9]

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867 Risk Factors for Preterm Birth in Pregnant Women Randomized To Lopinavir- or Efavirenz-Based ART

Catherine A. Koss[1], Paul Natureeba[2], Albert Plenty[3], Flavia Luwedde[2], Julia Mwesigwa[2], Edwin Charlebois[3], Tamara Clark[1], Bridget Nzarubara[2], Moses Kamya[4], Diane Havlir[1], Deborah Cohan[5]

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Session P-T3 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Pregnancy Incidence and Outcomes Among Women in ART Programs

868 Incidence and Predicting Factors of Pregnancy Post-ART Initiation in 9 West African Countries

Juan Burgos-Soto[1, 2], Eric Balestre[1, 2], Albert Minga[3], Samuel Ajayi[4], Adrien Sawadogo[5], Marcel D. Zannou[6], Valériane Leroy[1, 2], Didier K. Ekouevi[2, 7], François Dabis[1, 2], Renaud Becquet[1, 2], IeDEA West Africa Collaboration

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869 Pregnancy and Retention or Progression To AIDS/Death Post-ART in 9 West African Countries

Albert Minga[1], **Juan Burgos-Soto[2, 3]**, Eric Balestre[2, 3], Benson Okwara[4], Moussa Y. Maiga[5], Akouda Patassi[6], Eugène Messou[7], Christian Wesje[8], François Dabis[2, 3], Renaud Becquet[2, 3], IeDEA West Africa Collaboration

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Session P-T4 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Cellular and Immune Correlates of MTCT

870 Maternal HIV Envelope V3-Specific IgG Responses Are a Correlate of Risk of Perinatal Transmission

Sallie P. Permar[1], Youyi Fong[2], Geneveive Fouda[1], Nathan A. Vandergrift[1], Peter Gilbert[2], Guido Ferrari[1], Munir Alam[1], Georgia D. Tomaras[1], Thomas N. Denny[1], Barton F. Haynes[1], Women and Infant Transmission Study Group

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871 Ontogeny of HIV-Targeted CD4+ T Cells During Exclusive and Non-Exclusive Breastfeeding

Elizabeth J. McFarland[1], Tina Powell[1], Weiming Zhang[2], Carolyne Onyango-Makumbi[3, 4], Kelsey Melander[5], Prossy Naluyima[6], Samuel Okurut[7], Michael A. Eller[8, 9], Mary Glenn Fowler[10, 11], Edward N. Janoff[12]

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872 Infant Variants Require More CD4 for Entry Than Maternal Variants Regardless of Transmission Route

Kyle J. Nakamura[1], Edwin R. Sobrera[1], Vicken Khatchadourian[1], Moses Sinkala[2], Chipepo Kankasa[3], Donald M. Thea[4], James I. Mullins[5], Louise Kuhn[6], Grace M. Aldrovandi[1]

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Session P-T5 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Characteristics of Pregnant Women in PMTCT

873 HIV Viral Load and CD4 Cell Count in Untreated Pregnant Women Entering Care in Cape Town, South Africa

Landon Myer[1], Tamsin Phillips[1], Marvin Hsiao[2], Allison Zerbe[3], James McIntyre[4], Linda-Gail Bekker[5], Elaine Abrams[3]

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874 **Detectable Viraemia Among Pregnant Women On Antiretroviral Therapy Initiating Antenatal Care**

Landon Myer[1], Tamsin Phillips[1], Allison Zerbe[2], Marvin Hsiao[3], James McIntyre[4], Elaine Abrams[2]

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875 **Steady Decline: Temporal Changes in Substance Use by HIV-Positive Pregnant Women in the US**

Kathryn Rough[1], Katherine Tassiopoulos[1], Deborah Kacanek[2], Raymond Griner[3], Ram Yogev[4], Kenneth C. Rich[5], George R. Seage[1], for the Pediatric HIV/AIDS Cohort Study

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Session P-T6 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Early Infant HIV Diagnosis

876 **Modeling the Performance and Cost of Early Infant HIV Diagnosis at Birth**

Intira J. Collins[1], Martina Penazzato[2], Dick Chamla[3], Anisa Ghadrshenas[4], Teri Roberts[5], Jennifer Cohn[5], Nicole Ngo-Giang-Huong[6], Nathan Shaffer[2], Meg Doherty[2], Lisa J. Nelson[2]

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877 **Access To Early Infant Diagnosis and Antiretroviral Therapy in Abidjan, Côte d'Ivoire, 2011-2013**

Divine Avit[1], Madeleine Folquet-Amorissani[2], Clarisse Amani-Bosse[1], Jeanne Eliam-Kouakou[1], Véronique Méa-Assandé[3], Edmond Aka[4], Irma Ahoba[5], Didier K. Ekouévi[6], Marguerite Timité-Konan[7], **Valériane Leroy**[8, 9], for the MONOD ANRS 12206 Study Group

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Session P-T7 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Risk Factors for MTCT

878 **Impact of Maternal Incident HIV Infection On Early HIV Vertical Transmission, South Africa in 2011**

Thu-Ha Dinh[1], Kevin Delaney[1], Debra Jackson[2], Selam Woldesenbet[3], Yogan Pillay[4], Ameena Goga[5]

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879 **Syphilis in HIV-Infected Mothers and Infants: Results From the NICHD/HPTN 040 Study**

Nava Yeganeh[1], Heather Watts[2], Margaret Camarca[3], Esau Joao[4], Jose Henrique Pilotto[5], Glenda Gray[6], Gerhard Theron[7], Valdilea G. Veloso[8], Lynne M. Mofenson[2], Karin Nielsen-Saines[1], NICHD HPTN 040/ P1043 Study Team

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880 **Antiretroviral Adherence Associated With Reduced Breastmilk HIV-1 Transmission: The BAN Study**

Nicole L. Davis[1], William C. Miller[2], Michael G. Hudgens[3], Charles S. Chasela[4], Dorothy S. Sichali[4], Dumbani Kayira[4], Athena P. Kourtis[5], Sascha R. Ellington[5], Denise J. Jamieson[5], Charles M. van der Horst[6]

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881 **Cytomegalovirus and Possibly Epstein-Barr Virus in Breast Milk May Facilitate HIV-1 Transmission**

Johannes Viljoen[1], Edouard Tuaillon[2], Nicolas Nagot[2], Siva Danaviah[1], Marianne Peries[2], Prevashinee Padayachee[1], Vincent Foulongne[2], Ruth Bland[1], Nigel Rollins[3], Marie-Louise Newell[1], **Philippe Van de Perre**[2]

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Session P-T8 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

PMTCT Approaches: Implementation and Outcome

882 **Programmatic Implementation of WHO Option B in Botswana Associated With Increased Projected MTCT**

Scott Dryden-Peterson[1, 2], Sajini Souda[3], Rebecca Zash[2, 4], Jennifer Chen[5], Chipo Petlo[6], Eldah N. Dintwa[6], Refeltetswe Lebelonyane[6], Mompati Mmalane[2], Shahin Lockman[1, 2], Roger L. Shapiro[2, 4]

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883 **Impact of Option B+ On Uptake, Retention, and Transmission: A Pre/Post Study in Lilongwe, Malawi**

Maria H. Kim[1, 2], Saeed Ahmed[1, 2], Peter N. Kazembe[2], Mina C. Hosseinipour[3, 4], Thomas P. Giordano[5], Elizabeth Y. Chiao[5], Xiaoying Yu[6], Debora Nanthuru[2], Mary E. Paul[1], Elaine J. Abrams[7]

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884 **Home, Antenatal Clinic or VCT: Preferences of Pregnant Women and Their Partners for Male HIV Testing**

Alfred Osoti[1, 2], Grace John-Stewart[3], James Kairie[4], John Kinuthia[4, 5], Barbra Richardson[1], Daisy Krakowiak[1], Carey Farquhar[6]

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885 **Early Infection Among Ugandan HIV-Exposed Infants Whose Mothers Received Option B+ vs Option A**

Julie N. Mugerwa[1], Zikulah Namukwaya[1], Adeodata Kekitiinwa[2, 3], Albert Maganda[2], Racheal Ayanga[1], Ayoub Kakande[1], Joyce Matovu[1], Josaphat Byamugisha[4], Godfrey Esiru[5], Mary G. Fowler[1, 6]

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886 **Lay Health Worker Support To Strengthen PMTCT: A Randomised Controlled Trial in South Africa**

Kathryn Stinson[1], Debbie van Zyl[2], Hlengiwe Mdebuka[1], Jean-Pierre Zeelie[2], Christopher J. Colvin[1], Leigh F. Johnson[1], David Coetzee[1], Helen Schneider[3]

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Session P-T9 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

ART Pharmacokinetics During Pregnancy and Breast-Feeding

887 **Low Darunavir Exposure During Pregnancy With 800/100 mg Darunavir/r QD Dosing**

Angela Colbers[1], José Moltó[2], Jelena Ivanovic[3], David Hawkins[4], Tariq Sadiq[5], Kabamba Kabeya[6], Andrea Gingelmaier[7], Katharina Weizsäcker[8], Graham Taylor[9], David Burger[1]

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888 **Pharmacogenetics of Efavirenz Excretion Into Human Breast Milk and Transfer To Breastfed Infants**

Adeniyi Olagunju[1, 2], Marco Siccardi[1], Ogechi Okafor[3], Oluseye Bolaji[2], 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

889 **Safety, Efficacy, and PK of Atazanavir/Ritonavir (300/100 mg QD) in HIV+ Pregnant Women Cohort**

Minh P. Lê[1], Charlotte Charpentier[2], Cathia Soulie[3], Houria Ichou[4], Julien Potier[1], Roland Tubiana[5], Sophie Matheron[6], Roland Landman[6], Laurent Mandelbrot[7], Gilles Peytavin[1]

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890 **A Comparison of the Pharmacokinetics of Raltegravir During Pregnancy and Postpartum**

Maren Blonk[1], Angela Colbers[1], Carmen Hidalgo-Tenorio[2], Katharina Weizsäcker[3], José Moltó[4], David Hawkins[5], Marchina van der Ende[6], Andrea Gingelmaier[7], Graham Taylor[8], David Burger[1], PANNA Network

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891 **Intensive Etravirine PK and HIV-1 Viral Load in Breast Milk and Plasma in HIV+ Women Receiving HAART**

LaShonda Y. Spencer[1], Siyu Liu[2], Chia-Hao Wang[1], Michael Neely[1], Stan Louie[2], Andrea Kovacs[1]

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892 **Effective Exposure To Atazanavir During Pregnancy, Regardless of Tenofovir Use**

Angela Colbers[1], David Hawkins[2], Carmen Hidalgo-Tenorio[3], Marchina van der Ende[4], Kabamba Kabeya[5], Andrea Gingelmaier[6], Katharina Weizsäcker[7], John Lambert[8], Jürgen Rockstroh[9], David Burger[10]

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Session P-U1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

ART in Children and Adolescents

893 **P1073: Immune Reconstitution Inflammatory Syndrome - Wide Spectrum and Severity in Children**

Mark F. Cotton[1], Hilda Mujuru[2], Raziya Bobat[3], Boniface Njau[4], Avy Violari[5], Vidya Mave[6], Charles Mitchell[7], James Oleske[8], Bonnie Zimmer[9], Savita Pahwa[10]

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894 **sdNVP Exposure and ART Response in Children <3 Years Initiating ART in the ARROW Trial**

Philippa Musoke[1], Victor Musiime[2], Kusum Nathoo[3], Patricia Nahirya-Ntege[4], Alexander J. Szubert[5], Kuda Mutasa[6], David E. Williams[2], Moira Spyer[5], Ann Sarah Walker[5], **Diana M. Gibb**[5], and the ARROW Trial Team

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895 **Virologic Response To Efavirenz vs Nevirapine-Containing ART in the ARROW Trial**

Adeodata Kekitiinwa[1], Moira Spyer[2], Richard Katuramu[3], Victor Musiime[4], Tawanda Mhute[5], Sabrina Kitaka[1], Oscar Senfuma[4], Marshall Munjoma[5], Ann Sarah Walker[2], Diana M. Gibb[2], and the ARROW Trial Team

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896 **Growth Recovery Among HIV+ Children Randomized To Lopinavir/Ritonavir or NNRTI-Based Therapy**

Theodore Ruel[1], Abel Kakuru[2], Gloria Ikilezi[2], Florence Mwangwa[2], Albert Plenty[3], Edwin Charlebois[3], Diane Havlir[3], Moses Kamya[4], Jane Achan[5]

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Session P-U2 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

HIV Drug Resistance and Tropism in Children and Youth

897 Prevalence and Predictors of HIV Drug Resistance Among US Children and Youth With Perinatal HIV

Russell B. Van Dyke[1], Kunjal Patel[2], Ron M. Kagan[3], Shirley Traite[4], William A. Meyer[5], Katherine Tassiopoulos[2], George R. Seage[2], Lorna M. Seybolt[6], Sandra Burchette[7], Rohan Hazra[8], and the Pediatric HIV/AIDS Cohort Study

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898 HIV-1 Resistance After Randomized Virologic Switch at 1000 or 30,000 c/ml in Children

Linda Harrison[1], Diana Gibb[2], Susan Fiscus[3], Yacine Saidi[4], Eleni Nastouli[5], Lynda Harper[2], Alexandra Compagnucci[4], Abdel Babiker[2], Ann Melvin[6], Gareth Tudor-Williams[7], and the PENPACT 1 (PENTA 9/PACTG 390) Study Team

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899 Longitudinal Evolution of Tropism in Perinatal HIV-1 Infection: The HICCUP Study

Caroline Foster[1], Steve Kaye[2], Colette Smith[3], Nicola Mackie[4]

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Session P-U3 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

ARV Pharmacokinetics, Pharmacogenetics, and Safety in Children and Adolescents

900 Rilpivirine Pharmacokinetics in HIV-1-Infected Adolescents: A Substudy of PAINT (Phase II Trial)

Herta Crauwels[1], Annemie Hoogstoel[1], Simon Vanveggel[1], Wayne Yarnall[2], Marita Stevens[1], Katia Boven[2]

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901 Safety, Pharmacokinetics and Efficacy of Dolutegravir in Treatment-Experienced HIV+ Children

Rolando M. Viani[1], Carmelita Alvero[2], Terry Fenton[2], Edward Acosta[3], Rohan Hazra[4], Ellen O'Gara[5], Barbara Heckman[6], Debra Steimers[7], Sherene Min[7], Andrew Wiznia[8]

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902 Bioequivalence of Two Pediatric Formulations vs Adult Tablet Formulation of Elvitegravir

Joseph M. Custodio[1], Xiang Yin[2], Hiba Graham[3], Mischa Hepner[4], Lauren Wiser[5], Erin Quirk[3], Brian P. Kearney[1], Srinivasan Ramanathan[1]

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903 CYP2B6 Polymorphisms Challenge Generalized FDA Efavirenz Dosing Guidelines in Children < 3 Yrs

Carolyn Bolton Moore[1], Edmund Capparelli[2], Pearl Samson[3], Mutsa Bwakura-Dangarembizi[4], Patrick Jean-Philippe[5], Carol Worrell[6], Barbara Heckman[7], Lynette Purdue[6], Stephen A. Spector[2], Ellen G. Chadwick[8], IMPAACT P1070 team

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904 High Nevirapine and Low Lopinavir/Efavirenz Exposures in Resource-Poor Ugandan Children

Imke H. Bartelink[1], Rada M. Savic[1], Grant Dorsey[2], Henriette J. Scherpbier[3], Edmund Capparelli[4], Jane Achan[5], Albert Plenty[6], Moses Kamya[5], Diane Havlir[2], Francesca T. Aweeka[7]

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905 Bone and Renal Safety at 96 Weeks of TDF-Containing Regimens in HIV-Infected Thai Children

Wasana Prasitsuebsai[1], Thanyawee Puthanakit[1, 2], Tanakorn Apornpong[1], Siriwan Keadpudsa[1], Torsak Bunupuradah[1], Thongsuai Chuanjaroen[1], Narukjaporn Thammajaruk[1], Thidarat Jupimai[1], Stephen J. Kerr[1, 3], Jintanat Ananworanich[2, 4]

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906LB Safety and Efficacy of Dolutegravir in HIV Treatment-Experienced Adolescents: 48-Week Results

Rolando M. Viani[1], Carmelita Alvero[2], Terry Fenton[2], Edward Acosta[3], Rohan Hazra[4], Ellen O'Gara[5], Barbara Heckman[6], Debra McCarty-Steimers[7], Sherene Min[8], Andrew Wiznia[9]

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907 Simulation and Exposure-Based Assessment of Pediatric Lopinavir Fixed-Dose Combination Product

Saïk Urien[1], Naïm Bouazza[1], Frantz Foissac[1], Floris Fauchet[1], David Burger[2], Jean-René Kiechel[3], Edmund Capparelli[4], Jean-Marc Tréluyer[1], Marc Lallemant[3]

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908 **Bioequivalence of Two Pediatric Formulations vs Adult Tablet Formulation of Cobicistat**

Joseph M. Custodio[1], Xiang Yin[2], Hiba Graham[3], Mischa Hepner[4], Joanna Koziara[5], Erin Quirk[3], Brian P. Kearney[1], Srinivasan Ramanathan[1]

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909 **Pharmacokinetics, Efficacy, and Safety of an Integrase Inhibitor STR in HIV-Infected Adolescents**

Aditya Gaur[1], Jan Fourie[2], Kulkanya Chokephaibulkit[3], Linda-Gail Bekker[4], Xiang Yin[5], Joseph M. Custodio[5], **Sean R. Bennett**[5], Andrew Cheng[5], Erin Quirk[5]

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Session P-U4 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Host and Immune Response in Children and Adolescents

910 **Complex Pattern of Inflammatory Biomarkers After ART Initiation in HIV-Infected African Children**

Nigel Klein[1], Chipo Berejena[2], Godfrey Pimundu[3], Pietro Pala[4], Tichaona Vhembo[2], Victor Musiime[3], Philip Kasirye[5], Hannah Poulsom[1], **Ann Sarah Walker**[6], Andrew J. Prendergast[7], and the ARROW Trial Team

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911 **Preferential Preservation of Helios+Foxp3+ Regulatory T Cell Subset in HIV Infected Children**

Guenet Degaffe, Ramia Zakhour, Weihe Zhang, German Contreras, Cynthia Bell, Gilhen Rodriguez, Gabriela Del Bianco, James Murphy, **Gloria P. Heresi**, Dat Q. Tran

Pediatrics, UT Health, Houston, TX, United States

912 **Perturbation of Regulatory T Cell Subsets in HIV Infected Children**

Alka Khaitan[1], Mussa Mwamzuka[2], Fatma Marshed[2], Adam Kravietz[3], Tiina Ilmet[1], Swale Said[2], Aabid Ahmed[2], William Borkowsky[1], Derya Unutmaz[4]

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913 **Incomplete Immune Reconstitution in HIV-1-Infected Children With Virological Suppression**

Paul Krogstad[1], Kunjal Patel[2], Brad Karalius[2], Mark Abzug[3], James Oleske[4], George Seage[2], Andrew Wiznia[5], Rohan Hazra[6], Russell Van Dyke[7], for The Pediatric HIV/AIDS Cohort Study and NISDIInvestigators

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914 **Lower Inflammatory Biomarkers in Children Randomized To Prolonged Cotrimoxazole Prophylaxis**

Andrew J. Prendergast[1], Mutsawashe Bwakura Dangarembizi[2], Victor Musiime[3], Joseph Lutaakome[4], Adeodata Kekitiinwa[5], Godfrey Pimundu[3], Annie Shonhai[2], Moira Spyer[6], Nigel Klein[7], **Ann Sarah Walker**[6], and the ARROW Trial Team

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915 **CD127 Expression On Naive T-Cells and HIV Replication in Youths Infected in the Perinatal Period**

Daniel Scott-Algara[1], Jérôme Le Chenadec[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]

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Session P-U5 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Complications of HIV and ART in Children and Adolescents

916 **Pediatric HIV Infection and Dental Caries in the Era of Antiretroviral Therapy in West Africa**

Noella Rajonson[1], David G. Meless[2], Boubacar Ba[3], Malick Faye[4], Jean-Serge Diby[5], Serge N'zoré[6], Sébastien Datté[6], François Dabis[1], Shiboski Caroline[7], **Elise Arrivé**[1]

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917 **Preclinical Atherosclerosis in Eastern Africa: Results From a Pediatric Ethiopian Cohort**

Julia C. Rosebush[1], Rudolph L. Gleason[2], Alexander Caulk[2], Daniel Seifu[3], Allison Eckard[1], Workeabeba Taye[4]

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918 **Insulin Resistance in HIV-Infected Youth Is Associated With Decreased Mitochondrial Respiration**

Jody K. Takemoto[1], Jiajia Wang[2], Denise L. Jacobson[2], Tracie L. Miller[3], Mitchell E. Geffner[4], Russell B. Van Dyke[5], Daniel E. Libutti[1], Patricia Graham[3], Mariana Gerschenson[1], for the Pediatric HIV/AIDS Cohort Study

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919 **The Effect of Long-Term Zidovudine On Hematological Parameters in the ARROW Randomized Trial**

Victor Musiime[1], Adrian Cook[2], Patricia Nahirya-Ntege[3], **Mutsawashe Bwakura-Dangarembizi**[4], Adeodata Kekitiinwa[5], Margaret Thomason[2], Richard Katuramu[3], Philippa Musoke[5], Ann Sarah Walker[2], Diana M. Gibb[2], and the ARROW Trial Team

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920 **Bone Quality Determination by Ultrasonometry in Young South African HIV-Infected Children**

Stephen M. Arpadi[1], Stephanie Shiau[1], Jonathan J. Kaufman[2], Ashraf Coovadia[3], Renate Strehlau[3], Francoise Pinillos[3], Michael T. Yin[1]

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Session P-U6 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Response To Early ART Initiation in Infants

922 **Routine Antibody Tests Have No Place in Determining HIV Status After Early ART: Evidence From CHER**

Helen Payne[1,2], Nonhlanhla Mkhize[3], Lynn Morris[3], Kennedy Otwombe[4], Ravindre Panchia[4], Avy Violari[4], Nigel Klein[1], Abdel G. Babiker[5], Mark F. Cotton[2], Diana M. Gibb[5]

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923 Different Profiles of HIV in Early Treated HIV-Infected Children Seronegative by ELISA in Cameroon

Mathurin C. Tejiokem[1], Anfumbom Kfutwah[2], Francis Ateba Ndongo[3], Suzie Tetang Ndiang[4], Ida Calixte Penda[5, 6], William Mbanzouen[2], Félicité Owona[1], Josiane Warszawski[7, 8], Christine Rouzioux[9, 10], Albert Faye[11, 12]

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924 Greater Virologic Control in Infants Initiated On ART Before 6 Months of Age

Stephanie Shiau[1], Ashraf Coovadia[2], Karl-Gunter Technau[2], Renate Strehlau[2], Leigh Martens[2], Francoise Pinillos[2], Elaine J. Abrams[1], Louise Kuhn[1]

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925 Early Viral Suppression Improves Neurocognitive Outcomes in HIV-Infected Children

Claudia S. Crowell[1], Yanling Huo[2], Katherine Tassiopoulos[2], Kathleen M. Malee[3], Ram Yogev[3], Rohan Hazra[4], Richard M. Rutstein[5], Sharon L. Nichols[6], Renee A. Smith[7], William J. Muller[3], for the IMPAACT 219C Study Team and the PediatricHIV/AIDS Cohort Study

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926 Early Cytomegalovirus Viraemia and Clinical Outcomes of HIV-Infected Children in the Early ART Era

Nei-yuan Hsiao[1], Kennedy Otwombe[2], Landon Myer[3], Avy Violari[2], Diana Gibb[4], Ravindre Panchiar[2], Abdel Babiker[4], Patrick Jean-Phillipe[5], Mark Fredric Cotton[6]

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Session P-U7 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Co-Infections and Treatment Responses in Children and Adolescents

927 Risk Factors Associated With TB in Children Receiving ART in a South African Multicenter HIV Cohort

Alana T. Brennan[1, 2], Mhairi Maskew[2], Kate Schnippel[2], Ian Sanne[1, 2], Lawrence Long[2], Matt P. Fox[1, 2]

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928 Hepatitis B Treatment Response To TDF in 3TC-Experienced Perinatally HIV-Infected Adolescents

Linda Aurpibul[1], Pagakrong Lumbiganon[2], Pope Kosalaraksa[2], Rawiwan Hansudewechakul[3], Pawinee Taeprasert[3], Torsak Bunupuradah[4], Thanyawee Puthanakit[4, 5], **Khuanchai Supparatpinyo**[1]

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929 T-Cell Senescence and CMV Positivity and Viremia Status in Perinatally HIV-Infected Children

Suad Kapetanovic[1], Lisa Aaron[2], Grace Montepiedra[2], Andrea Kovacs[3]

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Session P-U8 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Outcomes Among Adolescents: Perinatally and Behaviorally Acquired HIV Infection

930 Outcomes of Perinatally HIV-Infected Adolescents On Antiretroviral Therapy in Southern Africa

Mary-Ann Davies[1], Kathryn Stinson[1], Karl Technau[2, 3], Sam Phiri[4], Helena Rabie[5], Maureen Wellington[6], Janet Giddy[7], Robin Wood[8, 9], Lynne Mofenson[10], Harry Moultrie[11, 12], for International Epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA)

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931 Greater Early CD4 Responses To cART Initiation Not Maintained for Non-Perinatal Youth

Allison Agwu[1], Guy Mahiane[2], Bareng A. S. Nonyane[3], Keri Althoff[2], Baligh Yehia[4], Stephen Berry[5], Richard Rutstein[6], Kelly A. Gebo[5], for the HIV Research Network

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932 Parental Absence From Clinic Predicts Virologic Failure in Adolescents in Botswana

Elizabeth Lowenthal[1, 2], Tafireyi Marukutira[3], Ontibile Tshume[3], Jennifer Chapman[2], Tebo Dipotso[3], Omphile Lepodisi[3], Keboletse Mokete[3], Jean Nachega[4, 5], Gabriel Anabwani[3], Robert Gross[6, 7]

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933LB **ART De-Intensification To ATVr Monotherapy in Adolescents Sustains CD4 and Activation Responses**

Bret J. Rudy[1], Bill Kapogiannis[2], Craig Wilson[3], Allison Agwu[4], Maureen Goodenow[5], Carol Worell[6], John W. Sleasman[7], Sue X. Li[8], James Bethel[8], Kathleen Squires[9]

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934 **Factors Associated With Successful Retention Among Non-Perinatally HIV-Infected Youth**

Charles Farmer[1], Baligh Yehia[2], Richard Rutstein[3], Stephen Berry[4], Kelly Gebo[5], Allison Agwu[6], for the HIV Research Network

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Session P-V1 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Pre-Clinical Studies of Microbicides

935 **PCR as a Virological Endpoint for Testing Microbicide Efficacy in the Colorectal Explant Model**

Laura Janocko[1], Alexiy Nikiforov[1], Ian McGowan[2]

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936 **Irreversible Inactivation and Breakdown of HIV1 With Env-gp120 Targeting Peptide Triazole Thiols**

Arangassery Rosemary Bastian[1], Lauren D. Bailey[2], Diogo R. D. Moreira[3], Kevin Freedman[4], Karyn McFadden[5], Caitlin Duffy[2], Ali Emileh[6], Jefferey Jacobson[7], James A. Hoxie[8], Irwin Chaiken[2]

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937 **Labyrinthopeptin A1 Demonstrates Potent and Dual Anti-HSV and Anti-HIV Activity**

Geoffrey Férir[1], Mariya Petrova[2], Graciela Andrei[1], Robert Snoeck[1], Jos Vanderleyden[2], Roderich Süssmuth[3], Mark Brönstrup[1], **Dominique Schols**[1]

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938 **GSK1265744 Demonstrates Robust In Vitro Activity Against Various Clades of HIV-1**

Sharon L. Karmon[1], Hiroshi Mohri[1], William Spreen[2], Zhi Hong[2], David Ho[1], Martin Markowitz[1]

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Session P-V2 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Animal Models of Clinical Studies and PrEP

939 **Does Tenofovir Gel Alter HIV Disease Progression in CAPRISA 004 Trial Seroconvertors?**

Nigel J. Garrett[1], Lise Werner[1], Nivashnee Naicker[1], Thabile Mthembu[1], Vivek Naranbhai[1], Sengeziwe Sibeko[1], Natasha Samsunder[1], Carolyn Williamson[2], Quarraisha Abdool Karim[1, 3], Salim Abdool Karim[1, 3]

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940 **Efficacy of Vaginal Gel Containing Tenofovir and Emtricitabine Against Rectal SHIV Transmission**

Charles W. Dobard[1], Natalia Makarova[1], Rolieria West[1], Andrew Taylor[1], Chuong Dinh[1], Amy Martin[1], James Mitchell[1], Debra Hanson[2], Chou-Pong Pau[1], Walid Heneine[1]

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941LB **GSK1265744 Long-Acting Protects Macaques Against Repeated High-Dose Intravaginal Challenges**

Chasity D. Andrews[1], William R. Spreen[2], Yun Lan Yueh[2], Agegnehu Gettie[1], Kasi Russell-Lodrigue[3], Hiroshi Mohri[1], Cecilia Cheng-Mayer[1], Zhi Hong[2], David D. Ho[1], Martin Markowitz[1]

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942 **SHIV Infection Risk After Rectal Application of a Highly Osmolar Personal Lubricant**

Sundaram A. Vishwanathan[1], Monica Morris[2], Charles Rose[1], Richard J. Wolitski[1], Leecresia Jenkins[1], Shanon Ellis[1], Michael Hendry[1], Janet M. McNicholl[1], **Ellen N. Kersh**[1]

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Session P-V3 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Identifying and Reducing HIV Risk

943 **Controlled Trial of an Internet-Based Risk Reduction Intervention in HIV+ Men Who Have Sex With Men**

Joel Milam[1], Sonia Jain[2], Eric Daar[3], Michael Dube[1], Edward Seefreid[2], Eric Ellorin[2], Gustavo A. Jimenez-Maggiora[2], **Sheldon R. Morris**[2], Richard H. Haubrich[2], CCTG 592 Team

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944 **Changes in the Contribution (PAR%) of STIs To HIV Acquisition Among Kenyan FSWs From 1993 To 2012**

Linnet Masese[1], Jared M. Baeten[1], Barbra A. Richardson[1], Susan M. Graham[1], Elizabeth Bukusi[2], Juma Shafi[3], Walter Jaoko[3], James Kiarie[3], R. Scott McClelland[1]

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945 **Intervention To Reduce HIV/STI Among High-Risk Patients in China: Cluster Randomized Trial**

Don Operario[1], Debin Wang[2], Mei-Fen Yang[1], Kathleen Blaney[1], Jing Cheng[2], Hong Qian[2], Hongbo Zhang[2], Gregory Szekeres[3], Jerome Galea[3], Thomas Coates[3]

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946 **Validation of the Refined Denver HIV Risk Score Using a National HIV Testing Cohort**

Jason Haukoos[1], Emily Hopkins[1], Meggan Bucossi[1], Michael Lyons[2], Richard Rothman[3], Douglas White[4], Alia Al-Tayyib[5], Lucy Bradley-Springer[6], Allison Sabel[7], Mark Thrun[5]

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Session P-V4 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

PrEP, PEP, TasP

947 **Cost Effectiveness of Antiretrovirals in HIV Control in Rural Zambia: A Stochastic League Approach**

Brooke E. Nichols[1], Rob Baltussen[2], Janneke H. van Dijk[3], Phil E. Thuma[3], Jan L. Nouwen[4], Charles A. B. Boucher[1], David A. M. C. van de Vijver[1]

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948 **Darunavir(DRV)/r-Based PEP Versus Standard of Care (SOC) - the Randomized PEPDar Study**

Gerd Fätkenheuer[1], Norma Jung[2], Heiko Jessen[3], Albrecht Stoehr[4], Keikawus Arasteh[5], Johannes Bogner[6], Christoph Stephan[7], Christoph D. Spinner[8], Olaf Degen[9], Britta Ranneberg[10]

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949 **High Initiation of PrEP and ART in a Demonstration Project Among African HIV-Discordant Couples**

Renee Heffron[1], Connie Celum[1], Nelly Mugo[1, 2], Elly Katabira[3], Elizabeth Bukusi[2], Elioda Tumwesigye[4], Jessica Haberer[5, 6], Jared Baeten[1], for the Partners Demonstration Project Team

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950 **PrEP Is Efficacious for HIV Prevention Among Women Using DMPA for Contraception**

Renee Heffron[1], Nelly Mugo[1, 2], Edwin Were[3], James Kiarie[4, 5], Elizabeth Bukusi[2], Andrew Mujugira[1], Deborah Donnell[1, 6], Allan Ronald[7], Connie Celum[1], Jared Baeten[1], for the Partners PrEP Study Team

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951 **PrEP Interest, Uptake, and Adherence Among Young Men Who Have Sex With Men (YMSM) in the United States**

Sybil Hosek[1], Jaime Martinez[2], Kristine Santos[3], Megha Mehrotra[4], Christopher Balthazar[1], Pedro Serrano[1], Kelly Bojan[3], Robert Grant[4], The Adolescent Medicine Trials Network for HIV/AIDS Interventions

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952 **Early Adopters: Correlates of Chemoprophylaxis Use in an Online Sample of US Men Who Have Sex With Men**

Kenneth H. Mayer[1, 2], Catie Oldenberg[1, 3], David Novak[4], Douglas Krakower[1, 2], Matthew Mimiaga[1, 3]

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953 **Measuring Intermittent and Daily PrEP Adherence by Hair Levels, Self-Report and MEMS Caps Openings**

Sanjiv M. Baxi[1], Albert Liu[2], Peter Bacchetti[3], Gaudensia Mutua[4], Eduard Joachim Sanders[5], Freddie M. Kibengo[6], Jessica E. Haberer[7], James Rooney[8], Frances Priddy[9], Monica Gandhi[1]

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954 **Implementation of PrEP in STD Clinics: High Uptake and Drug Detection Among MSM in the Demonstration Project**

Stephanie E. Cohen[1], Eric Vittinghoff[2], Peter Anderson[3], Susanne Doblecki-Lewis[4], Oliver Bacon[1], Wairimu Chege[5], Richard Elion[6], Susan Buchbinder[7], Michael Kolber[4], Albert Liu[7]

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955 **High Medication Adherence Among HIV-1 Uninfected Women Experiencing Pregnancy in a PrEP Trial**

Lynn T. Matthews[1, 2], Renee Heffron[3], Nelly R. Mugo[3, 4], Craig R. Cohen[5], Craig W. Hendrix[6], Connie Celum[3, 7], David R. Bangsberg[1], Jared M. Baeten[3, 7], for the Partners PrEP Study Team

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956 **Willingness To Use Pre-Exposure Prophylaxis Among Community-Recruited Injection Drug Users**

Irene Kuo[1], Gregory L. Phillips[2], Manya Magnus[2], Jenevieve Opoku[3], Anthony L. Rawls[2], James Peterson[2], Michael Kharfen[3], Alan E. Greenberg[2]

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957 **PrEP Does Not Diminish the Pregnancy Prevention Effectiveness of Hormonal Contraception**

Pamela M. Murnane[1], Renee A. Heffron[1], Connie Celum[1], Elizabeth Bukusi[2], Deborah Donnell[1], James Kiarie[2], Nelly Mugo[2], Allan Ronald[3], Edwin Were[4], Jared Baeten[1]

[1]University of Washington, Seattle, WA, United States, [2]University of Nairobi, Nairobi, Kenya, [3]University of Manitoba, Winnipeg, MB, Canada, [4]Moi University, Eldoret, Kenya

958 **Uptake of Treatment as Prevention and Continuum of Care Among Men Who Have Sex With Men in Nigeria**

Christopher Akolo[1, 2], Stefan Baral[3], Julie Ake[4], Sara Kennedy[1], Benjamin Emmanuel[1], Ifeanyi Orazulike[5], Marc Boulay[6], Babajide Keshinro[4], William Blattner[1], Manhattan Charurat[1]

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959LB **FEM-PrEP: Participant Explanations for Non-Adherence**

Amy Corneli[1], Brian Perry[1], Kawango Agot[2], Khatija Ahmed[3], Kevin McKenna[1], Fulufhelo Malamatsho[3], Jacob Odhiambo[2], Joseph Skhosana[3], Lut Van Damme[4], FEM-PrEP study team

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960 **Prevention of HIV Transmission With Post-Exposure Prophylaxis After Infected-Blood Transfusion**

Sami H. Al Hajjar[1], Husn H. Frayha[1], Mohammad Al Hazmi[2], Reem Batawi[1], Kenneth McIntosh[3], Paul E. Sax[4], Emily Hanhauser[5], Daniel R. Kuritzkes[5], Jonathan Z. Li[5], Timothy J. Henrich[5]

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961 **Contingency Management Facilitates PEP Completion Among Stimulant-Using MSM**

Raphael J. Landovitz[1], Jesse B. Fletcher[2], Steve Shoptaw[3], Cathy J. Reback[2]

[1]Center for Clinical AIDS Research & Education, University of California, Los Angeles, Los Angeles, CA, United States, [2]Friends Community Center, Friends Research Institute, Los Angeles, CA, United States, [3]Family Medicine, University of California, Los Angeles, Los Angeles, CA, United States

Session P-V5 Poster Session

Wednesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Circumcision

962 **Male Circumcision: Association With HIV Prevalence, Knowledge, and Attitudes Among Women**

Bertran Auvert[1], Pascale Lissouba[2], Dirk Taljaard[3], Gilles Peytavin[4], Beverley Singh[5], Adrian Puren[6]

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963 **Lower Odds of HIV Among Circumcised MSM in China and Interaction With Anal Sexual Role**

Han-Zhu Qian[1], Yuhua Ruan[2], Yu Liu[1], Douglas F. Milam[1], Hans M. L. Spiegel[3], Lu Yin[1], Yiming Shao[2], Sten H. Vermund[1]

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964 **Client Experiences of Odor Associated With PrePex™ Device Male Circumcision in Botswana**

Adrian Musiige[1], Tigistu A. Ashengo[2], Lesego Busang[3], Kenanao Motlhoiwa[1], Alex Chipara[4], Galina Stolarsky[1], Frank Mwangemi[3], Conrad Ntsuape[5]

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965 **Penile Cytokines Correlate With HIV Target Cells and Decrease After Circumcision in Rakai, Uganda**

Jessica L. Prodger[1], Brett Shannon[1], Kamnoosh Shahabi[1], Xiangrong Kong[2], Cindy M. Liu[3], Lance Price[4,5], Godfrey Kigozi[6], David Serwadda[6], Ronald H. Gray[2], Rupert Kaul[1]

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966 **HIV Shedding From Male Circumcision Wounds in Rakai, Uganda**

Aaron A. R. Tobian[1], Jordyn G. Manucci[1], Godfrey Kigozi[2], Mary K. Grabowski[1], David Serwadda[2], Ronald H. Gray[1], Fred Nalugoda[2], Anthony Ndyanabo[2], Thomas C. Quinn[3], Maria J. Wawer[1]

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Session P-W1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Cascade of Care and Testing

967 **Finding Unawares: High Levels of Undiagnosed HIV Infection Among Moscow Men Who Have Sex With Men**

Andrea L. Wirtz[1,2], Carla E. Zelaya[2], Noya Galai[3], Alena Peryshkina[4], Vladimir Moguilnyi[4], Petr Dzhigun[4], Irina Kostetskaya[4], Carl Latkin[5], **Chris Beyrer[2]**

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968 **Increases in HIV Testing Among MSM: US National HIV Behavioral Surveillance System, 2008-2011**

Laura A. Cooley, Alexandra M. Oster, Cyprian Wejnert, Binh C. Le, Charles E. Rose, Gabriela Paz-Bailey

Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, Atlanta, GA, United States

969 **Feasibility of HIV Self-Test Vouchers To Raise Community-Level Serostatus Awareness, Los Angeles**

Robert Marlin[1], Sean Young[1], Greg Wilson[2], Jeffrey P. Rodriguez[3], Joe Montes[4], Jose Ortiz[5], Rhea Mathew[5], Zoe Glick[6], Jeffrey D. Klausner[1]

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970 **Availability, Accessibility, Price of Rapid HIV Self-Tests, New York City Pharmacies, Summer 2013**

Julie E. Myers[1,2], Olivia El-Sadr Davis[3], Elliott R. Weinstein[3], Molly Remch[3], Amy L. Edelstein[4], Blayne H. Cutler[1], Julia A. Schillinger[5,6]

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971 **Acceptability & Affordability of Self HIV Testing in an Urban Neighborhood With 3% Seroprevalencee**

Amy Nunn[1], Philip Chan[1], Caitlin Towey[1], Joanna Poceta[1], Sophie Feller[2], Stacey Trooksin[3]

[1]Division of Infectious Diseases, Warren Alpert Medical School of Brown University, Providence, RI, United States, [2]Jefferson Medical Collage, Philadelphia, PA, United States, [3]Drexel University College of Medicine, Philadelphia, PA, United States

972 **Getting To Zero: HIV Testing and Counselling in Kenya - Results From a Population-Based Survey**

Anne Nganga[1], Wanjiru Waruiru[2], Carol Ngare[1], Victor Ssempijja[3], Patricia Oluoch[4], Inviolata Njoroge[5], Thomas Gachuki[6], William Maina[1], Rex Mpazanje[7], Andrea A. Kim[3]

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973 Counselor Based Versus Integrated Routine HIV Screening in an Urban Emergency Department

Georgina Osorio[1], Anca Giurgiulescu[1], Zachariah Hennessey[1], Andrea Wood[2], Daniel Egan[3], Dan Wiener[2], Rituparna Pati[1], Victoria Sharp[1]

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974 Low Feasibiliy Rate of Self Testing With a Finger-Stick Whole Blood Test

Guillaume Gras[1], Pascal Le Bret[2], Jean Francois Dailloux[2], Gwenael Le Moal[3], Aurelia Raoult[4], Gaelle Fajole[5], Penelope Hodges[5], Claire Poirier[1], Frédéric Bastides[1], Louis Bernard[1]

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975 Estimating the Size of the Undiagnosed HIV Population in the Netherlands by Disease Stage

Ard van Sighem[1], Fumiyo Nakagawa[2], Daniela Bezemer[1], Daniela De Angelis[3], Eline Op de Coul[4], Matthias Egger[5], Frank de Wolf[6], Christophe Fraser[6], Andrew Phillips[2]

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976 Prenatal HIV Testing Coverage of Medicaid-Insured Women – United States, 2009–2010

Christine E. Ross, Guoyu Tao, Karen W. Hoover

DSTDP, CDC, Atlanta, GA, United States

977 Measuring Late HIV Diagnosis Among Men Who Have Sex With Men: AIDS Diagnosis vs. Testing Frequency

David A. Katz[1,2], Julia C. Dombrowski[1,2], Amy Bennett[2], Susan Buskin[1,2], Christina Thibault[2], Matthew R. Golden[1]

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Session P-W2 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Cascade of Care, Linkage, and Retention

978 Using HIV Surveillance Registry Data To Re-Link Patients To Care: The RSVP Project in San Francisco

Kate A. Buchacz[1], Miao-Jung Chen[2], Maree Kay Parisi[2], Maya Yoshida[2], Erin Antunez[2], Viva Delgado[2], Nicholas J. Moss[3], Susan Scheer[2]

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979 Disentangling Roles of Internalized Stigma and Depression in Women's Linkage To Care

Kristi L. Stringer[1], Bulent Turan[2], Maricianah Onono[3], Elizabeth A. Bukusi[3], Craig C. Cohen[4], Janet M. Turan[5]

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980 Longitudinal Treatment Outcomes in HIV-Infected Prisoners and Influence of Re-Incarceration

Jaimie P. Meyer[1,2], Javier Cepeda[3], Johnny Wu[4], Robert L. Trestman[4], Frederick L. Altice[1,3], Sandra A. Springer[1]

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981 Imprisonment Among a Large US Clinical Cohort of HIV-Positive Outpatients

David L. Rosen[1], Carol E. Golin[2], Catherine A. Grodensky[3], Samuel Stinnette[1], Becky L. White[4], Sonia Napravnik[1], David A. Wohl[4]

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982 A Surveillance-Based Risk-Scoring Tool To Prioritize Cases for HIV Care Re-Linkage Efforts

Julia C. Dombrowski[1,2], James P. Hughes[1], Amanda D. Castel[3], Kathleen A. Brady[4,5], Susan Buskin[1,2], Amy Bennett[2], Matthew R. Golden[1,2]

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983 Beyond Core Indicators of Retention in HIV Care: Added Prognostic Value of Missed Clinic Visits

Michael J. Mugavero[1], Andrew O. Westfall[1], Elvin Geng[2], Stephen R. Cole[3], Heidi M. Crane[4], Mari M. Kitahata[4], W. Christopher Mathews[5], Sonia Napravnik[6], James L. Raper[1], CFAR Network of Integrated Clinical Systems (CNICS)

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984 National ART Monitoring System Enables Robust Transfer-Adjusted Retention Analyses in Namibia

Anna Jonas[1], Andrew Maher[2], Ray W. Shiraishi[3], Michael de Klerk[1], Francina Kaindjee-Tjituka[1], Gram Mutandi[2], Sadhna V. Patel[2], Anne-Marie Nitschke[1], Alexinah Muadinohamba[1], David W. Lowrance[2]

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985 Migration After HIV Diagnosis, United States

Lorena Espinoza, H. Irene Hall, Aruna Surendera Babu, Tian Tang, Mi Chen

Division of HIV/AIDS Prevention, CDC, Atlanta, GA, United States

986 Early Linkage To HIV Care and Antiretroviral Therapy Use Among MSM — 20 US Cities, 2008 and 2011

Brooke Hoots, Teresa Finlayson, Cyprian Wejnert, Gabriela Paz-Bailey for the NHBS Study Group

CDC, Atlanta, GA, United States

987 The Impact of Opioid Substitution Treatment On Highly Active Antiretroviral Treatment Adherence

Bohdan Nosyk, Jeong Min, Viviane Lima, Guillaume Colley, Benita Yip, Evan Wood, Julio Montaner

BC Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada

988 **Correlation Between Community Variables and HIV Linkage To Care and Viral Suppression, Atlanta, GA**

Neela D. Goswami[1,2], Sharoda Dasgupta[2], Patrick Sullivan[2], Deepali Rane[3], Carlos del Rio[1,2], Travis Sanchez[2]

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Session P-W3 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Cascade of Care, Community Viral Load, and Viral Suppression

989 **Viral Suppression Among Foreign-Born HIV-Infected Persons in the United States**

Tanya R. Myers[1,2], Jacek Skarbinski[1]

[1]CDC, Atlanta, GA, United States, [2]LSHTM, London, United Kingdom

990 **Mapping Community Viral Load and Transmission Potential Prevalence of HIV Among MSM in New York City**

Hong Van Tieu[1,2], Vijay Nandi[1], James E. Egan[3], Victoria Frye[4], Donald R. Hoover[5], Eduardo Baez[1], Debbie Lucy[1], Magdalena Cerda[6], Danielle C. Ompad[7], Beryl A. Koblin[1]

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991 **HIV Care and Viral Suppression Among Persons Living With HIV/AIDS, New York City 2006-2010**

Lucia V. Torian, Qiang Xia, Ellen W. Wiewel

HIV Epidemiology Program, New York City Department of Health, Long Island City, NY, United States

992LB **Low Incidence and High Population Viral Suppression in Malawi: The Chiradzulu HIV Incidence Study**

David Maman[1], Sophie Masson[1], Benson Chilema[2], Charles Masiku[3], Elizabeth Szumilin[4], Ahidjo Ayouba[5], Benjamin Riche[6], Etard Jean-Francois[1,7]

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993 **Disparities in Viral Suppression Among a Large Cohort of HIV-Infected Persons in Washington, DC**

Amanda D. Castel, Alan E. Greenberg, Heather Young, Mariah M. Kalmin, DC Cohort Executive Committee

Dept. of Epidemiology and Biostatistics, The George Washington University, Washington, DC, United States

994 **Community Viral Load and HIV Incidence: A Multi-City Study of High-Risk Populations in India**

Sunil S. Solomon[1,2], Shruti H. Mehta[1], Aylur K. Srikrishnan[2], Oliver Laeyendecker[1,3], Shanmugam Saravanan[2], Allison McFall[1], Pachamuthu Balakrishnan[2], Suniti Solomon[2], David D. Celentano[1], Gregory M. Lucas[1]

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995 **Declines in Community Viral Load in the Context of Population Prevention Strategies in the Bronx**

David B. Hanna[1], Uriel R. Felsen[1,2], Mindy S. Ginsberg[1], Barry S. Zingman[1,2], Robert S. Beil[1,2], Donna C. Futterman[1,2], Howard D. Strickler[1], Kathryn Anastos[1,2]

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Session P-W4 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Cascade of Care

996 **New Epidemiological Indicator To Estimate the Gap Between WHO Eligibility ART Criteria and Reality**

Jacques D. A. Ndawinz[1], Xavier Anglaret[2,3], Eric Delaporte[4,5], Sinata Koulla-Shiro[6], Delphine Gabillard[2,3], Dominique Costagliola[7,8], Virginie Supervie[7,8]

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997 **Trends in Cascade of Care in the Eastern European Country of Georgia: 2008-2012**

Nikoloz Chkhartishvili[1], Otar Chokoshvili[1], Lali Sharvadze[1,2], Jack A. DeHovitz[3], Carlos del Rio[4], Tengiz Tsertsvadze[1,5]

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998 **Use of National Standards To Monitor HIV Care and Treatment in a High Prevalence City – Washington, DC**

Amanda D. Castel, Alan E. Greenberg, Mariah M. Kalmin, Heather Young, DC Cohort Executive Committee

Dept. of Epidemiology and Biostatistics, The George Washington University, Washington, DC, United States

999 **Potential Impact of Viral Load On ART Eligibility Criteria in Swaziland**

Naomi Bock[1], Ruth Emerson[2], Charles Azih[3], Deborah Donnell[2], George Bicego[1], Velephi Okello[3], Neena Philip[4], Rejoice Nkambule[3], Yen Duong[1], Jessica Justman[4]

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1000 **Health Insurance for PLWH: Establishing a Baseline To Monitor the Impact of the Affordable Care Act**

Baligh R. Yehia[1], Allison A. Agwu[2], Stephen A. Berry[2], Joshua P. Metlay[3], Kelly Gebo[2]

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Session P-W5 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Acute Infection

1001 **Atypical Clinical Presentations Occur in One Third of 293 Patients With a Primary HIV-1 Infection**

Dominique L. Braun, Roger Kouyos, Belinda Balmer, Christina Grube, Rainer Weber, Huldrych Günthard

Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, Zurich, Switzerland

1002 **Evaluating New Definitions of Acute and Early HIV Infection From HIV Surveillance Data**

Susan E. Buskin[1,2], Neway G. Fida[1], Amy B. Bennett[1], Matthew R. Golden[1,3], Joanne D. Stekler[1,4]

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1003 **Association Between Number of Acute Retroviral Symptoms and Extended High Viremia by HIV-1 Subtype**

Kimberly A. Powers[1], Matthew A. Price[2, 3], Etienne Karita[4], Anatoli Kamali[5], William Kilembe[6], Susan Allen[7], Eric Hunter[7], Omu Anzala[8], Pat Fast[2], Eduard J. Sanders[9, 10]

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1004 **Targeted Screening of Young Adults for Acute HIV-1 Infection at Care Seeking in Kenya**

Eduard J. Sanders[1, 2], Peter Mugo[1], Henrieke A. B. Prins[1], Elizabeth Wahome[1], Alexander Thiong'o[1], Grace Mwasigadi[1], Elisabeth M. Van der Elst[1], Anisa Omar[3], Adrian D. Smith[4], Susan M. Graham[1, 5]

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Session P-W6 Poster Session

Wednesday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Incidence Assays

1005 **Independent Evaluation of Predicate Incidence Assays for HIV Surveillance**

Reshma Kassanjee[1], Christopher Pilcher[2], Sheila Keating[3], Shelley Facente[2], Matt Price[4], Jeffrey Martin[2], Susan Little[5], Alex Welte[1], Michael Busch[3], Gary Murphy[6], Consortium for the Evaluation and Performance of HIV Incidence Assays (CEPHIA)

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1006 **Performance of the Limiting Antigen-Avidity EIA for Use With Dried Blood Spot Specimens**

Erin K. Rottinghaus, Trudy Dobbs, Bharat S. Parekh, Yen T. Duong

Centers for Disease Control and Prevention, Atlanta, GA, United States

1007 **The Impact of HIV Subtype On Specificity of Cross-Sectional HIV Incidence Assays in Rakai, Uganda**

Andrew F. Longosz[1], David Serwadda[2, 3], Fred Nalugoda[3], Godfrey Kigozi[3], Veronica Franco[4], Ronald H. Gray[3, 5], Thomas C. Quinn[1, 4], Susan H. Eshleman[4], Oliver Laeyendecker[1, 4]

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1008 **Incorrect Identification of Recent HIV Infection Using a LAg-Avidity Assay in Adults in the US**

Andrew F. Longosz[1], Ron Brookmeyer[2], Shruti Mehta[3], Greg D. Kirk[3], Joseph B. Margolick[4], Joelle Brown[5], Thomas C. Quinn[1, 6], Susan H. Eshleman[7], Oliver Laeyendecker[1, 6]

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Session P-W7 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Disease Progression/Mortality

1009 **Increasing Viral Suppression and Declining HIV/AIDS and Mortality in the Era of Expanded Treatment**

Susan E. Buskin[1, 2], Amy B. Bennett[1], Julia C. Dombrowski[1, 3], Matthew R. Golden[1, 3]

[1]Prevention Division, Public Health, Seattle & King County, Seattle, WA, United States, [2]Epidemiology Department, University of Washington, Seattle, WA, United States, [3]Department of Medicine, University of Washington, Seattle, WA, United States

1010 **BMI and CD4+ T-Cell Recovery at 12 Months Among Adults Initiating ART in the United States and Canada**

John R. Koethe[1], Cathy Jenkins[2], Bryan Lau[3], Bryan E. Shepherd[2], Michael J. Silverberg[4], Aaron J. Blashill[5], Aranka Anema[6], Amanda Willig[7], Samuel E. Stinnette[8], Timothy R. Sterling[1], North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD)

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1011 **Impact of Smoking On Life Expectancy Among HIV-Infected Individuals: The ART Cohort Collaboration**

Marie Helleberg[1], Margaret T. May[2], Jonathan A. C. Sterne[2], Niels Obel[1], for the ART-CC

[1]Department of Infectious Diseases, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark, [2]School of Social and Community Medicine, University of Bristol, Bristol, United Kingdom

1012 **Standardized Mortality Ratios Among Drug Users in Amsterdam Differ by HCV and HIV Infection Status**

Daniela K. van Santen[1], Jannie J. J. van der Helm[1], Bart P. X. Grady[1, 2], Anneke S. de Vos[3], Mirjam E. E. Kretzschmar[3, 4], Ineke G. Stolte[1], Maria Prins[1, 2]

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1013 **Prognostic Value of the VACS Index for Mortality in British Columbia, Canada**

Angela Cescon[1], Mark Hull[1], Wendy Zhang[1], Thomas Roston[2], **Susan Shurgold**[1], Guillaume Colley[1], Viviane D. Lima[1, 2], P. Richard Harrigan[1, 2], Julio S. G. Montaner[1, 2], Robert S. Hogg[1, 3]

[1]BC Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada, [2]University of British Columbia, Vancouver, BC, Canada, [3]Simon Fraser University, Burnaby, BC, Canada

1014 **Impact of Low-Level Viremia On Clinical and Virological Outcomes in Treated HIV Infected Patients**

Marie-Anne Vandenhende[1], Suzanne Ingle[2], Margaret May[2], Matthias Cavassini[3], Amanda Mocroft[4], Peter Reiss[5], Janet Tate[6], Heidi Crane[7], Jonathan Sterne[2], Geneviève Chêne[1], on behalf of the Antiretroviral Therapy Cohort Collaboration (ART-CC)

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1015 **Increase in HIV Plasma Viral Load Set-Point Among UK MSM**

Victoria Parsons[1,2], Andrew Phillips[2], Richard Gilson[2], Sarah Fidler[3], Martin Fisher[4], Anne Johnson[2], David Hawkins[5], Ken McLean[6], Margaret Johnson[7], Kholoud Porter[1], for the UK Register of HIV Seroconverters

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Session P-W8 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Co-Morbidities

1016 **HIV, Non-Communicable Chronic Diseases and Associated Factors in Tanzania and Uganda**

Saidi H. Kapiga[1], Kathy Baisley[2], Samuel Biraro[3], Bazil Baltazar[4], Fiona Ewings[1], Hashim Ramadhan[4], Robert Peck[5], Richard Hayes[6], Paula Munderi[3], Heiner Grosskurth[1]

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1017 **Female Partner Bacterial Vaginosis and the Penis Microbiota: Rakai, Uganda**

Cindy Liu[1], Bruce Hungate[2], Aaron Tobian[1], Jacques Ravel[3], Jessica Prodger[4], David Serwadda[5], Fred Nalugoda[5], Maria Wawer[6], Ronald Gray[6], Lance Price[7]

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1018 **Low Viral Suppression and High HIV Diagnosis Rate Among MSM With Syphilis - Baltimore, Maryland**

Laura A. Cooley[1], Marcia L. Pearl[2], Colin Flynn[2], David S. Blythe[2], Christine Ross[3], Geoffrey Hart-Cooper[3], James Morgan[4], Alexandra M. Oster[1]

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1019 **Trends in Comorbid Conditions Mentioned With HIV Disease On Death Certificates, US, 2000-2010**

Kpandja Djawe, Kate Buchacz, Charles E. Rose, John T. Brooks

Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, Epidemiology Branch, Atlanta, GA, United States

1020 **The Association Between HPV and HIV Shedding in Vaginal and Anorectal Specimens**

Julia Hood[1], Geoffrey Gottlieb[2], Papa Salif Sow[3], Macoumba Toure[3], Qinghua Feng[4], Nancy Kiviat[4], Stephen Hawes[5]

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1021 **Incidence of Sexually Transmitted Diseases Among Persons With HIV, New York City, 2000-2010**

Sarah L. Braunstein[1], Preeti Pathela[2], Laura Kersanske[1], Colin Shepard[1]

[1]Bureau of HIV/AIDS Prevention and Control, New York City Department of Health and Mental Hygiene, Queens, NY, United States, [2]Bureau of STD Control, New York City Department of Health and Mental Hygiene, Queens, NY, United States

1022 **Increasing Rates of STI Are Linked To Reduced Condom Use in Patients With Primary HIV-1 Infection**

Dominique L. Braun, Roger Kouyos, Raffael Ghenzi, Christina Grube, Rainer Weber, Huldrych Günthard

Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Zurich, Switzerland

1023 **Does Substance Use Compromise Depression Treatment? A Randomized Trial of Homeless HIV+ Persons**

David J. Grelotti[1,2], Gwendolyn P. Hammer[3], James W. Dilley[4], Dan H. Karasic[4], James L. Sorensen[4], David R. Bangsberg[5,6], Alexander C. Tsai[7]

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Session P-W9 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Transmission/Risk Factors

1024 **National Estimates of Key Populations at High Risk of HIV Exposure in Kenya, 2012**

George Githuka[1], Wolfgang Hladik[2], Samuel Mwalili[3], Davies Kimanga[1], Mamo Umuro[4], Mercy Mutui[3], Joshua Gitonga[5], William Maina[1], Andrea A. Kim[3]

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1025 **HIV Incidence in Rural Western Kenya Using Longitudinal Analysis From Home-Based HIV Testing**

Lisa A. Mills[1,2], George Olilo[2], Manase Amolloh[2], Daniel Kwaro[2], Victor Ssempijja[1], Fredrick Odongo[2], Fredrick Otieno[2], Maquins Sewe[2], John Williamson[1], Kayla Laserson[1]

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1026 **Temporal Trends in HIV-1 Incidence and Risk Behaviors Among MSM, Bangkok, Thailand, 2006-2013**

Timothy H. Holtz[1,2], Philip A. Mock[1], Warunee Thienkrua[1], Wannee Chonwattana[1], Wipas Wimonsate[1], Supaporn Chaikummao[1], Wichuda Sukwicha[1], Anupong Chitwarakorn[3], Marcel E. Curlin[1,2]

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1027 **The Potential Impact of Targeting Prevention Strategies To HIV-Discordant Households**

Ruth Emerson[1], Deborah Donnell[1], George Bicego[2], Khanya Mabuza[3], Stephane Helleringer[4], Jessica Justman[5]

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1028 **The Effect of Sexually Transmitted Infections On HIV Incidence Among MSM in Atlanta, GA**

Colleen F. Kelley, Adam S. Vaughan, Nicole Luisi, Travis Sanchez, Paula Frew, Carlos del Rio, Patrick S. Sullivan, Eli S. Rosenberg

Center for AIDS Research, Emory University, Atlanta, GA, United States

1029 Factors Associated With HIV Discordance Among Couples in Kenya: Results From a Population Survey

Wanjiru Waruiru[1], Agneta Mbithi[2], Anthony Waruru[3], Jennifer Galbraith[3], Timothy A. Kellogg[1], Scott Epperson[4], Anne Ng'ang'a[2], Sophie Mwanyumba[5], Lucy Kimondo[6], Andrea A. Kim[3]

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1030 Partners of Individuals With Acute HIV Infection Have a High Frequency of Known HIV Infection

Philip J. Peters[1], Emily Westheimer[2], Stephanie Cohen[3], Charles E. Rose[1], Cynthia L. Gay[4], Charles Fann[3], Steve Beagle[4, 5], Kate Washburn[2], Tonyka L. Jackson[1, 6], Lisa B. Hightow-Weidman[4]

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1031 Baseline Predictors of HIV-1 Acquisition Among Women Participating in MTN-003 (VOICE)

Gonasagrie Nair[1], Jennifer E. Balkus[2, 3], Jeanne M. Marrazzo[3], Gita Ramjee[4], Thesla Palanee[5], Baningi Mkhize[6], Clemensia Nakabiito[7], Marthinette Taljaard[8], Kailazarid Gomez[9], Zvavahera M. Chirenje[10]

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1032 Measuring Purposefully Adopted Seroadaptive Behaviors vs Reported Sexual Behaviors Among MSM

Christine M. Khosropour[1], Julia C. Dombrowski[2, 3], James P. Hughes[4], Lisa E. Manhart[1], Jane M. Simoni[5], Matthew R. Golden[2, 3]

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1033 Prevalence and Predictors of HIV Disclosure Among Adults Receiving Care in the United States

Christine L. Mattson[1], Mark S. Freedman[1], Linda Beer[1], Patrick Sullivan[2], Jacek Skarbinski[1]

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1034 Trends in HIV Diagnoses Among Persons Who Inject Drugs – United States, 2008-2011

Andrew J. Mitsch[1], H. I. Hall[1], Amy L. Lansky[1], Aruna Surendera-Babu[2]

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1035 An Emerging HIV Epidemic Among Injection Drug User Networks During Austerity in Athens, Greece

Ashley Tsang[1], **John Schneider**[2], Vana Sypsa[3], Georgios Nikolopoulos[4], Dimitrios Paraskevis[3], Samuel Friedman[5], Angelos Hatzakis[3]

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1036 High HIV Prevalence Among Injection Drug Users in India: Women Bear a Disproportionate Burden

Gregory M. Lucas[1], Sunil S. Solomon[1, 2], Aylur K. Srikrishnan[2], Syed H. Iqbal[2], Oliver Laeyendecker[1, 3], Allison McFall[4], Muniratnam S. Kumar[2], David D. Celentano[4], Suniti Solomon[2], Shruti H. Mehta[4]

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1037 HIV Prevalence Among Women Who Inject Drugs and Exchange Sex for Money or Drugs: 20 US Cities, 2009

Lina M. C. Nerlander, Kristen L. Hess, Dita Broz, Binh C. Le, Catlainn Sionean, Charles E. Rose, Gabriela Paz-Bailey, for the NHBS Group

Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, Atlanta, GA, United States

1038 Erectile Dysfunction Medication Use Associated With Unprotected Intercourse in HIV-Infected MSM

Xia Lin, Christine L. Mattson, Mark S. Freedman, Jacek Skarbinski

Centers for Disease Control and Prevention, Atlanta, GA, United States

1039 A Novel Analytical Approach Confirms Stabilization of HIV Epidemic in Pregnant Women in Namibia

Anna Jonas[1], Steven Gutreuter[2], Sadhna V. Patel[3], Andrew Maher[3], Michael de Klerk[1], Tuli Nakanyala[1], Francina Kaindjee-Tjituka[1], Ella Shihepo[1], David W. Lowrance[3]

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1040 Viral Load Strategy: Impact On Risk Behavior and Serocommunication of MSM in Specialized Care

Elisabeth Kuhn[1], Anja Potthoff[1, 2], Henrike Dirks[3], René Borgmann[3], Michael Wolter[3], Stefan Esser[4], Norbert Scherbaum[2, 3], **Norbert H. Brockmeyer**[1, 2]

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1041 Transmission Rates and Not Sexual Contact Patterns Drive HIV Epidemic Intensity in Africa

Steve E. Bellan[1], Jonathan Dushoff[2], David Champredon[3], Alison P. Galvani[4], Lauren A. Meyers[5]

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Session P-X1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

HIV Testing in Low Income Settings

1043 HTC Campaign in Households Reached the Majority of Women But Only 50% of Men in Botswana Community

Vlad Novitsky[1], Hermann Bussmann[2], Sikhulile Moyo[2], Erik van Widenfelt[2], Mompati Mmalane[2], Quanhong Lei[3], Joseph Makhema[2], Shahin Lockman[1], Victor DeGruttola[3], Max Essex[1]

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1044 Implementation of Routine, Opt-Out HIV Testing Does Not Increase Loss To Follow-up

Kate Clouse[1], Colleen Hanrahan[1], Jean Bassett[2], Nandipha Qangule[2], Lindi Matjeke[2], Sandra Mokonyane[2], Ian Sanne[3], Annelies Van Rie[1]

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1045 Assessment of the Potential Cost-Effectiveness of HIV Self-Testing in Resource Limited Settings

Valentina Cambiano[1], Debbie Ford[2], Travor Mabugu[3], Sue Napierala Mavedzenge[4], Alec Miners[5], Owen Mugurungi[6], Fumiyo Nakagawa[1], Paul Revill[7], Andrew Phillips[1]

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Session P-X2 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

HIV Treatment and Care

1046 Treatment Outcomes Before and After the Decentralization of ART in an Urban Setting in Mozambique

Jan Walter[1], Marie-Luce Tombo[1], Celeste Gracia Edwards[1], Johnny Lujan[2], Annick Antierens[2], Lucas Mofino[1]

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1047 CD4 Count at ART Initiation and Economic Restoration in Rural Uganda

Atheendar Venkataramani[1], Harsha Thirumurthy[2], Jessica Haberer[1], Yap Boum[3], Mark Siedner[4], Annet Kembabazi[5], Peter Hunt[6], Jeffrey Martin[6], David Bangsberg[5,7], Alexander Tsai[8]

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1048 48-Week Outcomes in Adults Starting ART at CD4>350 Using Streamlined Care in Rural Uganda

Vivek Jain[1], Dathan M. Byonanebye[2], Gideon Amanyire[2], Douglas Black[1], James Rooney[3], Gabriel Chamie[1], Elvin H. Geng[1], Edwin D. Charlebois[1], Moses R. Kamya[2], Diane V. Havlir[1]

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1049 Second-Line Failure and Protease Inhibitor Resistance in a Clinic in Johannesburg, South Africa

Rebecca H. Berhanu[1], Denise Evans[2], Prudence Ive[3], David Spencer[4], Cindy Firnhaber[3], Ian Sanne[3], Matthew P. Fox[5]

[1]*TB Focal Point, Right to Care, Johannesburg, South Africa,* [2]*Health Economics and Epidemiology Research Office, University of the Witwatersrand, Johannesburg, South Africa,* [3]*Clinical HIV Research Unit, University of the Witwatersrand, Johannesburg, South Africa,* [4]*Helen Joseph Hospital, University of the Witwatersrand, Johannesburg, South Africa,* [5]*Center for Global Health and Development Department of Epidemiology, Boston University, Boston, MA, United States*

1050 A 5-Year Comparison of Viral Load and CD4 Cell Count Monitoring for ART Patients in Rural Uganda

Jonathan Wangisi[1], Paul Ekwaru[2], Stephen Okoboi[1], James Campbell[3], Rachel King[4], Aggrey Egessa[1], Celestin Bakanda[1], Emmy Muramuzi[5], Frank Kaharuza[5], Sam Malamba[6], **David M. Moore**[7,8]

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1051 Success of Transfer of HIV Care From a PEPFAR Site To Community-Based Clinics in South Africa

Christie Cloete[1], Susan Regan[2,3], Janet Giddy[1], Tessa Govender[1], Melanie R. Gaynes[3], Kenneth A. Freedberg[2,3], Jeffrey N. Katz[4,5], Rochelle P. Walensky[3,6], Elena Losina[3,7], **Ingrid V. Bassett**[3,8]

[1]*McCord Hospital, Durban, South Africa,* [2]*Massachusetts General Hospital, Department of General Medicine, Boston, MA, United States,* [3]*Massachusetts General Hospital, Medical Practice Evaluation Center, Boston, MA, United States,* [4]*Brigham and Women's Hospital, Department of Orthopedic Surgery, Boston, MA, United States,* [5]*Brigham and Women's Hospital, Division of Rheumatology, Boston, MA, United States,* [6]*Division of Infectious Diseases, Massachusetts General Hospital, Boston, MA, United States,* [7]*Boston University School of Public Health, Departments of Biostatistics and Epidemiology, Boston, MA, United States,* [8]*Division of Infectious Disease, Massachusetts General Hospital, Boston, MA, United States*

1052 The Feasibility and Economic Impact of Time Designated Appointment System in a Busy HIV Care Clinic

Zachary A. Kwena[1], Betty Njoroge[2], Patrick Oyaro[1], Craig R. Cohen[3], Elizabeth A. Bukusi[2]

[1]*Center for Microbiology Research, Kenya Medical Research Institute, Kisumu, Kenya,* [2]*Center for Microbiology Research, Kenya Medical Research Institute, Nairobi, Kenya,* [3]*Ob/Gyn & RS, University of California, San Francisco, San Francisco, CA, United States*

1053 Long-Term Virologic Response in a Cohort of HIV-Infected Patients in South Africa

Kate Shearer[1], Alana T. Brennan[2], Mhairi Maskew[1], Rebecca Berhanu[3], Lawrence Long[1], **Matthew Fox**[1,2]

[1]*Health Economics and Epidemiology Research Office, Johannesburg, South Africa,* [2]*Center for Global Health & Development, Boston, MA, United States,* [3]*Right to Care, Johannesburg, South Africa*

1054 CD4 Cell Decline and Time To Reaching ART Eligibility in HIV Patients From Rwanda

Chloe A. Teasdale, Allison Zerbe, Veronicah Mugisha, Ruben Sahabo, Elaine J. Abrams, Wafaa M. El-Sadr, for Identifying Optimal Models of HIV Care in Africa Study

ICAP, Columbia University, New York, NY, United States

1055 Predictors of Late Engagement To HIV Care in Western Kenya: A Cross-Sectional Study

Charles M. Kwobah[1,2], Paula Braitstein[3,4], Julius Koech[2], Gilbert Simiyu[2], Ann W. Mwangi[2,5], Kara Wools-Kaloustian[2,6], **Abraham Siika**[2,3]

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1056 Cost Savings of Viral-Load Testing Before ART Second-Line Switch in a Resource-Limited Setting

Joanita Kigozi[1], Christine Mugasha[1], Alex Muganzi[1], Alex Coutinho[1], Yukari Manabe[2]

[1]*Infectious Disease Institute, Kampala, Uganda,* [2]*Johns Hopkins University, Baltimore, MD, United States*

1057 Peer Support and Engagement, HIV Care and Sexual Behaviors Among PLHIV Not On ART: A Randomized Trial

Larry W. Chang[1,2], Gertrude Nakigozi[3], Veena Billioux[2], David Serwadda[3], Thomas Quinn[4], Robert Bollinger[1,2], Maria Wawer[2], Ronald Gray[2], Steven Reynolds[4]

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1058 Community-Based ART Programs in Resource-Limited Settings

Stephen Okoboi[1], Ding Erin[2], Steven Persuad[3], Jonathan Wangisi[1], Darius Kato[1], Chen YaLin[2], Maureen Nyonyitono[2], Celestin Bakanda[1], Josephine Birungi[1], David Moore[2,3]

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Session P-X3 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

The Treatment Cascade and Loss To Follow-Up

1059 **Gender Differences in Loss To Follow-up and Mortality in Older Adults On ART in Sub-Saharan Africa**

Mansi Agarwal[1], Matthew R. Lamb[1], Veronicah Mugisha[1], Davies Kimanga[2], Bonita Kilama[3], Andrea A. Howard[1], Elaine J. Abrams[1], Wafaa M. El-Sadr[1], Batya Elul[1]

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1060 **Comparative Effectiveness of HIV Care and Treatment Programs in East Africa**

Elvin Geng[1], Thomas Odeny[2], Rita Lyamuya[3], Alice Nakiwogga-Muwanga[4], Mwebesa Bwana[5], Paula Braitstein[6], Andrew Kambugu[4], Elizabeth Bukusi[7], Geoffrey Somi[8], Lameck Diero[9], Jeffrey Martin[10]

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1061 **Loss To Follow-Up: Determining Outcomes for Adults Enrolled in HIV Services in Kenya**

William Reidy[1], Mansi Agarwal[1], Matthew Lamb[1], Mark Hawken[1], Duncan Chege[1], Batya Elul[1], Elaine J. Abrams[1], Elvin Geng[2]

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1062 **Community ART Delivery for High Patient Retention - TASO Uganda Operational Research**

Denis Mpiima[1,2], Birungi Josephine[1], Luzze Ceaser[3], Nanfuka[1] Masitula[4]

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1063 **HIV Care Cascade Among Hard To Reach Populations in India: Need To Expand HIV Counseling and Testing**

Shruti H. Mehta[1], Gregory M. Lucas[2], Suniti Solomon[3], Aylur K. Srikrishnan[3], Allison McFall[1], P. Nandagopal[3], Pachamuthu Balakrishnan[3], Muniratnam S. Kumar[3], David D. Celentano[1], Sunil S. Solomon[2,3]

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1064 **Unplanned Interruptions in HIV Care in Nigeria: Rates and Implications**

Aima A. Ahonkhai[1], Bolanle Banigbe[2], Juliet Adeola[2], Ifeyinwa Onwuatuelo[2], Ingrid V. Bassett[3], Elena Losina[4], Kenneth A. Freedberg[1], Propser Okonkwo[2], Susan Regan[1]

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1065 **Using the Side Door: Non-Linear Patterns Within the HIV Treatment Cascade in Zambia**

Charles B. Holmes[1,2], Angela Bengtson[1,2], Izukanji Sikazwe[1,2], Carolyn Bolton-Moore[1,2], Lloyd B. Mulenga[1], Patrick Musonda[1,3], Benjamin H. Chi[1,2]

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1066 **Effectiveness of Potential Improvements in the Cascade of HIV Treatment and Care in South Africa**

Valentina Cambiano[1], Silvia Bertagnolio[2], Michael Jordan[2], Jens Lundgren[3], Alec Miners[4], Deenan Pillay[1], Paul Revill[5], Francois Venter[6], Andrew Phillips[1]

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Session P-X4 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Mental Health in HIV Care

1067 **Trends in Depression Among Patients Presenting for ART in Rural Uganda**

Brian T. Chan[1,2], Sheri D. Weiser[3,4], Yap Boum[5], Jessica Haberer[2,6], Annet Kembabazi[7], Peter W. Hunt[4], Jeffrey N. Martin[8], David R. Bangsberg[2,6], Alexander C. Tsai[2,6]

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1068 **Mental Health and Mortality in an HIV Treatment Cohort in Rural Uganda**

Alexander C. Tsai[1], Brian T. Chan[1], Yap Boum[2], Jessica E. Haberer[1], Annet Kembabazi[3], Peter W. Hunt[4], Jeffrey N. Martin[4], David R. Bangsberg[1]

[1]Massachusetts General Hospital, Boston, MA, United States, [2]Medicins San Frontieres, Mbarara, Uganda, [3]Mbarara University of Science and Technology, Mbarara, Uganda, [4]University of California San Francisco, San Francisco, CA, United States

ORAL ABSTRACTS

MONDAY MARCH 3, 2014

Session W1 Workshop
9:00 AM – 1:15 PM Ballroom B/C
Program Committee Workshop for New Investigators and Trainees

1 HIV Pathogenesis: Current Understanding and Future Research

Dana H. Gabuzda, *Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, United States*

Background: HIV is transmitted via mucosal and intravenous routes, replicating initially in CD4+ T cells at mucosal sites and draining lymph nodes. Following systemic dissemination, a major reservoir of infection is established in gut-associated lymphoid tissues (GALT), which eventually leads to depletion of GALT CD4+ T cells, altered mucosal defenses, gut mucosal injury, and microbial translocation. Despite host immune responses and antiviral therapies that suppress viral replication, viral reservoirs persist in long-lived memory CD4+ T cells, including a stem-cell like population (Tscm). Additional reservoirs of viral persistence are established in macrophages in the brain and other macrophage-rich tissues. Chronic immune activation, a hallmark of HIV infection, is a strong predictor of disease progression, morbidity, and mortality that has also been linked to accelerated aging and age-related end-organ comorbidities involving the cardiovascular system, kidneys, liver, brain, endocrine system, and bone. Underlying causes of chronic immune activation include ongoing viral replication, persistently elevated interferon responses, and microbial translocation. Cofactors associated with the HIV epidemic, such as HCV and other co-infections, and substance abuse, can also increase innate immune activation and end-organ comorbidities. The mechanisms underlying immune dysregulation, chronic immune activation, and accelerated aging phenotypes in HIV infection are multifactorial and complex. Given this complexity, large multivariate datasets, systems biology, and computational approaches are needed to achieve systems-level understanding of HIV pathogenesis.

Conclusions: This talk will provide a systems-level overview of temporal events, pathogenic processes, and inter-relationships between immune dysregulation and end-organ dysfunction during the course of HIV infection. A better understanding of these processes at the cellular and host level, integration of knowledge from diverse types of high-density data, and temporal modeling of causal relationships and dependency networks is important for developing new therapies, and progress toward the ultimate goals of prevention and eradication.

2 HIV Cure Research

John W. Mellors, *University of Pittsburgh, Pittsburgh, PA, United States*

Background: Two highly-publicized cures of HIV infection, one in an adult who received complex therapies for leukemia including myeloablative chemotherapy, total body irradiation, anti-thymocyte globulin and allogeneic hematopoietic stem cell transplantation from CCR5 delta 32 homozygous donor, and one in an infant started on ART within 2 days of birth, have inspired worldwide efforts to cure HIV infection in more individuals. The recent relapse of HIV infection 3-8 months after stopping ART in two allogeneic bone marrow transplant recipients who had cleared HIV from blood is a sobering reminder of the difficulty in eliminating all replication-competent HIV from an infected host. In the context of data being presented at CROI 2014, I will review obstacles to curing HIV infection: i) long-lived cellular reservoirs (CD4+T-cells, microglia, other cell types); ii) latent-replication competent proviruses integrated across the human genome, iii) HIV diversity and immune escape variants, iv) clonal expansion of HIV-infected cells, v) persistent low-level viremia despite ART, and vi) highly-variable and incompletely effective host immune responses to HIV. I will then highlight curative approaches that are being explored: i) immediate ART after birth in HIV-infected infants; ii) ART in adults during acute/early HIV infection to prevent reservoir expansion and induce post-treatment immune control; iii) latency reversing agents to deplete HIV reservoirs; iv) reversal of exhaustion of HIV-specific through immune response by targeting inhibitory receptors (e.g. PD-1/PD-L1) on T-cells; iv) antibody- , cell-, and vaccine-based immunotherapies to enhance HIV immune responses; and v) host modification to confer resistance to HIV replication.

Conclusions: Progress towards a cure of HIV infection will undoubtedly occur but the challenge of developing and delivering effective and scalable therapies to most HIV-infected persons is a formidable one.

3 HIV Vaccine Immunology: Recent Progress and Continuing Challenges

Richard A. Koup, *Vaccine Research Center, National Institute of Allergy and Infectious Disease, National Institutes of Health, Bethesda, MD, United States*

Background: A vaccine is clearly needed to stem the spread of HIV. A phase IIB HIV vaccine trial was recently stopped due to futility. The immune profile generated in this trial, as compared to a previous moderately protective trial, will help inform the next generation of HIV vaccines.

Conclusions: This presentation will highlight the advances that have been made in the last 12-18 months in defining potentially protective immune responses to HIV, and determining how to stimulate them through vaccination. Information will derive from five different approaches: 1) evaluation of results from past and present vaccine efficacy trials, 2) the generation of broadly neutralizing antibodies, and their effects in preventing and treating SHIV/HIV

infection in monkeys and humanized mice, 3) solving the crystal structure of a stabilized cleaved trimer of HIV envelope, 4) studies of how antibody and envelope co-evolve during HIV infection, and 5) determination of the unique characteristics of CD8 T cells generated in response to rhCMV vaccination that are capable of clearing SIV infection in monkeys. Throughout the presentation, information will be provided on where and when the latest information will be presented at CROI.

4 HIV Prevention Research: Progress and Challenges

Sharon L. Hillier, *University of Pittsburgh School of Medicine, Magee-Womens Hospital, Pittsburgh, PA, United States*

Background: HIV prevention trials have been conducted assessing a range of approaches to decrease the incidence of HIV infection, including vaccination, circumcision, vaginal and rectal microbicides, oral pre-exposure prophylaxis (PrEP) and treatment as prevention (TasP). Of these, male circumcision, one vaccine combination, 1% tenofovir gel used at the time of sex, oral emtricitabine/tenofovir or tenofovir, and effective treatment resulting in reduced viral load have all been shown to reduce HIV acquisition by 30 to 97%. Scale up of circumcision, which decreases the risk of HIV in men by >50%, has increased globally with the availability of new devices which permit the delivery of this procedure at low cost and high safety. Oral and topical antiretrovirals have emerged as potent tools for the prevention of HIV, and since the approval of emtricitabine/tenofovir by the FDA for prevention of HIV in 2012, a number of programs have been initiated to scale up the availability of PrEP and to explore the public health impact of this intervention. At the same time, there is an increased recognition that adherence to oral and topical PrEP is critical to the success of this approach. The FemPrEP and VOICE trials, which were conducted in populations of young women living in high seroincidence communities in Africa, each reported low levels of adherence to daily products. This factor likely accounted for the lack of reported efficacy in these studies, in contrast to the studies performed in men who have sex with men and HIV serodiscordant couples. Tenofovir gel is in a phase 3 clinical trial among women using a coital rather than daily approach (FACTS-001), and as a rectal microbicide in MSM (MTN-017). For new PrEP agents, strategies are focused on the sustained delivery of ARVs. One example is a vaginal ring which delivers low doses of the NNRTI dapivirine over a month of use, and randomized efficacy trials evaluating this approach are underway. Injectable ARVs are in phase 1 studies, with promising results emerging from animal models. The success of the HPTN 052 study which demonstrated that effective treatment of HIV-infected persons, resulting in virological suppression reduced HIV transmission by 97%, has led to the increased rollout of TasP as a key strategy in the HIV prevention toolbox. Of the HIV vaccines tested to date, only the RV144 HIV vaccine has been successful in reducing HIV incidence. Although the reduction in HIV was 31% with this vaccine and the results of this study likely only apply to those patients with subtype E virus, the study has energized the vaccine field and has led to the development of a vaccine protocol to assess the efficacy of this strategy against clade C HIV in S Africa in a study planned for 2015.

5 Pathogenesis and Control of HCV Infection

David L. Thomas, *The Johns Hopkins University School of Medicine, Baltimore, MD, United States*

Background: Hepatitis C virus (HCV)-related liver disease has emerged as one of the most important causes of morbidity and mortality in HIV-infected persons. Compared to persons with just one infection, HIV/HCV-coinfected persons have a higher incidence of all liver complications and even some extrahepatic conditions raising the possibility of multiple pathogenic interactions. HCV can be cured, even without interferon alfa, and HCV drug development is an exceedingly active basic and clinical research field. Medications are in trials that target nearly all major steps in replication. Highly-efficacious, single-tablet, 8-12 week, pangenotypic therapies are already in development. Cure of infection reduces the incidence of liver disease complications and improves mortality. Cure rates among HIV/HCV coinfected persons are equivalent to those with just HCV.

Nonetheless, there remain enormous public health challenges. No more than 5% of the ~170 million persons has been prescribed treatment; no more than 10% worldwide and 50% in the US know their infection status. Moreover, most HCV treatment courses exceed $100,000 and yet their effectiveness can be completely abrogated by nonadherence or reinfection. Thus, models of disease control underscore the importance of coupling prevention with treatment.

Conclusions: 25 years after discovery of HCV, everything has changed for the 5% in care. But, enormous challenges remain and are even more urgent given the potential to cure.

Session MD Panel

1:30 PM – 2:30 PM **Ballroom B/C**

6 Martin Delaney Panel: Hepatitis C Virus: From Trials and Tribulations To Triumph

Jeff Taylor, *AIDS Treatment Activists Coalition, Palm Springs, CA, United States*
Tracy Swan, *Treatment Action Group, New York, NY, United States*
Isabelle Andrieux-Meyer, *Médecins sans Frontières, Geneva, Switzerland*
Jules Levin, *National AIDS Treatment Advocacy Project (NATAP), New York, NY, United States*
Lynn E. Taylor, *Brown University, Providence, RI, United States*

Background: Chronic hepatitis C virus (HCV) infection is a major global public health threat; at least 185 million people have been infected, and 2 to 3 million are newly infected each year.

Untreated HCV can progress to cirrhosis, hepatocellular carcinoma and hepatic decompensation; these complications cause over 350,000 deaths annually. In the United States and Spain, mortality from HCV now exceeds AIDS-related mortality. People with chronic hepatitis C are at risk for premature death from respiratory failure, cardiovascular disease, and other non-liver related causes.

Globally, an estimated 5 million people are HIV/HCV coinfected. HIV accelerates the risk for, and rate of HCV progression. Where antiretroviral access is widespread, HCV complications are a leading cause of death among HIV/HCV coinfected people.

Conclusions: HCV is curable, an outcome known as sustained virologic response (SVR). Once cured, the risk for liver-related morbidity and mortality_and all-cause mortality--decreases significantly, as does risk of AIDS-related death in HIV/HCV coinfection.

HCV treatment has rapidly evolved from peginterferon and ribavirin_a poorly tolerated, complex regimen with limited efficacy_to oral, direct-acting antiviral (DAA) combinations. In 2013, the first oral DAA regimen was approved in the U.S. and the E.U.

Many promising DAAs are in the pipeline. In clinical trials, SVR rates after 12-week regimens have exceeded 90 percent, regardless of HIV status and HCV treatment history. Another wave of DAA approvals is anticipated during 2014.

HCV is highly prevalent among marginalized groups facing significant barriers to health care: people who inject drugs, incarcerated, homeless and poor people, African-Americans, and people living with HIV/AIDS. HCV is most prevalent in low- and middle-income countries, yet limited access to diagnostics, care and treatment are commonplace in high-income countries such as the United States, where at least 75% of people with chronic HCV are undiagnosed.

DAAs offer the opportunity to eradicate HCV, if political will and adequate resources are mustered. DAA regimens will facilitate scale up by simplifying treatment and streamlining requirements for on- and post- treatment monitoring, but prices for drugs and diagnostics remain prohibitive in most of the world. Both infrastructure and capacity to deliver treatment must be developed. Activists, clinicians, researchers, implementers, and our allies are working to increase worldwide access to evidence-based HCV prevention, as well as screening, care and treatment through clinical trials, demonstration projects, development of treatment guidelines; with donor, non-governmental and inter-governmental organizations, and by pushing governments to address hepatitis C.

Session W2 Workshop

2:30 PM – 4:30 PM Ballroom B/C

Clinical Trial Design and Analysis

7 Adherence: The Achilles Heel for Trial Interventions

David R. Bangsberg, *Massachusetts General Hospital Center for Global Health, Boston, MA, United States*

Background: Recent studies of HIV pre-exposure prophylaxis (PrEP) in HIV-negative individuals revealed heterogeneous estimates of efficacy from 0% to 77%. Efficacy estimates in randomized clinical trials presume adherence to the intervention. Nonadherence biases efficacy estimates to the null and differences in adherence between studies will lead to differing efficacy estimates. Antiretroviral drug level data obtained during PrEP studies suggest that the heterogeneity in PrEP trial efficacy estimates can be explained by differences in adherence amongst the studies. This presentation will review the impact of nonadherence on efficacy estimates, and the approaches to measure adherence.

Conclusions: The presentation will conclude with post-hoc analyses that suggest that the level of protection against HIV transmission conferred by PrEP in HIV-negative individuals is comparable to the level of protection conferred by antiretroviral therapy in HIV-positive individuals.

8 Studying Multiple Interventions: Factorial Designs and Other Approaches

Richard J. Hayes, *London School of Hygiene and Tropical Medicine, London, United Kingdom*

Background: In the simplest randomized controlled trial (RCT) design, individual patients are randomly allocated to two study arms (Intervention vs Control) to measure the effects of a specified health intervention on a defined outcome. In some cases, however, we wish to examine the effects of multiple interventions in the same trial. Examples of such studies include (1) treatments with multiple dosage regimens or alternative drugs; (2) studies designed to compare the effects of two or more different interventions, alone or in combination; (3) combination interventions where we wish to unpick the effects of different components. We will discuss some of the study designs that can be used to address such questions.

A simple design compares two or more intervention conditions with a single control arm. There are sometimes issues of multiple comparisons and, depending on the mode of delivery of the interventions, there may be a need for multiple placebos if a blinded design is required (e.g. double-dummy trials). When the separate or joint effects of interventions are of interest, the factorial design may be an attractive choice, for example the 2x2 factorial in which patients are randomized to four groups given either intervention A alone, intervention B alone, neither or both. Under certain assumptions, the factorial design permits the effect of more than one intervention to be measured in a single trial at a similar cost to a study designed to evaluate a single intervention. The limitations and strengths of this design will be reviewed, and implications for sample size outlined. Such trials may be randomised either at individual or cluster levels. In some cases, the two approaches may be combined, such that clusters are randomly allocated to the presence or absence of one intervention, while individuals or households within clusters are randomly allocated to presence or absence of another intervention (sometimes referred to as a split-plot design).

The above design choices will be illustrated with RCTs conducted to measure the effects of interventions against HIV and related infections, including the Zamstar, VOICE and PopART trials.

Conclusions: While it is often best to aim for simplicity of design, resources for rigorously-designed RCTs are limited and it is important to ensure that such resources are used efficiently. Sometimes, by careful choice of study design, it may be possible to evaluate several interventions in a single study at little additional cost. Alternative approaches to unpick the effects of combination interventions also need to be considered. In particular mathematical modelling may sometimes be used to supplement RCT evaluations.

9 So Many Trials, So Little Time: Meta-Analysis Do's and Don'ts

Dean A. Follmann, *National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, United States*

Background: Meta-analysis is a powerful method for quantitatively synthesizing multiple clinical trials of similar interventions. By combining multiple sources of information a sharper signal about the interventions can be calculated, both overall and in subgroups. While meta-analysis is a summarization of finished studies, pre-specification of the essential research question, study inclusion criteria, and analytic strategy increase rigor of the analysis.

Conclusions: Two main statistical calculations for summarizing studies are discussed. The fixed effects approach is best when the intervention effects are relatively homogeneous and provides conclusions about the studies at hand. The random effects approach is more suited for more heterogeneous intervention effects and generalizes beyond the studies at hand. Techniques to explore and address heterogeneity will be discussed as well as more subtle issues such as the bias introduced by non-publication of null studies, the temptation to dismiss ``aberrant" studies, methods to accommodate differential quality of studies, and a perspective on the strength of evidence that can be achieved by meta-analysis. Examples involving vaccines and drugs will illustrate the use of meta-analysis to explore safety signals as well as variation in efficacy.

Session W3 Workshop

2:30 PM – 4:30 PM Ballroom A

Frontiers in Laboratory Science Workshop

10 Systems Immunology Approaches for Vaccine Profiling and Antibody Discovery

Sai Reddy, *Swiss Federal Institute of Technology Zurich, Basel, Switzerland*

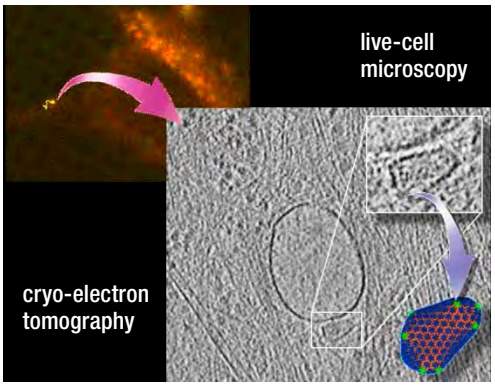
Background: A major part of the advancement of the field of systems immunology has been the emergence of next-generation sequencing (NGS); specifically the ability to use NGS for large-scale analysis of antibody variable gene repertoires. Here, I will provide an overview of this exciting new research field, which has applications related to answering basic questions of antibody diversity, development, and evolution; as well as applications for immune-diagnostics and immunotherapeutics. I will primarily focus on our research group's interests in applying NGS of antibody repertoires for the discovery and engineering of monoclonal antibody (mAb) therapeutics. This will include our recent development of a mAb discovery technology that requires no screening, which is based on NGS analysis of antibody repertoires obtained from immunized mouse plasma cells. This technology offers a powerful alternative to mAb discovery, which we are also utilizing for mAb discovery from immunized rabbits and chronically infected human patients.

Conclusions: We have also developed a number of experimental and computational methods to help advance NGS of antibody repertoires. These include a high-throughput bioinformatic pipeline for NGS analysis and annotation, operating at much faster times than currently used software (e.g., IMGT). Also, we have evaluated the robustness and reproducibility of antibody NGS sequencing methods using triplicate sample sequencing and mathematical ecology-based modeling. Finally, we have assessed experimental methods used to construct NGS antibody libraries, focusing on primer bias and the impact of adaptor addition by PCR or ligation. Our work on methods development should help researchers pursue their own goals related to antibody NGS and help advance the field of systems immunology.

11 3-D Structural Analysis of HIV Using Correlative CryoEM and Live Cell Imaging

Peijun Zhang, *University of Pittsburgh School of Medicine, Pittsburgh, PA, United States*

Background: Following fusion of the viral and host membranes, the HIV-1 capsid core is released into the cytoplasm of the host cell. The viral capsid plays critical roles during the early stages of infection before nuclear entry by interacting with host cell machines. However, direct observation of structural details of infecting HIV-1 core has not been realized due to technological challenges in working with rare and dynamic HIV-1 particles in human cells. While time-lapse live-cell imaging has yielded a great deal of information about many aspects of the life cycle of HIV-1, the resolution afforded by live-cell microscopy is limited. On the other hand, cryo-electron tomography (cryoET) provides three-dimensional (3D) still pictures of near-native state cells and organelles at molecular resolution. By combining high-speed 3D live-cell fLM and high-resolution cryoET, the correlative light and electron microscopy (CLEM) method provides a powerful means to not only expand the imaging scale and resolution but also to complement the dynamic information available from optical microscopy with the molecular-level, 3D ultrastructure detail provided by cryoET.



Conclusions: I demonstrate the capability of the correlative microscopy method by directly visualizing dynamic, small HIV-1 particles interacting with host HeLa cells. Furthermore, using high resolution cryoEM and helical reconstruction, the structure of HIV-1 capsid assembly is determined to 8Å resolution, clearly delineating all the α-helical motifs within the capsid structure. The structure allowed unambiguous modeling and refinement by large scale molecular dynamics simulations, resulting in an all-atom model of the HIV-1 capsid comprising 4 million atoms. The model revealed new hydrophobic interactions at the seam of capsid assembly, and provides a platform for further studies of capsid function and for targeted pharmacological intervention.

12 Virus-Host Interactions Revealed Through Proteomics/Phosphoproteomics

Beatrix Ueberheide, *New York University Langone Medical Center, New York, NY, United States*

Background: Mass Spectrometry has become an indispensable technique for studying proteins in biological systems. Thousands of proteins can be identified and quantified with state-of-the art instruments in a single experiment. Global changes in the proteome and certain post translational modifications can now be routinely characterized due to dramatic improvements in speed and sensitivity of mass spectrometric instruments and data analysis software. However, there are still areas of proteomics where analysis can be not as straight forward or need extra care in sample preparation. Examples are the characterization of disease specific circulating antibodies and the detection of virus-host protein protein interactions.

Conclusions: Protein-Protein interactions are critical for all cellular processes. Understanding with which host proteins the virus interacts is crucial for understanding the mechanism of infection. Current strategies of affinity purifications of tagged viral proteins, chemical cross-linking of host-virus proteins as well as changes in post translational modifications (i.e. phosphorylation) upon infection will be presented. Common problems of affinity purifications and characterizing infection dependent post translational modifications will be discussed with special emphasis on sample preparation strategies. Establishing antibody repertoires of infected individuals by high throughput DNA sequencing has been rapidly advancing, yet the antibody composition in the blood of infected individuals remains largely unknown. Here, mass spectrometry is emerging as an enabling technology in combination with a match personal antibody database. Characterizing and quantifying the circulating antibodies in the blood of infected individuals is however not a trivial task. The majority of the antibody is structurally identical and it is therefore difficult to unambiguously identify which antibody is present in the sera of individuals. The majority of antibody derived peptides will be identical and shared between many different antibodies. Here, current strategies for identifying antibody specific peptides are described.

13 CRISPRs and Other Genome Editing Systems

Paul F. Bates, *University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA, United States*

Background: Precise genome-editing techniques have been developed recently that allow researchers to delete, insert, and modify DNA in human cells and other animal cells grown in culture. These technologies include zinc-finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and the clustered regulatory interspaced short palindromic repeat (CRISPR) system. This review will focus mainly upon the most recently described Cas9/CRISPR system as a tool that can be readily employed in individual laboratories.

Conclusions: The emerging technology of genome editing is based on the use of engineered nucleases to produce specific DNA cleavages at defined target sites. Repair of these cleavages by host enzymatic machinery, either non-homologous end-joining (NHEJ) or homologous recombinational (HR) repair, results in either loss/insertion of some sequence or substitutions in the broken region. This review will describe site-specific nuclease technologies and discuss their employment for genetic analysis and manipulation for both research and potential therapeutic application.

ZFNs and TALENs rely upon sequence-specific DNA-binding domains fused to a nonspecific DNA cleavage module. Although the modular nature of the ZFN and TALEN DNA recognition domains permits design and production of nucleases targeting of virtually any sequence, they can be difficult to produce by individual labs prompting many to use commercial sources. Unlike ZFN or TALEN, the CRISPR/Cas9-mediated genome editing system utilizes a small guide RNA to recognize and direct activity of the endonuclease. This system can be effectively employed by individual labs and the tools for utilizing CRISPRs are readily available. In addition to gene editing in cultured cells where numerous groups have used CRISPRs to create genetic knockouts and gene replacements, they have also been used to create gene modifications in whole animals such as mice, rats, and zebrafish. Very recent advances have demonstrated application of the CRISPR and TALEN mutagenesis approaches in nonhuman primates where one can model disease and develop therapeutic strategies with obvious direct application to HIV infection. Finally, important hurdles that remain before CRISPR-mediated gene correction could be used for therapeutic applications will be discussed.

Session W4 Workshop

2:30 PM – 4:30 PM **Room 304**

Workshop for Clinicians Who Are New To Hepatitis C Management: A Case-Based Interactive Session

14 Liver Management

Kenneth E. Sherman, *University of Cincinnati College of Medicine, Cincinnati, OH, United States*

Background: New agents for HCV treatment have dramatically improved both ease and success of treatment intervention. It is imperative that healthcare providers managing HCV understand key concepts in the staging of liver disease, and critical management considerations.Staging of liver disease to determine if advanced fibrosis or cirrhosis is present remains important. Cirrhosis is associated with poorer treatment outcomes and increased risk of hepatic decompensation and liver cancer. A variety of modalities are now available for staging of liver disease including non-invasive measures such as transient elastography and biomarker algorithms. Liver biopsy may still play a role in a limited proportion of patients. Determination of advanced fibrosis/cirrhosis mandates enrollment in hepatocellular carcinoma (HCC) surveillance and evaluation of esophageal varices. Careful assessment is needed in the setting of cirrhosis to determine liver transplant candidacy prior to treatment intervention.

Conclusions: HCV healthcare providers should be familiar with the process of fibrosis staging, and appropriately identify patients who would benefit from surveillance for HCC and esophageal varices. Hepatic decompensation recognition is critical and should lead to rapid consultation with a liver transplant specialist.

15 Interactive Case Presentations

David L. Wyles, *University of California San Diego, San Diego, CA, United States*
Susanna Naggie, *Duke Clinical Research Institute, Durham, NC, United States*

Background: The recent approval of more potent and better-tolerated therapies for HCV infection, including in those with HIV-1 co-infection, heralds the beginning of a new era in HCV therapeutics. Interferon-free therapy is the new standard of care for patients with genotype 2 or 3 HCV infection; while highly efficacious IFN-containing triple therapies with a shortened duration are an option for those with genotype 1 HCV infection.

As HCV therapy becomes less complex and as expanded screening efforts are implemented, more providers will be needed to accommodate the increased number of patients wanting or requiring HCV therapy. While the recent advances have brought significant improvements in HCV therapy for genotype 1 infection, more advances are expected over the next 1-2 years, in particular the arrival of interferon-free therapy. Thus many clinicians are faced with the complex issue of deciding whether to initiate therapy now or defer with the promise of better therapies in the near future. An understanding of the clinical trial data summarizing new and future treatment regimens as well a review of the complexity of management in the HIV-1 infected patient population including but not limited to drug-drug interactions will be discussed.

Conclusions: This interactive case-based session is geared toward clinicians who are new to HCV care and will cover key aspects related to: 1) decision making on HCV treatment initiation versus deferral, 2) use of interferon-free therapy for HCV genotype 2 and 3 infection, 3) recognizing advanced and early decompensated liver disease, and 4) managing HCV therapy and drug interaction in a co-infected patient with genotype 1 infection.

Opening Session

5:00 PM – 7:00 PM **Auditorium**

Session NL1 Lecture

Bernard Fields Lecture

17 Making and Breaking Barriers To Cross-Species HIV-1 Transmission

Paul D. Bieniasz, *Aaron Diamond AIDS Research Center, The Rockefeller University, New York, NY, United States*

Background: The investigation of impeded viral replication in cells of particular types or species has uncovered great complexity in the interaction between retroviruses and their hosts. These studies have revealed that many mammals, including humans, are equipped with a diverse set of gene products that inhibit the replication of human and simian immunodeficiency viruses. Antiretroviral genes exhibit unusually high diversity in primates, presumably because selection pressures exerted by ancient viral infections have caused them to evolve at an unusually rapid pace. The adaptation of modern retroviruses to specific variants of antiviral proteins has resulted in viral specialization to particular host species and the creation of formidable barriers to replication in other species. These phenomena likely protect humans from infection by many modern retroviruses, but have also impaired the development of primate models of HIV-1 infection.

Conclusions: This presentation will (1) review some of the salient features of antiretroviral proteins, (2) discuss studies of Tetherin, an example of an antiviral protein that inhibits the release of virus particles from infected cells and (3) describe our attempts to break antiviral protein-imposed barriers to cross-species transmission of HIV-1 in order to generate better animal models of human AIDS.

Session NL2 Lecture

N'Galy-Mann Lecture

18 Application of Scientific Knowledge and Evidence To Limit the Progression of HIV/AIDS and Fight Other Endemic Diseases in West Africa

Souleymane Mboup, *Centre Hospitalier Universitaire Aristide le Dantec, Dakar, Senegal*

Background: Senegal has experienced long success in HIV control, maintaining an HIV prevalence below 1% within the adult general population aged 15 to 49 years.

Senegal's success has been attributed to a number of factors:

- Political leadership
- National Program And Related National Plans
- Control of STDs
- Safe blood supply
- Strong strategic information system
- Social and religious support
- Early availability of ARV therapy
- Research to inform the national effort

Research was able to show that the initial infections in-country were from the less virulent HIV-2 form. The first HIV-1 case was not observed until 1986.

Conclusions: Research was instrumental: It is now 29 years that HIV-2 has been described in Senegal. Since that time, several international research collaborations have sought to understand the pathogenicity of this closely related HIV virus and the impact of its interaction with the prototype HIV-1 infection in vivo. Co-existing in West Africa with HIV-1, HIV-2, by contrast, generally demonstrates an attenuated phenotype for transmission and disease.

Our group described the details of disease progression and pathogenesis of HIV-1 and HIV-2 and then translated that knowledge to begin a long-term investigation of disease transmission.

Our team made great efforts to lend our expertise to various other countries where the epidemic was much more severe. With our regional training we have also established a large number of AIDS experts who have moved back to various countries on the African continent to assist these countries in establishing their own programs for teaching and research.Now we lead a research group of about 120 junior colleagues mainly conducting AIDS research and this is widely seen by outsiders as the largest and most productive AIDS research program in Africa that is run and staffed by Africans. Key to this is the insistence on staying at our base in Dakar despite many very attractive offers to be based overseas. Over the past 15 years, we have expanded our scientific interests into other areas of infectious diseases important to Senegal and West Africa, including malaria and tuberculosis, where we have initiated research programs patterned on the successful HIV-AIDS programs. Importantly, the Senegal collaboration was the model that guided the collaborations in many countries, such as Tanzania, Botswana and Nigeria. This breadth of accomplishments has mainly the objective to demonstrate one of the best role models for young African scientists seeking to build a major research career in biomedical sciences.

TUESDAY MARCH 4, 2014

Session PL1 Plenary

8:30 AM – 9:00 AM **Auditorium**

19 HPV Vaccines: Progress To Date and Future Worldwide Directions

Douglas R. Lowy, *National Cancer Institute, Bethesda, MD, United States*

Background: Human Papillomaviruses (HPVs) cause several epithelial cancers as well as a range of benign lesions. Cervical cancer is the most serious cancer worldwide attributable to HPV infection, as it accounts for almost 10% of all cancer in women and is the most common female cancer in many developing countries. In the US, the incidence of HPV-positive "non-cervical" cancers, which include anal, vulvar vaginal, penile, and oropharyngeal cancer, is similar to that of cervical cancer. More than 10 HPV types have been shown to be oncogenic, although HPV16 and HPV18 (HPV16/18) together account for about 70% of the cervical cancers and an even higher proportion of the non-cervical cancers. There are two FDA-approved sub-unit HPV vaccines, both of which are based on the ability of the major L1 capsid protein of HPVs to self-assemble into virus-like particles (VLPs), which are highly immunogenic. The main protective activity of the vaccines is their induction of neutralizing antibodies, which are HPV type-restricted. A full course of vaccination involves 3 doses over a 6 month period. The vaccines are highly effective against the HPV types they target (vaccine types), but have more limited activity against non-vaccine types. Two important goals of second generation HPV vaccines are to safely reduce the number of doses required to induce long-term protection, and to increase the number of HPV types efficiently protected by HPV vaccination.

Conclusions: The presentation will focus on research efforts to accomplish these goals.

Session PL2 Plenary

9:00 AM – 9:30 AM **Auditorium**

20 HIV in People Who Use Drugs

Adeeba Kamarulzaman, *University of Malaya, Kuala Lumpur, Malaysia*

Background: Despite ample evidence of the effectiveness of several interventions to prevent HIV among people who use drugs, the global goal of reducing transmission by 50% by 2015 is not likely going to be achieved. Coverage of these key interventions such as needle and syringe programs and medically assisted therapy remain low particularly in low and middle income countries. In addition to HIV, people who use drugs are also at higher risk for a number of other medical complications including tuberculosis and viral hepatitis. In most countries however, access to treatment for these infections remains poor and treatment services are often segregated.

Implementing treatment as prevention for people who use drugs poses many challenges including delays in entering into care, provider reluctance to commence antiretroviral therapy and issues with adherence in those who are actively using drugs. Additionally, incarceration of people who use drugs further reduces access to HIV and other treatment as well as fuel the twin epidemic of HIV and tuberculosis in this population.

Conclusions: Despite evidence of effectiveness and cost-effectiveness of key interventions to prevent and treat HIV infection in people who use drugs, the current global response to the HIV epidemic in this population remains poor. Although policy shifts with increasing coverage of key interventions are beginning to take place in several countries with high disease burden, criminalisation of drug use, incarceration and stigma and discrimination continue to present as main barriers to an effective combination prevention and treatment response. A concerted global effort that addresses individual as well as structural and systematic barriers is needed if we are to expect a decline in HIV transmission among people who use drugs and improve the health and well-being of these individuals.

Session O-1 Oral Abstracts
10:00 AM – 12:15 PM Ballroom B/C
Hepatitis

21 Longitudinal Phenotypic Profiling of Early HCV-Specific CD4 T Cells in HIV- and HIV+ Individuals

Diana Y. Chen[1], Lyndon K. Matsubara[1], Joelle Brown[1], Stephanie S. Kulaga[2], Jasneet Aneja[2], Lia Lewis-Ximenez[3], Eddie James[4], William W. Kwok[4], Arthur Y. Kim[2], Georg M. Lauer[1]
[1]Gastrointestinal Unit, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States, [2]Infectious Disease Division, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States, [3]Laboratorio de Hepatites Virais, Instituto Oswaldo Cruz, Fundacao Oswaldo Cruz, Rio de Janeiro, Brazil, [4]Benaroya Research Institute at Virginia Mason, Seattle, WA, United States

Background: HCV infection generally progresses to chronic infection, but a minority of individuals can spontaneously clear the infection. CD4 T cells are critical for the spontaneous control of HCV but the mechanisms of protection and immune failure remain to be elucidated, especially in HIV+ individuals who generally have higher rate of chronic viremia.

Methodology: We longitudinally analyzed the immunophenotype of early HCV-specific CD4 T cell responses in 45 genotype-1 HCV- infected individuals with well-defined clinical outcomes, including 6 patients with a pre-existing HIV-1 infection. HCV-specific CD4 T cells were studied directly ex vivo using a panel of HCV- MHC class II tetramers, and analyzed for their expressions of various immune makers in multicolor flow cytometry. All statistical analyses were performed with the Spearman correlation test.

Results: HCV-specific CD4 T cells were initially detectable directly ex vivo by MHC class II tetramers in15/15 (100%) resolvers and 16/24 (67%) progressors with mono-HCV infection, as well as in 6/6 (100%) HIV+ individuals, including one who spontaneously cleared HCV. HCV-specific CD4 T cells disappeared from most progressors within 13-41 weeks after onset of infection, while these cells persisted in patients with resolving infection. Early HCV-specific CD4 T cells were mostly comprised of activated effector memory cells expressing high levels of PD-1, CTLA-4, and CD95, and low levels of CD127, irrespective of infection outcomes and HIV status. Interestingly, CD38, PD-1, CTLA-4, and CD95 were quickly downregulated with resolution of infection. Furthermore, decreased expressions of CD38 ($p<0.0001$), PD-1 ($p<0.0001$), and CTLA-4 ($p<0.0001$) were associated with increased expression of CD127 on HCV-specific CD4 T cells. In contrast, in persisting infection HCV-specific CD4 T cells continued to express high levels of CD38, PD-1, CTLA-4, and CD95, and failed to upregulate CD127 before disappearing from blood. Finally, HCV-specific CD4 T cells in resolving infection predominantly expressed CCR4 while expressing intermediate levels of CXCR3 and low levels of CCR6, CXCR5, and Foxp3. In contrast, there was a trend towards more Foxp3, CXCR5, and CXCR3 and fewer CCR4 expressing HCV-specific CD4 T cells in persisting infection.

Conclusions: Both HIV+ and HIV- patients generate HCV-specific CD4 T cell responses with a uniform phenotype in the early phase of acute infection, indicating that priming of response does not explain infection outcomes. However, with persistent viremia, HCV-specific CD4 T cells quickly display the phenotypes, resembling those of exhausted and dysfunctional T cells, irrespective of HIV-1 status. These changes may contribute to viral persistence and the rapid disappearance of HCV-specific CD4 T cells.

22 Rapid Peripheral In Vivo Cellular Changes During Interferon-Free Treatment of Hepatitis C

Eric G. Meissner[1], Brian Santich[1], Yu-Jin Lee[1], Olga Prokunina[1], Anuoluwapo Osinusi[1,2], Anita Kohli[1,2], Henry Masur[3], Susan Moir[1], Shyamasundaran Kottilil[1]
[1]Laboratory of Immunoregulation, NIAID/NIH, Bethesda, MD, United States, [2]SAIC-Frederick, Inc, Frederick, MD, United States, [3]CCMD/NIH, Bethesda, MD, United States

Background: Treatment of chronic hepatitis C virus (HCV) infection is evolving from interferon (IFN)-based to IFN-free directly acting antiviral (DAA) regimens. IFN-based therapy causes treatment-induced cytopenias, while cellular changes on DAA therapy are not well described. Because cellular changes on DAA therapy may reflect the host response to viral decline rather than a treatment side effect, we explored changes in peripheral cell populations during two DAA trials conducted at the NIAID.

Methodology: We evaluated chronic HCV genotype-1 treatment-naïve patients treated with sofosbuvir/ribavirin for 24 weeks (SPARE trial, n=55) or sofosbuvir/ledipasvir for 12 weeks (SYNERGY trial Arm A, n=20). Peripheral cell populations were quantitated by flow cytometry and results were analyzed using a mixed model (SPARE) or by non-parametric ANOVA (SYNERGY). Chemokine

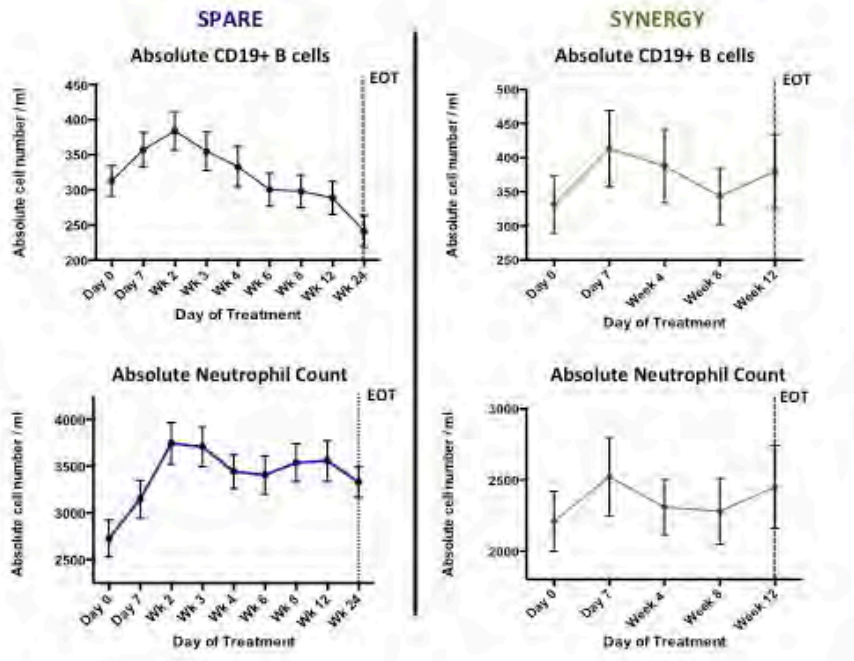


Figure 1: Early increase in absolute peripheral cell counts of CD19+ B cells and neutrophils on the SPARE (n=55) and SYNERGY (n=19) trials. Shown are means with standard error bars. Dotted lines indicate end of treatment (EOT).

receptor expression was measured by flow cytometry and serum chemokines were quantitated by ELISA. Histologic inflammation was quantitated on paired pre- and post-treatment liver biopsies where available. Viral load was measured using the Roche assay.

Results: Treatment led to rapid HCV decline, with 96% and 90% of patients on SPARE and SYNERGY Arm A, respectively, achieving undetectable viral load by week 4. The pro-inflammatory chemokine IP-10 (SPARE) and hepatic AST/ALT (SPARE, SYNERGY) normalized in most patients within 10 days of initiating therapy. B -cells and neutrophils increased from baseline and peaked 1-2 weeks into therapy; the increase in neutrophils was maintained through therapy while the increase in B-cells was transient (Figure 1). Detailed evaluation of B-cells from 12 SPARE patients at day 7-10 of treatment revealed higher surface expression of CXCR3 ($p = 0.049$) and CCR6 ($p = 0.029$), but not CCR4 or CXCR4, compared to baseline. By end of treatment, levels of both receptors had normalized. For CXCR3, this early increase was most notable on activated ($p = 0.049$) and resting memory B cells ($p = 0.0044$). Histologic hepatic inflammation decreased in 36/39 patients (SPARE) and 4/4 patients (SYNERGY) with paired biopsies.

Conclusions: In these DAA-based HCV treatment trials there is an early decline in IP-10, increase in peripheral B-cells, and increase in CXCR3 expression on peripheral memory B-cells. These data suggest a dynamic reduction in hepatic immigration and/or increase in hepatic egress of tissue-resident CXCR3-expressing B-cells associated with suppression of HCV.

23 Faldaprevir Plus Pegylated Interferon Alfa-2a/Ribavirin in HIV/HCV Coinfection: STARTVerso4

Douglas Dieterich[1], Cristina Tural[2], Mark Nelson[3], Keikawus Arastéh[4], Vicente Soriano[5], Josep Guardiola[6], Sanjay Bhagani[7], Jürgen K. Rockstroh[8], Jerry O. Stern[9], Anne-Marie Quinson[9]

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Background: Faldaprevir (FDV) is a potent, once-daily HCV NS3/4A protease inhibitor being developed for the treatment of chronic HCV infection in mono-infected patients and patients co-infected with HIV. The objective of STARTVerso4 is to assess efficacy and safety of FDV + pegylated interferon alfa-2a/ribavirin (PR), and evaluate response-guided treatment duration in HIV patients co-infected with HCV genotype (GT) 1.

Methodology: This phase III, open-label, sponsor-blinded study included HCV/HIV co-infected patients who were HCV treatment naïve (TN) or relapsed after prior interferon-based HCV therapy. The study had 2 arms: arm A, 120 mg FDV for 24 weeks (W); arm B, FDV 240 mg for 12W or 24W (duration determined by on-treatment response). Both arms investigated response-guided duration of the PR backbone. At W24, all patients who achieved early treatment success (ETS, HCV RNA <25 IU/mL at W4 and undetected at W8) were re-randomized to stop all treatment at W24 or continue PR up to W48. Patients without ETS received PR through W48. Patients on protease inhibitor-based antiretroviral regimens were assigned to arm A and patients on efavirenz-based regimen were assigned to arm B. All other patients were randomized. The primary endpoint was sustained virologic response 12W after the end of treatment (SVR12).

Results: A total of 308 patients were treated (mean age 47 years, 81% male, 83% White, 14% Black/African American, 29% ≥F3 liver fibrosis, 79% GT1a, 66% IL28B non-CC rs12979860, 78% TN). HAART was used by 96% of patients. SVR4 data were available for all patients. Efficacy endpoints are summarized in the table. SVR4 rates were 72%-84% across FDV doses/durations. Among patients who achieved ETS, SVR4 rates were comparable in patients who stopped PR at W24 (98/107 [92%]) and those who stopped PR at W48 (108/114 [95%]). The AE profile was consistent with historical data on PR treatment and HAART in HIV/HCV co-infected patients. Most common AEs were nausea (37%), fatigue (34%), and diarrhea (27%). Study medication was discontinued due to AEs in 7% of patients in both arms. Serious AEs occurred in 14% and 8% of patients in arms A and B, respectively.

Conclusions: In this interim analysis, the safety profile and SVR4 rate (74%) for FDV + PR in HIV/HCV GT-1 co-infected patients were comparable with those obtained in HCV mono-infected patients, suggesting that FDV + PR might represent an important option for the treatment of HCV GT-1 infection in patients co-infected with HIV with or without HAART.

Summary of efficacy results

n/N (%)	Arm A: FDV 120 mg	Arm B: FDV 240 mg			All patients (N=308)
	24W (N=123)	12W (N=84)	24W (N=86)	Total[a] (N=185)	
ETS	95/123 (77)	70/84 (83)	73/86 (85)	150/185 (81)	245/308 (80)
SVR4	89/123 (72)	66/84 (79)	72/86 (84)	140/185 (76)	229/308 (74)
ETS and SVR4[b]	85/95 (90)	62/70 (89)	67/73 (92)	131/150 (87)	216/245 (88)
SVR4 with PR 24 wks[c]	40/43 (93)	23/26 (89)	35/38 (92)	58/64 (91)	98/107 (92)
SVR4 with PR 48 wks[d]	41/42 (98)	40/43 (93)	27/29 (93)	67/72 (93)	108/114 (95)

[a]Includes patients who discontinued prior to Week 12.
[b,c,d]Denominator = [b]patients with ETS,[c]patients randomized to 24 wks PR, [d]patients randomized to 48 wks PR.
ETR, end of treatment response; ETS, early treatment success; FDV, faldaprevir.

24 Simeprevir (TMC435) Plus PegIFN/Ribavirin in HCV Genotype-1/HIV-1 Coinfection (Study C212)

Douglas Dieterich[1], Jürgen K. Rockstroh[2], Chloe Orkin[3], Félix Gutiérrez[4], Marina B. Klein[5], Jacques Reynes[6], Lotke Tambuyzer[7], Monika Peeters[7], Alan Jenkins[8], Wolfgang Jessner[7]

[1]Icahn School of Medicine at Mount Sinai, New York, NY, United States, [2]Medizinische. Universitätsklinik I, Bonn, Germany, [3]Royal London Hospital, London, United Kingdom, [4]Hospital General de Elche and Universidad Miguel Hernández, Alicante, Spain, [5]McGill University Health Centre, Montreal, QC, Canada, [6]Gui De Chauliac University Hospital, Montpellier, France, [7]Janssen Infectious Diseases BVBA, Beerse, Belgium, [8]Janssen Research & Development, Raritan, NJ, United States

Background: Simeprevir (TMC435, SMV) is a potent, oral, once-daily (QD), investigational HCV NS3/4A protease inhibitor with activity against HCV genotypes 1, 2, 4, 5, and 6. This ongoing Phase III, open-label trial is investigating efficacy and safety of SMV plus peginterferon/ribavirin (PR) in treatment-naïve or -experienced patients (pts) co-infected with HCV genotype 1 and HIV-1.

Methodology: Pts received SMV 150 mg QD (12 wks) + PR (24/48 wks). Non-cirrhotic treatment-naïve pts or prior relapsers received response-guided treatment with PR for 24 or 48 wks. Prior partial or null responders and cirrhotic pts received PR for 48 wks. Primary endpoint for HCV: sustained virologic response (SVR) rate 12 wks after end of treatment. SVR12 was determined in key subgroups (HCV genotype 1a/1b; METAVIR score; concomitant HAART). Secondary endpoints included HIV virologic response, safety. A pre-defined single-sided z-test was used to compare SVR12 rates for treatment-naïve and prior null responders with historic controls.

Results: 106 pts were treated (84.9% male; 82.1% white; 14.2% black/African American; median age 48 years; median baseline absolute CD4+ count 628.5/mm^3, median baseline $\log_{10}$ HIV RNA 4.18 copies/mL [pts not on HAART]). Most (82.1%) were infected with HCV genotype 1a, 12.3% had cirrhosis, and 87.7% were receiving HAART (NRTI, 98.9%; INI, 87.1%; NNRTI, 15.1%). SVR12 rate was 73.6% overall (treatment-naïve 79.3%; prior relapsers 86.7%; prior partial responders 70.0%; prior null responders 57.1%) and was high in subgroups, albeit pt numbers were low (Table 1). SVR12 was achieved by 7/9 (77.8%) pts with METAVIR F4. HIV virologic failure (confirmed HIV RNA ≥200 copies/mL) rate among pts on HAART was 2.2% (2/93), which occurred 36 and 48 wks after completion of SMV, respectively. Incidence/profile of adverse events (AEs) was comparable to that in HCV mono-infected pts. During SMV and PR treatment, 35 (33%) pts had a Grade 3/4 AE, 6 (5.7%) had serious AEs, and 4 (3.8%) discontinued SMV due to an AE (mostly together with PR); in pts on HAART, 33/93 (35.5%) had Grade 3/4 AEs, 6 (6.5%) had serious AEs, and 4 (4.3%) discontinued SMV due to an AE.

Conclusions: SMV 150 mg QD with PR led to high SVR rates in pts co-infected with HCV genotype 1 and HIV-1, regardless of prior HCV treatment response, HCV genotype 1a/1b, baseline METAVIR score, and concomitant HAART. SMV with PR was well tolerated when co-administered with HAART and did not impact HIV treatment outcome.

Table 1. SVR12 rates (ITT population)

% (n/N)	Overall (n=106)	Treatment-naïve (n=53)	Relapsers (n=15)	Partial responders (n=10)	Null responders (n=28)
Primary analysis	73.6 (78/106)	79.2* (42/53)	86.7 (13/15)	70.0 (7/10)	57.1* (16/28)
HCV genotype					
1a/other	70.5 (62/88)	76.7 (33/43)	83.3 (10/12)	66.7 (6/9)	54.2 (13/24)
1a/other with Q80K	66.7 (20/30)	85.7 (12/14)	33.3 (1/3)	100.0 (1/1)	50.0 (6/12)
1a/other without Q80K	72.4 (42/58)	72.4 (21/29)	100.0 (9/9)	62.5 (5/8)	58.3 (7/12)
1b	88.9 (16/18)	90.0 (9/10)	100.0 (3/3)	100.0 (1/1)	75.0 (3/4)
METAVIR F0-F2	80.0 (36/45)	88.9 (24/27)	77.8 (7/9)	50.0 (1/2)	57.1 (4/7)
METAVIR F3-F4	63.6 (14/22)	57.1 (4/7)	100.0 (2/2)	66.7 (2/3)	60.0 (6/10)
On HAART	75.3 (70/93)	81.4 (35/43)	86.7 (13/15)	77.8 (7/9)	57.7 (15/26)
Not on HAART	61.5 (8/13)	70.0 (7/10)	—	0 (0/1)	50.0 (1/2)

*p<0.001 vs historical PR-only control (SVR12 for control: 29.0% in treatment- naïve patients and 5.4% in null responders)
ITT, intent-to-treat; n, number; SVR, sustained virologic response

25 All-Oral Combination of Daclatasvir, Asunaprevir, and BMS-791325 for HCV Genotype 1 Infection

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Background: The all-oral triple combination of daclatasvir (DCV; NS5A inhibitor), asunaprevir (ASV; NS3 inhibitor), and BMS-791325 ('325; non-nucleoside NS5B inhibitor) achieved sustained virologic response (SVR) rates >90% in pilot cohorts of non-cirrhotic patients with chronic HCV genotype (GT)1 infection. The present study expansion (AI443-014) evaluates this regimen in larger cohorts that include cirrhotic patients, with all components dosed BID to support coformulation development.

Methodology: 166 treatment-naïve, HCV GT1-infected patients were randomly assigned (1:1) to receive a twice-daily regimen of DCV 30mg, ASV 200mg, and '325 75mg (n=80) or 150mg (n=86) for 12 weeks. Randomization was stratified by GT1 subtype and presence of cirrhosis. The primary endpoint is HCV RNA <LLOQ (25 IU/mL) at 12 weeks posttreatment (SVR_{12}). SVR_4 results are reported here; SVR_{12} will be presented.

Results: Baseline characteristics were comparable across treatment groups; overall, patients were 56% male, 83% white, 82% GT1a, 67% *IL28B* non-CC genotype, and 9% cirrhotic. Among all patients with available data at posttreatment Week 4, SVR_4 was achieved by 72/78 (92.3%) and 77/84 (91.7%) patients in the '325 75mg and 150mg groups, respectively, including 13/15 (86.7%) cirrhotic patients (Table. Efficacy Outcomes). Overall, 5/166 patients experienced on-treatment virologic breakthrough and, to date, 6/166 relapsed posttreatment; all of these patients had GT1a infection. In each group, 1 patient discontinued due to an AE (unrelated esophageal neoplasm, throat tightness); there were no deaths and no treatment-related serious AEs or grade 3/4 AEs. The most frequent AEs in both groups were headache, diarrhea, fatigue, and nausea. The only grade 3/4 liver-related lab abnormalities were single events of elevated AST (grade 3) and total bilirubin (grade 3) in different patients.

Conclusions: Twelve weeks of all-oral treatment with DCV + ASV + BMS-791325 achieved an overall SVR_4 rate of 92% in a predominantly GT 1a population, with comparable response rates in cirrhotic and non-cirrhotic patients and low rates of virologic failure. The regimen was generally well tolerated, with similar safety profiles for both '325 dose groups. Further evaluation of this triple regimen is ongoing in broader patient populations, including GT4 infection and prior GT1 null responders.

Efficacy Outcomes				
n/N (%)	DCV+ ASV + '325 75mg		DCV+ ASV + '325 150mg	
	Observed	mITT	Observed	mITT
HCV RNA <LLOQ at end of treatment	78/80 (97.5)	78/80 (97.5)	81/86 (94.2)	81/86 (94.2)
HCV RNA <LLOQ at PT week 4 (SVR_4)	72/78 (92.3)*	72/80 (90.0)*	77/84 (91.7)*	77/86 (89.5)*
On-treatment virologic breakthrough (n)	2		3	
Posttreatment relapse (n)	4		2	
* 2 patients in each treatment group missed posttreatment Week 4 visit, counted as failures in mITT analysis				

26 Sofosbuvir Plus Ribavirin for HCV Genotype 1-3 Infection in HIV Coinfected Patients (PHOTON-1)

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Background: Interferon-free treatments for HCV that can be safely co-administered with antiretroviral therapy (ART) are needed for HIV/HCV co-infected patients. We evaluated the safety and efficacy of sofosbuvir (SOF), a pan-genotypic HCV NS5B inhibitor, with ribavirin (RBV) in HCV genotype (GT) 1-3 patients co-infected with HIV.

Methodology: HCV patients with stable HIV disease received SOF 400 mg QD and RBV 1000-1200 mg/day; treatment-naïve (TN) GT 1 and treatment experienced (TE) GT 2/3 patients received 24 weeks and treatment naïve GT 2/3 patients received 12 weeks of treatment. Multiple ART regimens were permitted, as were patients with compensated cirrhosis. The primary efficacy endpoint was sustained virologic response 12 weeks after treatment (SVR12); safety assessments included HIV RNA and CD4 cell count.

Results: Baseline characteristics and virologic responses are shown in the table. Among treatment naïve GT 2 and 3 patients, SVR12 was achieved in 88% (23/26) and 67% (28/42), respectively. Among the 13 virologic failures, only one had on-treatment virologic breakthrough due to study drug non-adherence, all other failures were due to relapse. No S282T resistance mutations have been detected from virologic failures to date. Complete SVR24 results for all groups, including treatment-experienced GT 2 and GT 3 patients, will be presented. In all groups, treatment discontinuations due to adverse

events (AEs) have been uncommon (3%) and grade 3/4 AEs were reported in 25 (11%) patients. Two patients had HIV breakthrough: one in the setting of ART non-adherence, and one regained HIV control without ART change.

Conclusions: Treatment-naïve HCV GT 2 and 3 patients coinfected with HIV achieved high rates of SVR12 with an interferon-free, all-oral regimen of SOF+RBV. These data suggest that SOF+RBV treatment is well-tolerated and safely co-administered with multiple ART regimens and may be equally safe and efficacious in patients with and without HIV coinfection.

Demographics and SVR12/24					
	GT 1 TN N=114	GT 2 TN N=26	GT 3 TN N=42	GT 2 TE N=24	GT3 TE N=17
Male, n (%)	93 (82)	21 (81)	34 (81)	23 (96)	14 (82)
Black, n (%)	37 (33)	6 (23)	2 (5)	6 (25)	1 (6)
IL28B CC genotype, n (%)	30 (27)	10 (39)	15 (36)	10 (42)	10 (59)
Cirrhosis, n (%)	5 (4)	1 (4)	6 (14)	4 (17)	6 (35)
Log10 HCV RNA (IU/mL), mean (SD)	6.6 (0.8)	6.5 (0.6)	6.2 (0.6)	6.5 (0.8)	6.4 (.5)
CD4 T-cell count (cells/μL), mean (SD)	636 (251)	627 (278)	559 (224)	649 (330)	671 (346)
On ART, n (%)	112 (98)	22 (85)	39 (93)	23 (96)	16 (94)
Tenofovir/Emtricitabine PLUS Efavirenz, n (%) Atazanavir/ritonavir, n (%) Darunavir/ritonavir, n (%) Raltegravir, n (%)	42 (37) 24 (21) 15 (13) 21 (18)	7 (27) 4 (15) 6 (23) 2 (8)	13 (31) 3 (7) 11 (26) 6 (14)	9 (39) 5 (22) 0 4 (17)	7 (44) 3 (19) 2 (12) 3 (19)
SVR12, n/N (%)	[To be presented]	23/26 (88)	28/42 (67)	[To be presented]	[To be presented]
SVR24, n/N (%)	[To be presented]	[To be presented]	[To be presented]	[To be presented]	[To be presented]

27LB Combination Oral, Hepatitis C Antiviral Therapy for 6 or 12 Weeks: Final Results of the SYNERGY Trial

Anita Kohli[1,2], Zayani Sims[1], Amy Nelson[3], Anu Osinusi[3,4], Geb Tefari[5], Phil Pang[6], William Symonds[6], John McHutchison[6], Henry Masur[1], Shyam Kottilil[3]

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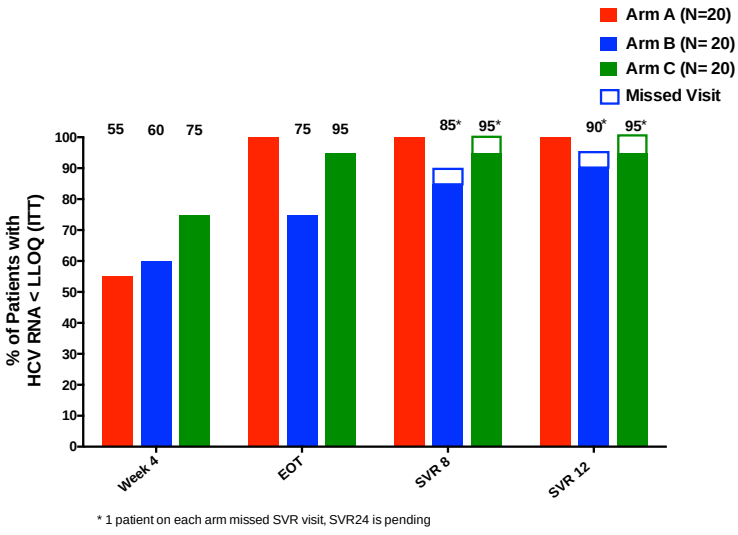
Background: Combining multiple directly acting antiviral agents (DAA) is a plausible approach to reduce the duration of therapy require to cure HCV infection. In this study treatment regimens targeting multiple stages of HCV replication were evaluated for safety and efficacy in a historically difficult to treat population.

Methodology: Sixty HCV mono-infected, treatment naïve, GT-1, patients were consecutively enrolled into 3 arms of a phase 2 prospective cohort study and received: Arm A - sofosbuvir with ledipasvir (400mg/90mg respectively once daily in a fixed dose combination (FDC)) for 12 weeks, Arm B - FDC + GS-9669 (500mg/day), a non nucleoside NS5B inhibitor for 6 weeks, or Arm C - FDC + GS-9451 (80mg/day), an HCV protease inhibitor for 6 weeks. Serial measurements of safety parameters, virologic (HCV RNA by Roche Taqman PCR and Abbott assay; deep sequencing of baseline mutations) and host correlates (intrahepatic and peripheral by flow cytometry) were performed.

Results: Patients enrolled were predominantly African American (88%), male (72%), infected with GT-1a (70%), had a high HCV VL (>800k) (70%) with an IL28B non-CC haplotype (82%). Baseline demographics were similar between patients across arms and 35%, 25% and 25% of subjects on Arm A, B and C, respectively, had stage ≥3 liver fibrosis. No patients with cirrhosis were included in Arm B or C. The end of treatment response (HCV RNA <LLOQ) was 100%, 75% and 95% of subjects in Arms A, B and C respectively using a more sensitive HCV assay with lower limit of quantification of 12 IU/mL (Fig 1). Using an HCV RNA assay with a lower limit of quantification of <43 IU/mL 100% of patients on all arms were suppressed at EOT. 100%, 90% and 95% of patients in Arm A, B and C respectively achieved SVR12. One patient in Arm B experienced viral relapse. One patient on Arms A and B each missed their SVR12 visit. The combination was well tolerated with no grade 4 adverse events or drug discontinuations.



* 1 patient on each arm missed SVR visit, SVR24 is pending

Conclusions: In this inner city patient population addition of a third antiviral agent allowed successful eradication of HCV in 6 weeks in a difficult to treat patient population. This study presents a new paradigm of combination therapy to reduce HCV treatment duration, which may be vital in the treatment and eradication of HCV globally.

28LB Daclatasvir in Combination With Simeprevir ± Ribavirin for Hepatitis C Virus Genotype 1 Infection

Stefan Zeuzem[1], **Christophe Hezode[2]**, Jean-Pierre P. Bronowicki[3], Veronique Loustad-Ratti[4], Francisco Gea[5], Maria Buti[6], Maria Beumont-Mauviel[7], Navdeep Boparai[8], Gaston Picchio[9], Stephanie Noviello[8], on behalf of the LEAGUE-1 Study Team

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Background: All-oral combinations of direct-acting antivirals offer potential for effective and well tolerated HCV therapies. We assessed the efficacy and safety of daclatasvir (DCV; NS5A inhibitor) combined with simeprevir (SMV; NS3/4A protease inhibitor), with or without ribavirin (RBV), in patients with HCV genotype (GT) 1 infection.

Methodology: In this open-label study (AI444-062), HCV GT1b treatment-naive patients (N=104) and prior null responders (N=43) were randomly assigned (1:1) to receive DCV 30mg QD (low dose) + SMV 150mg QD (N=76) or DCV + SMV + weight-based RBV (N=71). Two treatment durations were evaluated: patients who completed 12 weeks were re-randomized (1:1) to stop at Week 12 or continue treatment through Week 24. In an exploratory evaluation of GT1a, naive (N=12) and null responder patients (N=9) received DCV + SMV + RBV for 24 weeks. The primary endpoint was HCV RNA below the assay limit of quantitation at posttreatment Week 12 (SVR_{12}).

Results: Baseline parameters were well-balanced across treatment groups. Overall, patients were 92% white, 49% male, 21% cirrhotic, and 76% *IL28B* non-CC genotype. SVR_{12} (mITT) was achieved by 45/53 (84.9%) and 38/51 (74.5%) treatment-naïve GT1b patients receiving DCV + SMV or DCV + SMV + RBV, respectively (Table). SVR_{12} (mITT) in GT1b null responders was 95% (19/20) with DCV + SMV + RBV and 65% (15/23) with DCV + SMV. Estimated SVR_{12} rates in GT1b (adjusted for pre-Week 12 discontinuations) were similar after 12 or 24 weeks of treatment in naive patients but higher after 12 than 24 weeks in null responders. In patients with GT1a, 8/12 (66.7%) naive patients achieved SVR_{12}; all null responders were offered pegIFN/RBV + DCV + SMV rescue therapy due to frequent breakthroughs and were counted as failures. There were 2 treatment-related serious AEs (neurotoxicity, liver disorder) and 1 on-treatment death (unrelated intracranial hematoma). Three patients experienced treatment-related AEs leading to discontinuation (neurotoxicity, constipation, insomnia). 17 patients experienced grade 3/4 total bilirubin elevations without concurrent transaminase elevations, mostly in patients receiving RBV (14/17), consistent with RBV-induced hemolysis and known effects of SMV on bilirubin transporters.

Conclusions: The all-oral combination of DCV + SMV, with or without RBV, was generally well tolerated and achieved SVR_{12} in 75-85% of treatment-naïve patients and 65-95% of prior null responders with GT1b infection after 12 or 24 weeks of treatment.

Parameter	GT1b				GT 1a	
	Naive		Null		Naive	Null†
	DCV+SMV	DCV+SMV+RBV	DCV+SMV	DCV+SMV+RBV	DCV+SMV+RBV	DCV+SMV+RBV
N	53	51	23	20	12	9
SVR12, mITT; n/N (%)	45/53 (84.9)	38/51 (74.5)	15/23 (65.2)	19/20 (95.0)	8/12 (66.7)	0/9 (0)
SVR12, observed; n/N (%)	45/50 (90.0)	38/46 (82.6)	15/19 (78.9)	19/20 (95.0)	8/12 (66.7)	0/9 (0)
Estimated SVR12, 12 week treatment (IPW)*, (%)	80.8	75.0	82.6	100	-	-
Estimated SVR12, 24 week treatment (IPW)*, (%)	88.7	73.5	49.6	88.9	-	-

*IPW, Inverse Probability Weighting to adjust for patients who discontinued prior to Week 12 and were not re-randomized.
†All GT1a null responders were offered the addition of pegIFN alfa-2a as rescue therapy and are considered failures.
mITT, modified intention-to-treat analysis; includes all patients who received at least one dose of study medication.
As-observed analysis excludes only patients with missing data at posttreatment Week 12

29LB PEARL III: SVR ≥99% After 12 Wks of ABT-450/r/267 + ABT-333 ± RBV in Treatment Naïve HCV GT1b Infection

Peter Ferenci[1], Anders Nyberg[2], David Bernstein[3], Yaacov Baruch[4], Vladimir Chulanov[5], Wangang Xie[6], Daniel Cohen[6], Thomas Podsadecki[6], **K Rajender Reddy[7]**, on behalf of the PEARL-III Study Group

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Background: ABT-450 is an HCV protease inhibitor (dosed with ritonavir 100mg, ABT-450/r) identified by AbbVie and Enanta. ABT-267 is an NS5A inhibitor, and ABT-333 is a nonnucleoside polymerase inhibitor. Genotype 1b (GT1b) infection is more common globally than GT1a; thus there is a large unmet need for safe, efficacious and simple therapy. In a prior study, 100% of 50 treatment-naïve subjects with GT1b infection who received this regimen for 12 weeks with or without ribavirin (RBV) achieved SVR. We report findings from a multinational phase 3 trial of co-formulated ABT-450/r/ABT-267 and ABT-333 (3D regimen), with and without RBV, in non-cirrhotic treatment-naïve adults with GT1b HCV infection.

Methodology: PEARL-III was a double-blind controlled trial. Subjects were randomized (1:1) to 12 weeks of treatment with ABT-450/r/ABT-267 (150mg/100mg/25mg QD) and ABT-333 (250mg BID), with weight-based RBV (1000mg or 1200mg daily divided BID, Arm A) or placebo for RBV (Arm B).

Results: 419 subjects received the 3D regimen, baseline characteristics as shown (Table). SVR12 rates (intent-to-treat) were 99.5% (Arm A) and 99.0% (Arm B.) There was no on-treatment virologic failure or post-treatment relapse among subjects receiving the 3D regimen without RBV. 19 subjects in Arm A and 0 in Arm B ($P<0.001$) had hemoglobin decrease to <10g/dL. The most common adverse events in Arms A and B were headache (24.3% vs. 23.4%, P=NS) and fatigue (21.4% vs. 23.0%, P=NS.) No subjects discontinued due to adverse events.

Conclusions: In this large phase 3 trial, the 3D regimen was highly efficacious and safe with or without RBV for the treatment of HCV GT1b-infected non-cirrhotic treatment-naïve adults. RBV is not needed in this population.

Baseline Characteristics and Efficacy

	Arm A (3D+RBV) N=210	Arm B (3D) N=209
Male, n (%)	106 (50.5)	86 (41.1)
White race, n (%)	198 (94.3)	196 (94.2)
Age, mean (SD)	48.4 (11.9)	49.2 (12.0)
IL28B CC, n (%)	44 (21.0)	44 (21.1)
Baseline HCV RNA, log_{10} IU/mL, mean (SD)	6.29 (0.77)	6.33 (0.67)
SVR_{12}, n (%)	209 (99.5)	207 (99.0)
On-treatment virologic failure	1 (0.5)	0
Relapse by post-treatment Week 12	0	0
Missing SVR_{12} data	0	2 (1.0)

Session O-2 Oral Abstracts

10:00 AM – 12:00 PM **Room 304**

NeuroHIV: Developments in Treatment and Pathogenesis

30 Early Antiretroviral Therapy Appears To Normalize Intrathecal Markers of Immune Activation

Julia Peterson[1], Evelyn Lee[1], Dietmar Fuchs[2], Richard W. Price[1], Serena Spudich[3]

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Background: Central nervous system (CNS) viral invasion and accompanying neuroinflammation occur early after systemic HIV infection, and are a substrate for neurological injury in untreated disease. Markers of inflammation in the CNS have been shown to remain elevated in the presence of antiretroviral therapy (ART) initiated during chronic infection, yet the extent to which elevations may persist in the setting of treatment initiation early during infection is unknown. We investigated soluble and cellular markers of immune activation in the blood and cerebrospinal fluid (CSF) during primary HIV infection (PHI) and evaluated to what extent these markers may normalize after early ART initiation.

Methodology: 24 subjects with primary HIV infection (PHI, defined as <1 year HIV infection) had blood and CSF sampling at baseline and at a 6-12 month interval after starting ART. Subjects initiated ART at variable times after infection, for reasons independent of this protocol. To assess immune activation, we measured the following both at baseline and after ART initiation: CSF white blood cells (WBC), protein, CSF: plasma albumin ratio, CSF and blood neopterin. To investigate abnormality after early treatment initiation, PHI subjects were compared to a group of 20 age-matched HIV-uninfected subjects (HIV-) by Mann Whitney's test. Additionally, baseline predictors of post-ART marker elevations were explored by Spearman's correlation.

Results: At baseline, PHI subjects were 139 days post-infection (dpi) and 38 years old (all values medians). Most immune and inflammatory measures were abnormal in PHI compared to HIV- ($p<0.01$), including: CD4 count 507 cells/uL, CSF WBC 6 cells/uL, CSF neopterin 8.8 nmol/L, and plasma neopterin 13.89 nmol/L. Baseline CSF protein and CSF: plasma albumin ratio were not different from HIV-. Subjects started ART 532 dpi and had repeat sampling at 242.5 days after ART initiation. After ART, median values included: CSF WBC 2 cells/uL, CSF protein 36 cells/uL, CSF: plasma albumin ratio 4.57, CSF neopterin 4.95 nmol/L, and plasma neopterin 7 nmol/L. A significant elevation in PHI after sustained ART compared to HIV- was detected only in blood neopterin ($p=0.03$). Post-ART blood neopterin was predicted only by the number of days on ART ($p=0.034$, $r=0.45$), while post-ART CSF neopterin was predicted by baseline CSF and blood neopterin values ($p=0.005$, $r=0.59$ and $p=0.029$, $r=0.47$, respectively), as well as baseline albumin ratio ($p=0.02$, $r=0.49$).

Conclusions: In PHI subjects evaluated a median 8 months after ART was initiated 1.5 years after infection, levels of CSF markers of inflammation normalized. These findings are in contrast to prior reports of persistent CNS immune activation in chronic infection, and may suggest a benefit of early initiation of ART.

31 Immediate Antiretroviral Therapy Mitigates the Development of Neuronal Injury in Acute HIV

Michael J. Peluso[1], Victor Valcour[2], Jintanat Ananworanich[3, 4], Pasiri Sithinamsuwan[5], Thep Chalermchai[4], Nitiya Chomchey[4], Bonnie Slike[6], Magnus Gisslen[7], Henrik Zetterberg[7], Serena Spudich[8], on behalf of the RV254/SEARCH 010 and 011 Study Teams

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Background: Neurofilament light chain (NFL) in cerebrospinal fluid (CSF) is a sensitive marker of axonal injury that is elevated in neurodegenerative disorders, HIV-associated dementia, and some neuroasymptomatic subjects during the early and late stages of HIV infection. We sought to determine whether axonal injury can be detected acutely after HIV transmission, and if initiation of combination antiretroviral therapy (cART) during acute HIV is associated with lower levels of CSF NFL compared to cART initiated during chronic HIV.

Methodology: Acute (n=32) and chronic (n=33) HIV infected Thai subjects naïve to cART underwent blood and CSF sampling, followed by immediate cART initiation. CSF was then sampled at 24 (n=26) and 96 weeks (n= 15) in the acute and at 48 weeks (n=10) in the chronic subjects. HIV RNA levels and soluble immune biomarkers were measured in CSF and blood at each visit. CSF NFL was analyzed using a highly sensitive, two-site enzymatic quantitative immunoassay with a lower limit of detection of 50 ng/L. Cross-sectional analyses employed the Mann-Whitney test and Spearman correlations; paired analyses were used to compare subjects across time points.

Results: At baseline (median 18 days post infection in acute subjects), median CD4 T cell count was 401 and 228 cells/uL in the acute and chronic groups, respectively (p<0.0001). Baseline CSF NFL was lower in acute than in chronic subjects (median, 234 versus 327 ng/L; p=0.003), and only 1/32 (3.1%) acute subjects had NFL above the upper limit of normal for age, compared to 10/33 (30.3%) chronic subjects. Baseline CSF NFL did not correlate with blood or CSF HIV RNA or soluble immune biomarkers in acute subjects, and modestly correlated only with the macrophage activation marker CSF neopterin in chronic subjects (r=0.35, p=0.049). In acute subjects, there was no change in NFL from baseline values to 24 and 96 weeks after cART. After at least 6 months of sustained cART (24 weeks duration of cART in acute cases and 48 weeks duration of cART in chronic cases), the acute group had a lower median CSF NFL than chronic subjects (216 vs 490 ng/L; p=0.015), and only 1/26 (3.9%) of acute subjects had CSF NFL above the upper limit of normal for age, compared to 5/10 (50%) in the chronic group.

Conclusions: Neuronal injury as measured by CSF NFL was not detected during very acute HIV infection. Immediate initiation of cART may mitigate development of neuronal injury, which may be more difficult to reverse during later stages of infection.

32 Replication of HIV-1 in the Central Nervous System of Adults Early After Infection

Christa Buckheit Sturdevant[1], Gretja Schnell[1], Richard W. Price[2], Serena Spudich[3], Ronald Swanstrom[1]

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Background: Viral replication within the central nervous system (CNS) facilitates neurological complications and reflects a potentially important tissue reservoir. The timing of emergence and character of this local CNS replication is unknown. We examined phylogenetic relationships and viral characteristics of paired cerebrospinal fluid (CSF) and blood samples obtained over the first two years of HIV infection.

Methodology: Subjects with primary HIV infection (PHI, <1 year after initial infection) were enrolled in San Francisco, USA, in a longitudinal neurological study including serial paired CSF and blood sampling. Using single genome amplification (SGA) and phylogenetic analysis of the full-length env gene, we compared viral populations from blood and CSF in samples obtained up to two years post-infection from 72 ART-naïve PHI subjects infected with HIV-1 subtype B.

Results: At baseline, subjects were a median 106 (IQR 73, 158) days post infection, had 567 (411, 732) CD4 T cells/ul, 4.66 (4.09, 5.08) plasma HIV RNA log10 copies/ml, and 2.62 (1.74, 3.32) CSF HIV RNA log10 copies/ml. Independent replication in the CNS (compartmentalization) was detected in 12% of all sample pairs, predominantly after four months of infection. Approximately 20% of the time there was either compartmentalization or marked pleocytosis, which we propose are dynamic and interrelated. Longitudinal assessment of individual subjects demonstrated that compartmentalized replication was present either as a transient state, or was maintained within the CSF and diversified independently over a period of time during early infection. Two subjects had one of two transmitted lineages (or their recombinant) largely sequestered within the CNS shortly after transmission, indicating a second mechanism for establishing independent replication in the CNS early. All viruses examined required high levels of CD4 for entry, indicative of replication in CD4+ T cells.

Conclusions: Examination of the relationships between CSF viral populations, blood and CSF viral loads, and inflammatory responses identified four distinct states of viral population dynamics, and revealed putative mechanisms of local viral replication and the early influx of virus into the CNS. We observed genetically complex, compartmentalized viral replication within the CSF/CNS suggestive of sustained replication in CD4+ T cells during the first two years of HIV infection.

33 Persistent CSF, But Not Plasma HIV RNA Is Associated With Increased Risk of New-Onset Depression

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Background: Major depressive disorder is the most common neuropsychiatric complication in persons with HIV and is associated with worse clinical outcomes. It is unknown whether detectable cerebrospinal fluid (CSF) human immunodeficiency virus (HIV) ribonucleic acid (RNA) at thresholds ≥50 copies/ml, is associated with increased risk of new-onset depression. We hypothesized a priori that detectable CSF HIV RNA is associated with increased risk of depressive symptoms and increasing depression scores.

Methodology: The CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) cohort is a six-center US-based prospective cohort with bi-annual follow-up 674 participants. We fit linear mixed models (N=223) and discrete-time survival models (N=154), a total of 832 observations, among participants on combination antiretroviral therapy (cART) enrolled from 2004 to 2007, and followed through 2009 over 2,496 person-months. Participants were included in these analyses if they were free of depression at study entry and received a minimum of three CSF exams during follow-up. The main outcome measures were incidence of new-onset moderate-to-severe depressive symptoms (BDI ≥17), and trajectories of BDI scores.

Results: The mean age was 44.8 years, majority were male (81.6%), 44.8% Black, 39.5% White, and mean duration of current cART use was 18.1 months. At study entry, 32 (14.4%) participants had detectable CSF HIV RNA (≥50 copies/ml). Detectable CSF HIV RNA at any visit was associated with a 4.7-fold increase in new-onset depression at subsequent visits adjusted for plasma HIV RNA and treatment adherence; hazard ratio (HR)=4.76, (95% CI: 1.58_14.3); P=0.006. BDI scores were 2.53 points higher (95% CI: 0.47_4.60; P=0.02) over 6 months if CSF HIV RNA was detectable at a prior study visit in fully adjusted models including age, sex, race, education, plasma HIV RNA, duration and adherence of cART, and lifetime major depressive disorder by Diagnostic Statistical Manual of Mental Disorders, Fourth Edition criteria. Throughout follow-up in adjusted linear mixed models, BDI scores for persons with detectable CSF HIV RNA increased, whereas BDI scores decreased when CSF HIV RNA was undetectable. Unlike the findings for CSF HIV RNA, plasma HIV RNA was not associated with an increase in BDI scores over time.

Conclusions: Persistent CSF but not plasma HIV RNA is associated with an increased risk for new-onset depression. Persons with persistent or worsening depression may benefit from CSF testing for HIV RNA, which may help guide HIV and depression treatment. Further research evaluating the role of immune activation and inflammatory markers will improve our understanding of this association. We speculate that depression may be a surrogate of ongoing CNS inflammation and injury.

34 CSF Metabolomics Reveals Altered Waste Clearance and Accelerated Aging in HIV Patients With HAND

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Background: HIV-associated neurocognitive disorders (HAND) remain prevalent in HIV-infected populations on antiretroviral therapy (ART). Factors associated with increased risk of HAND in HIV patients on suppressive ART include older age, low nadir CD4, and active HCV co-infection, but underlying pathophysiological mechanisms remain unclear.

Methodology: Untargeted metabolite profiling of cerebrospinal fluid (CSF) from 90 subjects (36 HIV+ subjects on ART from CHARTER and NNTC [median CD4 count 141 cell/ul, median plasma VL 268 copies/ml, median CSF VL 50 copies/ml; n=17 and 19 with and without HAND [median global T-scores 36 and 48, respectively)] and 54 healthy controls [ages 30-78]) was performed using liquid or gas chromatography followed by mass spectrometry. Cytokine profiling was performed by Bioplex array. Pathway mapping and PLS-DA, were performed using Metaboanalyst and Cytoscape. Integrative analysis of CSF metabolites, cytokines, and global and domain-specific T-scores was performed in R.

Results: Of 107 named metabolites detected in CSF, 20 were altered in HIV+ subjects on ART compared to age/gender-matched healthy controls (FC>1.2, p<0.05, FDR<5%) including metabolic waste products (ketone bodies, phenylacetylglutamine, p-cresol sulfate), neurotransmitters (glutamate, NAA), and markers of mitochondrial dysfunction (3-dehydrocarnitine, succinate, malate) and oxidative stress (5-oxoproline and purine metabolites). 53% of metabolites altered in HIV subjects (< age 50) overlapped with those altered in aging healthy controls (≥ age 50 vs. < age 50), including glutamate, succinate, ketone bodies, and phenylacetylglutamine, suggesting a pattern indicative of accelerated aging. Fold change and PLS-DA analysis identified glutamate, glycine, succinate, ketone bodies (3-hydroxybutyrate, acetoacetate, and 1,2 propanediol), and myo-inositol as top-ranked classifiers of HAND. Integrative analysis of cytokine, metabolomic, and clinical data revealed positive correlations (p<0.05, FDR<10%) between persistent elevation of CSF IFN-γ and IL-8, plasma IFN-γ and IL-6, and a metabolite cluster consisting of neurotransmitters (glutamate and glycine), ketone bodies (3-hydroxybutyrate and 1,2 propanediol), and markers of glial responses (myo-inositol), and suggested associations between systemic and intrathecal inflammation, metabolic alterations in CSF that overlap those detected in older controls, and classifiers of HAND.

Conclusions: Alterations in the CSF metabolome of HIV patients on ART suggest that persistent inflammation, glial responses, glutamate/glycine neurotoxicity, and age-dependent effects on brain waste-disposal systems contribute to mechanisms involved in development of HAND that may be augmented with aging.

35 Cerebral Small Vessel Disease and HAND in ARV-Treated Subjects

Virawudh Soontornniyomkij, Anya Umlauf, Benchawanna Soontornniyomkij, Ben Gouaux, Will Toperoff, David J. Moore, Eliezer Masliah, Igor Grant, **Cristian L. Achim**
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Background: Despite the widespread use of highly active antiretroviral therapy, HIV-associated neurocognitive disorders (HAND) remain prevalent and may be associated with cumulative exposure to antiretroviral (ARV) medications and other factors. We proposed that chronic toxic effects of ARV drugs on the blood vessel walls could contribute to cerebral small vessel disease (CSVD), which even at its early stages could lead to disturbance of cerebrovascular autoregulation and deficiency in functional hyperemia.

Methodology: We assembled 144 consecutive autopsy HIV-infected cases that had detailed data on ARV medications ever used during the entire period of follow-up observation and died during 1999–2011. In studying associations between the use of ARV drugs and the occurrence of blood vessel pathology in the brain, we included three major drug classes: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). We employed multinomial logistic regression to determine associations between the use of ARV drugs and the occurrence of CSVD. Forebrain CSVD was defined as concentric intramural hyalinization of small arteries or arterioles in the forebrain leptomeninges and parenchyma. CSVD was graded as absent, mild, or severe.

Results: Mild CSVD was present in 24.8% and severe CSVD in 47.4% of 137 cases. On multinomial logistic regression analysis, the use of NRTIs or PIs was associated with the higher odds of mild CSVD (relative to absent) [OR 19.23 and 2.84, P=0.003 and =0.06, respectively]. No association was found between mild CSVD and any of the potential covariates. In contrast, the occurrence of severe CSVD (relative to absent) was associated with older age or

diabetes (OR 2.56 and 6.55, P=0.035 and =0.01, respectively), but not with any of the ARV-related predictors. Notably, HAND was associated with mild CSVD (OR 4.82). No other significant associations between pathologic changes and HAND were found.

Conclusions: The clinical importance of mild CSVD in our study was substantiated by the finding that mild CSVD was predictive of HAND. Our findings suggest that the use of NRTIs or PIs may increase the risk of mild CSVD and consequently neurocognitive impairment. Interestingly, we found no significant association between the use of any ARV drug classes during life and the presence of HIV encephalitis at autopsy. Although our study analyzed the adverse effects of individual major ARV drug classes, different ARV drugs even in the same class might carry differential degrees of toxicity on cerebral vessels. We are pursuing now studies of the molecular mechanisms of ARV toxicity to the cell components of cerebral vessels and identification of potential biomarkers for CSVD in HIV-infected patients.

Session O-3 Oral Abstracts

10:00 AM – 12:30 PM **Ballroom A**

Prevention and Epidemiology: Evolving Trends

36 Temporal Trends in Prognostic Markers of HIV-1 Virulence and Transmissibility

Nikos Pantazis[1], Kholoud Porter[2], Dominique Costagliola[3], Andrea De Luca[4], Jade Ghosn[5], Marguerite Guiguet[3], Anthony D. Kelleher[6], Charles Morrison[7], Rodolphe Thiebaut[8], Giota Touloumi[1], on behalf of the CASCADE Collaboration in EuroCoord

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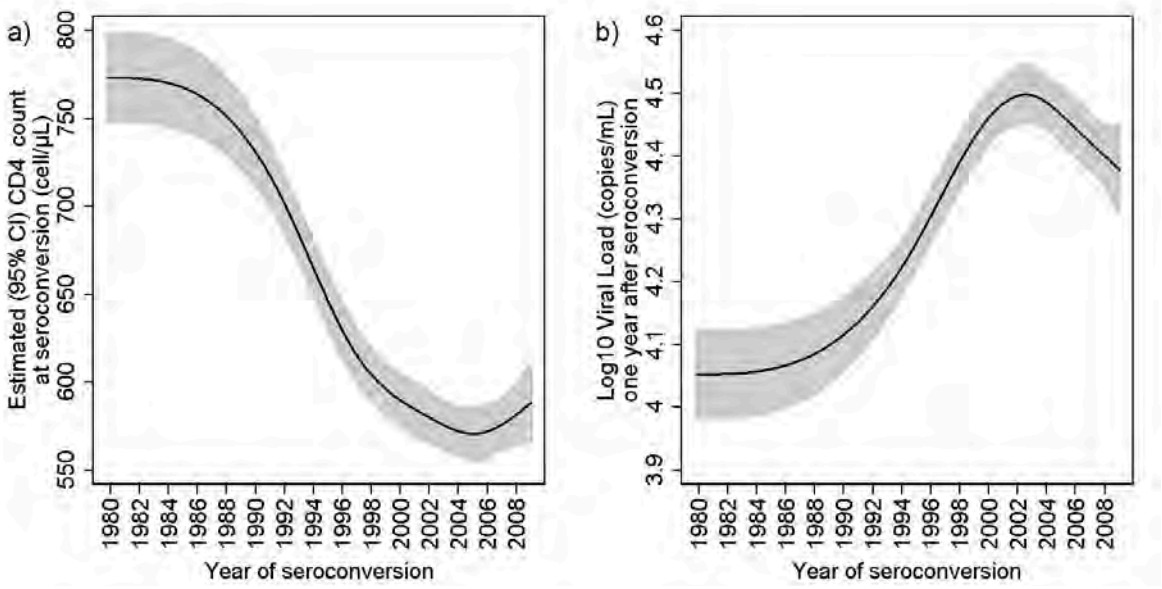
Background: Measures of CD4 T-cell count (CD4) and HIV-1 plasma viral load (pVL) are proxies for HIV-1 virulence. Whether these proxies are changing over time has serious implications for prevention and treatment. The aim of this study is to investigate these trends.

Methodology: Data were derived from the CASCADE collaboration (updated in 2011) excluding African cohorts, recent seroconverters (≥2009) and children <15 years old at seroconversion (SC). Follow-up was censored at the time of antiretroviral initiation or clinical AIDS onset. CD4 at SC, CD4 rate of decline and pVL measurements were analyzed using linear or fractional polynomials mixed models adjusting for all available potential confounders. Calendar time effects were modelled through natural cubic splines.

Results: 15,875 individuals seroconverting from 1979-2008 fulfilled the inclusion criteria. Estimated (95% CI) CD4 at SC for a typical individual declined from ~770 (750-800) in the early `80s to a plateau of ~570 (560-580) cells/μL after 2000. Rates of CD4 loss were relatively stable up to 1996 becoming faster between 1996 and 2004. Estimated (95% CI) pVL set-point increased from 4.05 (3.98-4.12) in 1980 to 4.50 (4.45-4.54) log10 copies/mL in 2002 with a tendency of returning to lower levels thereafter. Estimated (95% CI) CD4 at SC and pVL set-point for white men, infected through sex between men (MSM), aged 30-39 years at seroconversion are shown in Figure (a and b, respectively). Results were similar when restricting the analyses to various subsets (e.g. those with a 'midpoint' method of seroconversion determination and a test interval <180 days; white MSM etc.), adjusting for pVL assay, censoring follow-up at 3 years or using variations of the main statistical approach.

Conclusions: Our results provide strong indications of an increased HIV-1 virulence and transmissibility during the course of the epidemic and a potential plateau effect after ~2000. Continued monitoring and basic science studies are needed to detect further virulence changes and to assess the consistency of our findings.



37 Transmission Clusters, Recent Infection and STIs Among New HIV Cases: Implications for Prevention

Hong-Ha M. Truong[1,2], Sharon Pipkin[3], Kara O'Keefe[3], Brian Louie[3], Teri Liegler[1], Willi McFarland[1,3], Robert M. Grant[1,2], Mark Pandori[3], Kyle Bernstein[3], Susan Scheer[3]

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Background: Only HIV transmission that is occurring in the present can be interrupted. Recent infection, a new diagnosis of a sexually transmitted infection (STI) and phylogenetically-linked transmission clusters are factors that may help direct prevention efforts towards current chains of HIV transmission. We therefore examined correlates associated with recent and longer-standing infection among persons newly-diagnosed with HIV in San Francisco.

Methodology: San Francisco residents newly-diagnosed with HIV from 2005 through 2011, linked to care at publicly-funded facilities and had viral genotypes were included in the analysis. This study received IRB approval. Transmission clusters were identified based on bootstrap values of ≥ 90% and mean pairwise genetic distances of ≤ 0.03%. Recent HIV infection was defined as having a documented negative antibody test within 6 months of HIV diagnosis and/or being acutely infected (RNA+/Ab-). A recent STI diagnosis was defined as being diagnosed with a new STI within the 6 months preceding HIV diagnosis. Associations were assessed by multivariate logistic regression.

Results: Overall, there were 1,311 persons newly-diagnosed with HIV, of whom 45% were part of a transmission cluster, 16% were recently infected and 12% had a recent STI diagnosis. Demographically, 57% were non-white, 32% were under 30 years old and 76% were MSM. Among persons recently infected with HIV, 57% were linked to a transmission cluster, 25% had a recent STI diagnosis, 56% were non-white, 44% were under 30 years old and 86% were MSM. Individuals with recent HIV infection were more likely to belong to a transmission cluster (OR=1.8; p<0.001), have a recent STI diagnosis (OR=2.5; p<0.001) and be under 30 years old (OR>2.7; p<0.01) than persons with longer-standing infections.

Conclusions: These findings help to pinpoint where HIV transmission continues to propagate in San Francisco, including highlighting that many newly-diagnosed infections are participating in phylogenetically-linked transmission chains. Recent HIV infection was associated with being diagnosed with a STI during the time interval that overlapped with when HIV transmission most likely occurred, thereby pointing to intervention opportunities to interrupt HIV transmission. The high rate of clustering observed indicates that recent infections may be associated with increased risk of onward transmission of HIV but also suggests these individuals may be reached to prevent the further spread of infections.

38 Race and Age Disparities in HIV Incidence and Prevalence Among MSM in Atlanta, GA

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Background: HIV prevalence and incidence race disparities exist among US men who have sex with men (MSM); individual-level risk factors do not explain these differences.

Methodology: InvolveMENt is a longitudinal cohort of black (BMSM) and white (WMSM) HIV-negative MSM aged 18-39, recruited via venue time-space sampling. Eligible men reported any sex with a man in the previous 3 months. Every 3-6 months, participants were tested for HIV/STI and completed CASI surveys of individual- and sexual dyad-level risk behaviors. Race- and age-specific HIV and STI prevalence, prevalence-ratios (PR), incidence rates and incidence-density ratios (IDR) were estimated with exact 95% confidence intervals (CI). Age-scaled Cox proportional hazards estimated time-independent and -dependent mediators of disparate HIV incidence.

Results: 803 MSM (454B, 349W) were enrolled: 197 BMSM and 46 WMSM were HIV-positive at baseline. Except for 18-19 year olds, BMSM had higher HIV prevalence than WMSM (BMSM: 34% at 25 years, 45% by 30 years, 60% ≥30 years). In 755 person-years (PY) of followup, 23 incident HIV infections were diagnosed (19 BMSM, 4 WMSM). Among participants < 25 years, HIV incidence for BMSM was 9.6% and 0% for WMSM (RR undefined but > 2.1 (95% CI: [2.1, +∞]). Among participants ≥ 25 years, HIV incidence was nonsignificantly higher for BMSM (3.4%) than WMSM (1.2%; IDR = 2.8 (CI: [0.7, 13.1]). Compared to BMSM ≥ 25 years, those < 25 had significantly higher incidence (RR = 2.9, CI: [1.1, 7.7]). Similar significant disparities were found for urethral gonorrhea, rectal chlamydia, rectal gonorrhea, and syphilis incidence. Results from a change-in-hazard approach found that the racial disparity in HIV incidence was explained by poverty and partner race, but not employment, insertive vs. receptive sex roles, drug use, and time-dependent homelessness, arrest, anal intercourse, and known serodiscordant partners (unadjusted HR: 5.4, CI: [1.8, 16.6]; adjusted HR: 1.4, CI: [0.4, 5.5]).

Conclusions: Relative to WMSM, BMSM in Atlanta experience substantially higher HIV and STI incidence. Nearly 1 in 10 black MSM under age 25 is infected with HIV annually. Observed incidence levels are consistent with large observed prevalence disparities and highlight the 18-24 year period as critical for prevention, and that educational and other prevention services need to start before 18. It is critical to identify mechanisms, such as choice of sexual partners and access to clinical and prevention services, through which poverty shapes other risks. In a setting where partner pool risk is a driver of disparities, it is also important to maximize care and treatment for HIV-positive MSM to reduce transmission potential.

39 Correlating GSK1265744 Plasma Levels To Prevention of Rectal SHIV Transmission in Macaques

Chasity D. Andrews[1], William Spreen[2], Yun Lan Yueh[2], Agegnehu Gettie[1], Kasi Russell-Lodrigue[3], Hiroshi Mohri[1], Cecilia Cheng-Mayer[1], Zhi Hong[2], Martin Markowitz[1], David D. Ho[1]

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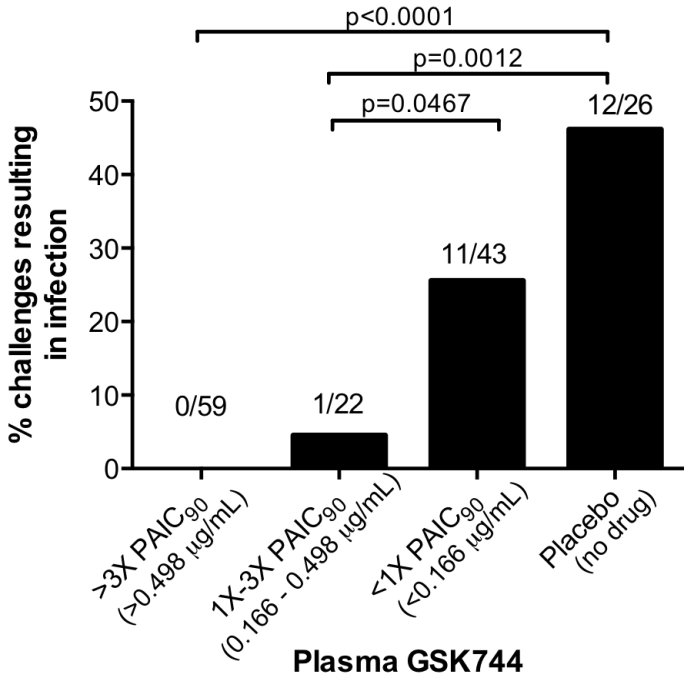
Background: GSK1265744 (GSK744) is an InSTI with properties permitting formulation as a long-acting (LA) injectable nanoparticle suspension (200 mg/mL). We reported at CROI 2013 that GSK744LA is effective as PrEP against repeated low-dose intrarectal (IR) SHIV exposures in 8 male rhesus macaques

(RM). This follow-up study was performed to confirm our initial findings and determine the plasma levels of GSK744 at which protection is maintained and lost during repeated low-dose IR SHIV challenges in male RM to guide further clinical development.

Methodology: Twelve male RM were injected IM with 50 mg/kg GSK744LA one week prior to the first challenge. Four RM remained untreated as placebo controls, with 1 placebo RM beginning challenge every four weeks. All animals were challenged IR each week with SHIV162P3 (50 $TCID_{50}$) until infection was established. Infection status was monitored by real-time PCR amplification of viral *gag* sequences from plasma obtained weekly. We assumed a two-week eclipse phase between infection and virus detection. Plasma GSK744 levels were measured by HPLC-MS/MS.

Results: Of the 12 GSK744LA-treated RM, none had detectable systemic viremia following the first 4 weekly challenges confirming that monthly administration of GSK744LA protects an additional 12 male RM against repeated IR low-dose SHIV challenges. GSK744LA-treated RM became infected after 6 to 17 challenges compared with 1 to 7 challenges for the 12 placebo controls (4 current and 8 historical). One dose of GSK744LA delayed infection by 5 to 10 (median 8) challenges compared with untreated RM. GSK744 plasma levels are reported at the time of infection. The percent of challenges resulting in infection were calculated relative to the plasma GSK744 protein-adjusted IC_{90} ($PAIC_{90}$) value. None of 59 challenges resulted in infection when plasma levels were >3X $PAIC_{90}$, compared with 1 of 22 challenges when plasma levels were between 1X to 3X $PAIC_{90}$ and 11 of 43 challenges when plasma levels were <1X $PAIC_{90}$ (see figure). 12 of 26 challenges resulted in infection in placebo RM.



Conclusions: We have shown that GSK744LA can protect 20/20 male RM against repeated IR SHIV challenges. Furthermore, GSK744 plasma concentrations >3X $PAIC_{90}$ result in 100% protection while the efficacy appears to be 97% at plasma levels ≥1X $PAIC_{90}$. These plasma levels of GSK744 can be readily achieved in man with quarterly 800 mg IM injections. Phase 2 evaluations of GSK744LA as PrEP will initiate in 2014 in anticipation of Phase 3 efficacy trials.

40LB Monthly GSK744 Long-Acting Injections Protect Macaques Against Repeated Vaginal SHIV Exposures

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Background: Pre-exposure prophylaxis (PrEP) with long-acting antiretroviral drugs has the potential to overcome the challenges of adherence associated with daily PrEP. The HIV integrase inhibitor GSK1265744 has been formulated as a long-acting injectable nanosuspension (GSK744 LA) and is an attractive candidate for PrEP. We used a pigtail macaque model to investigate systemic and vaginal GSK744 LA pharmacokinetics (PK) and evaluate efficacy against vaginal SHIV infection. This model assesses PrEP under physiologic conditions because pigtails have menstrual cycles similar to women, do not require the use of depo Provera to ensure vaginal infection, and can be infected with lower and more physiologic virus doses.

Methodology: Drug PK was evaluated in plasma and vaginal secretions from 6 macaques receiving two intramuscular (IM) injections of GSK744 LA (50 mg/kg) administered 4 weeks apart. The prophylactic efficacy of GSK744 LA was investigated in macaques repeatedly challenged with SHIV. Macaques received GSK744 LA (n = 6) or placebo (n = 6) IM every 4 weeks (total of 3 injections), and were concurrently exposed twice a week to low (50 $TCID_{50}$) doses of $SHIV_{162P3}$. Infection was monitored by serology and PCR amplification of SHIV RNA and proviral DNA.

Results: Peak plasma drug concentrations (C_{max} = 3,753 ng/ml; range = 2,488-9,903) were within the range reported in humans receiving 400 mg IM, with levels remaining above the protein adjusted IC_{90} (166 ng/ml) for a median of 49 days (range = 28->63) after the last dose. Peak GSK744 concentrations in vaginal secretions (911 ng/ml; range = 427-1,877) were lower than in plasma. Area under the curve values over 28 days were also lower in vaginal secretions (11,511 ng*day/ml; range = 3,956-14,011) relative to plasma (70,333 ng*day/ml; range = 40,265-169,341). All 6 macaques receiving GSK744 LA remained seronegative and viral RNA and DNA negative during the 22 SHIV challenges and 12 weeks after the last GSK744 LA injection. In contrast, all 6 controls were SHIV RNA positive after a median of 4 (range = 2-20) exposures (p<0.001).

Conclusions: We show that single, monthly injections of GSK744 LA that reproduce the human dose fully protect macaques against repeated vaginal SHIV exposures. The high protection seen despite lower vaginal drug concentrations suggest a contribution of mucosal and systemic GSK744 to the observed protection. These data support advancement of GSK744 LA as a PrEP candidate for women.

41 Safety and Pharmacokinetics/Pharmacodynamics of Dapivirine and Maraviroc Vaginal Rings

Beatrice A. Chen[1], Lori Panther[2], Craig Hoesley[3], Craig Hendrix[4], Ariane van der Straten[5], Marla Husnik[6], Lydia E. Soto-Torres[7], Annalene Nel[8], Sherri Johnson[9], Charlene S. Dezzutti[10]

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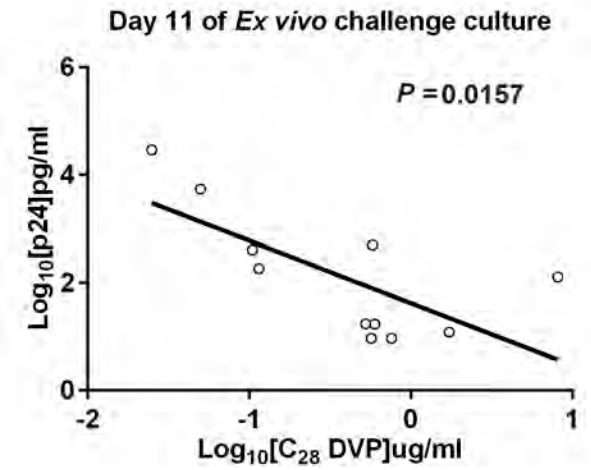
Background: Vaginal rings offer sustained multi-drug delivery for pre-exposure prophylaxis of HIV infection. A dapivirine (DPV) vaginal ring, an NNRTI, is in Phase III trials. Maraviroc (MVC), a CCR5 co-receptor antagonist, is approved for oral HIV treatment but has not been studied intravaginally. This trial evaluated the safety and pharmacokinetic/pharmacodynamics of vaginal rings containing DPV and MVC alone or in combination compared to placebo.

Methodology: We conducted a multi-site, double-blind, randomized, placebo-controlled trial in 48 HIV-negative sexually abstinent women to evaluate vaginal rings containing 25 mg DPV plus 100 mg MVC, DPV only, MVC only or placebo used for 28 days followed by 24 days off product. Safety was assessed by adverse events (AE). Adherence was assessed by self-report and residual drug levels in returned rings. DPV and MVC plasma and vaginal fluid levels were quantified. Cervical biopsies were obtained on day 28 immediately after ring removal to quantify drug and for the HIV ex vivo challenge assay.

Results: Mean age was 29.6 years (range 20-40); 50% were white and 38% were black. Retention was 98% at the final visit. There were 33 grade 1 and one grade 2 related genitourinary AEs from 22 women with no difference between each of the treatment arms and placebo arm. There were 20 grade 2 or higher AEs from 13 women, of which two grade 2 AEs were related to study product. Ninety-four percent were fully adherent by self-report; ring use was confirmed by residual drug levels. Plasma DPV Cmax was not significantly different between DPV and DPV/MVC users (272 vs 294 pg/mL, respectively). MVC plasma concentrations were below limits of quantification (LOQ). Day 28 mean DPV vaginal fluid levels were 14.9 µg/mL and 10.0 µg/mL in DPV and DPV/MVC users, respectively. Day 28 mean DPV tissue levels were 0.6 µg/mL and 1.6 µg/mL in DPV and DPV/MVC users. Day 28 mean MVC vaginal fluid levels were 6.7 µg/mL and 1.1 µg/mL in MVC and DPV/MVC users. Only 4 of 24 MVC and DPV/MVC users had tissue levels above LOQ for MVC.. Fresh cervical tissue from DPV and DPV/MVC users showed a significant inverse linear relationship between HIV replication and tissue DPV drug levels.



Conclusions: Vaginal rings were safe and well tolerated. DPV but not MVC delivered by a vaginal ring for 28 days blocked HIV-1 infection in cervical tissue. There was a linear correlation between DPV levels in tissue and protective effect. These data suggest that delivery of NNRTIs via vaginal rings is a viable approach for HIV prevention.

42LB FAME-02: A Phase I Trial To Assess Safety, PK, and PD of Gel and Film Formulations of Dapivirine

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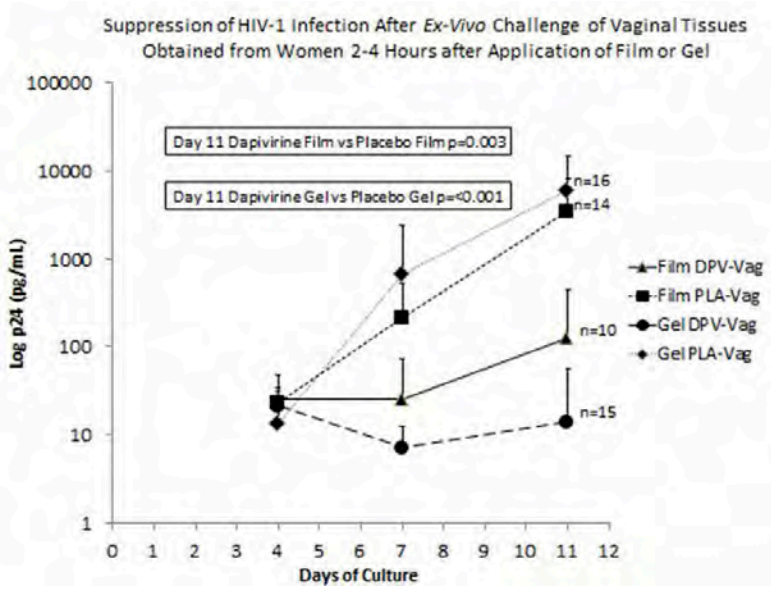
Background: Film formulations of topical microbicides have theoretical advantages over gels and intravaginal rings. Relying on physiologic fluids to dissolve, the product may provide more efficient drug delivery while minimizing disruption of innate immune defenses, product application may ensure privacy while avoiding leakage, and the cost associated with scale up of vaginal films compares favorably to gels. In this first in human trial of a film for delivery of ARVs, we sought to compare the safety, PK, and PD of film and gel formulations of dapivirine versus placebo.

Methodology: 60 healthy HIV negative women were randomized to placebo gel, dapivirine (0.05%) gel, placebo film, or dapivirine (1.25mg) film. Participants were instructed to use product daily for seven days. Adverse event (AE) data were collected via questionnaire and physical exam at two follow-up visits. The proportion of participants experiencing Grade 2 and higher AEs deemed related to study product were compared across treatment arms using Fisher's exact



test. After seven daily doses plasma dapivirine levels were measured. Cervical and vaginal biopsies obtained 2-4 hours after the last dose were analyzed for tissue drug levels or were exposed to HIV-1 in an *ex-vivo* challenge model. Tissue HIV infection was monitored by p24 levels in culture supernatant.

Results: The mean age of the participants was 26.7 years; 53.3% of evaluable participants were white and 36.7% black. There were two Grade 2 related AEs; both were in the placebo film group. Five of 29 women assigned to film were noted to have visible film at or outside of the introitus just prior to biopsies which suggested poor film placement; all were in the active film arm. Women randomized to gel and film products had comparable plasma dapivirine levels (302.47 vs 227.13 pg/ml) after one week. However, tissue levels of dapivirine were 4 times higher in the gel users when compared to film users, possibly due to residual gel product adherence to the tissue surface. Both active products when placed correctly were protective against HIV-1 infection in the *ex-vivo* challenge model (Figure 1).

Conclusions: This proof of concept study demonstrated that the dapivirine film was safe and released dapivirine to plasma and genital tissue at levels comparable to the dapivirine gel and intravaginal ring. While safe and effective when placed correctly, the dapivirine film was difficult to insert for some women, and further development is needed to optimize ease of placement for this dosage form.

43 Single-Agent TDF Versus Combination FTC/TDF PrEP Among Heterosexual Men and Women

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Background: Antiretroviral pre-exposure prophylaxis (PrEP), using daily oral tenofovir (TDF) alone or combination emtricitabine/tenofovir (FTC/TDF), has been demonstrated to be an efficacious HIV-1 prevention intervention in four clinical trials. Whether single-agent TDF PrEP has comparable efficacy to dual-agent FTC/TDF PrEP is unknown.

Methodology: The Partners PrEP Study was a randomized, double-blind, placebo-controlled three-arm trial of daily oral TDF and FTC/TDF PrEP among heterosexual HIV-1 uninfected members of HIV-1 serodiscordant couples from Kenya and Uganda. In July 2011, the trial's placebo arm was discontinued because of clear demonstration of HIV-1 protection from PrEP; compared to placebo, HIV-1 prevention efficacy was 67% for TDF and 75% for FTC/TDF, and TDF and FTC/TDF efficacy were not significantly different ($p=0.23$). After July 2011, to gather additional comparative information about single- versus dual-agent PrEP, the trial's active arms were continued in a blinded fashion and the participants initially randomized to placebo were offered re-randomization to TDF or FTC/TDF PrEP. Data collection was completed in December 2012.

Results: 4747 HIV-1 serodiscordant couples were enrolled and followed; for 62%, the HIV-1 uninfected partner was male. A total of 52 post-randomization HIV-1 infections occurred among individuals assigned to the active PrEP arms: 30 prior to and 22 after July 2011. Of these 52 infections, 31 were among those assigned TDF (incidence 0.7 per 100 person-years) and 21 were among those assigned FTC/TDF (incidence 0.5 per 100 person-years); for comparison, HIV-1 incidence in the placebo arm prior to July 2011 was 2.0 per 100 person-years. HIV-1 prevention efficacy for FTC/TDF compared to TDF alone was not statistically significantly different: HR 0.67, 95% 0.39-1.17, $p=0.16$. Detection of tenofovir in plasma samples, measured in seroconverters and a subset of non-seroconverters, was associated with an 85% relative risk reduction in HIV-1 acquisition for the TDF arm and 93% for the FTC/TDF arm (both $p<0.001$). By consensus sequencing, no cases of HIV-1 antiretroviral resistance related to TDF or FTC were identified in HIV-1 seroconverters after July 2011.

Conclusions: Among heterosexual men and women, once-daily oral TDF and FTC/TDF are safe and provide high and comparable risk reduction against HIV-1 acquisition.

44 Divergent Adherence Estimates With Pharmacokinetic and Behavioral Measures in VOICE (MTN003)

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Background: The level of protection conferred by tenofovir (TFV)-based PrEP correlates with product adherence in some studies. In VOICE, daily oral tenofovir disoproxil fumarate (TDF), oral TDF-emtricitabine (FTC), and 1% vaginal TFV gel were not effective and poor adherence was determined based on plasma TFV detection in a subset of participants in the active product random pharmacokinetic (PK) cohort.We compare behavioral measures of adherence to (PK) assessment of TFV in plasma and vaginal swabs.

Methodology: From 9/2009 to 8/2012, 5029 HIV-negative, sexually active, non-pregnant women were enrolled and followed up to 36 months at 15 sites in South Africa, Uganda and Zimbabwe. Adherence assessments included face-to-face interviews (FTFI; assessed frequency of product use, past 7 days) and clinic product counts (CPC) conducted monthly; audio-computer assisted self-interview (ACASI; frequency of product use, past 7 days) and 6 point rating scale (*very low* to *excellent,* past 4 weeks) conducted quarterly. Plasma concentration < 0.3 ng/mL in oral arms and vaginal swab < 8.5 ng/swab in gel arm correspond with no product use in the past week, and were defined dichotomously as "PK non-adherent". We randomly selected one single quarterly visit for each participant from the random PK cohort (visit range: 3-24 months). Logistic regression models were fit to calculate the combined predictive ability of the behavioral measures as summarized by the area under the ROC curve (AUC).

Results: Of 472 participants in the random subset, 314 were in the active oral arms and 158 in the TFV gel arm. Mean age was 25.4 years, 79% were unmarried, and 79% had a main male sex partner; 79%, 14% and 7% were from South Africa, Zimbabwe and Uganda, respectively. PK non-adherence was 69% in the oral arms and 64% in the gel arm. For both oral and gel arms, modal adherence was "Good" per ACASI self-rating, and mean adherence

was ≥94% (FTFI-dose frequency), ≥93% (CPC), ≥89% (ACASI-dose frequency). Reporting ≤75% use in the past month by CPC, or no doses in the past week had good specificity (≥89%) at identifying PK non-adherence; however, <10% of the sample reported such use with any behavioral measure. None of the regression models had an AUC >0.65 for any single or combined behavioral measures, indicating slightly better prediction than a coin toss (0.5).

Conclusions: In this random sample of VOICE participants, PK thresholds based on route of administration indicated similarly low adherence for the oral and vaginal gel arms. None of the behavioral measures correctly predicted PK non-adherence. Accurate real-time, low-cost objective and/or biological measures that minimize opportunities for manipulation or respondent-bias are urgently needed to facilitate real-time adherence monitoring in PrEP trials.

153LB HIV Transmission Risk Through Condomless Sex If HIV+ Partner On Suppressive ART: PARTNER Study

Alison Rodger[1], Tina Bruun[2], Valentina Cambiano[1], Pietro Vernazza[3], Vicente Estrada[4], Jan Van Lunzen[5], Simon Collins[6], Anna Maria Geretti[7], Andrew Phillips[1], Jens Lundgren[8], for the PARTNER Study Group

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Background: The absolute risk of sexual HIV transmission on stable ART (HIV RNA viral load (VL) <200 c/mL) from condomless sex is unknown. Current limited data are largely focusing on vaginal sex

Methodology: The international, observational multi-centre PARTNER study prospectively follows serodifferent couples (heterosexual (HT) and MSM) who had condomless penetrative anal or vaginal sex in the month prior to study entry, and where the HIV+ve partner is on ART. Every 6 months, each partner completes a sexual behaviour questionnaire and the negative partner tests for HIV. Eligibility of follow-up time in this transmission rate analysis required: continued condomless sex; not using PEP or PrEP; and latest VL <200 c/mL. For new diagnoses, phylogenetic analysis compared HIV-1 pol and env sequences by couple, after samples were anonymised. This planned analysis reports the rate of occurrence of linked transmissions.

Results: By 1st November 2013, 1110 couples were enrolled. Of 1151 couple-years of follow-up (CYFU), 894 were eligible (586 in HT and 308 in MSM). At baseline, the median duration on ART was 4.9 years (IQR: 1.9-11.4) and couples reported having condomless sex for a median 2 years (IQR: 0.5-6.3). Condomless sex with a different partner outside the partnership during follow-up was reported by 27% MSM and 2% HT HIV-negative partners. During follow-up, couples had condomless sex a median of 45 times/ year (IQR: 16-90). Although some negative partners became HIV positive during FU, no phylogenetically linked transmissions occurred, giving a rate of within-couple HIV transmission during eligible couple-years of zero (95% CI: 0-0.40/100 CYFU)(Table). The upper limit of the 95% CI for the rate of transmission was 0.96/100 CYFU for condomless anal sex (HT and MSM) and 1.97/100 CYFU for condomless receptive anal sex with or without ejaculation (MSM).

Conclusions: The overall risk of HIV transmission (in the context of previous sex without transmission) through condomless anal or vaginal sex from HIV positive people on ART with plasma VL < 200 copies/mL is extremely low, but uncertainty over the risk remains, particularly over receptive anal sex. Additional follow-up in MSM is essential to provide more precise estimates for transmission risk given the current assumptions of safety in some communities.

Risk Behaviour Reported by the HIV Negative Partner and Rates of Transmission							
HIV status and sexual orientation of couples	Risk behaviour reported by HIV -ve partner	Number of events (linked HIV transmissions)	Couple-years of follow up (CYFU)	Estimated number of sex acts	Transmission risk per condomless sexual contact (95% CI)	Rate of within couple HIV transmission (per 100 CYFU) (95% CI)	10 year risk of within couple HIV transmission (95% CI)
Overall	Condomless sex	0	894	44,439	0 (0 - 0.00008)	0 (0-0.40)	0 (0 - 3.9%)
	Condomless sex VL<50	0	836	41,479	0 (0 - 0.00009)	0 (0-0.43)	0 (0 - 4.2%)
	Condomless anal sex	0	374	21,032	0 (0 - 0.00017)	0 (0-0.96)	0 (0 - 9.2%)
HT m+/f- partners	Condomless sex	0	288	13,728	0 (0 - 0.00028)	0 (0-1.25)	0 (0 - 11.7%)
	Condomless vaginal sex with ejaculation	0	191	8,915	0 (0 - 0.00043)	0 (0-1.88)	0 (0 - 17.1%)
	Condomless vaginal sex without ejaculation	0	174	6,377	0 (0 - 0.00060)	0 (0-2.07)	0 (0 - 18.7%)
HT m-/f+ partners	Condomless sex	0	298	14,295	0 (0 - 0.00027)	0 (0-1.21)	0 (0 - 11.4%)
	Condomless vaginal sex	0	272	14,149	0 (0 - 0.00027)	0 (0-1.32)	0 (0 - 12.4%)

MSM	Condomless anal sex	0	308	16,416	0 (0 - 0.00023)	0 (0-1.17)	0 (0 - 11.0%)
	Condomless receptive anal sex (with or without ejaculation)	0	182	7,738	0 (0 - 0.00050)	0 (0-1.97)	0 (0- 17.9%)
	Condomless insertive anal sex	0	262	11,749	0 (0 - 0.00033)	0 (0-1.37)	0 (0 - 12.8%)

Session O-4 Oral Abstracts

10:00 AM – 12:00 PM Room 312

Host Factors and HIV/SIV Replication

45 Inhibition of Cul4A Neddylation Causes a Reversible Block To SAMHD1-Mediated Restriction of HIV-1

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NYU School of Medicine, New York, NY, United States

Background: The deoxynucleoside triphosphohydrolase SAMHD1 restricts retroviral replication in myeloid cells. It is thought to work by depleting the pool of intracellular deoxynucleotide triphosphates but has also been reported to have exonuclease activity that could allow it to degrade the viral genomic RNA or viral reverse transcribed DNA. HIV-2 and SIVmac, but not HIV-1, encode Vpx, a virion-packaged accessory protein that counteracts SAMHD1 by inducing its degradation in the nucleus of a newly infected cell. To induce the degradation of SAMHD1, Vpx co-opts the cullin4a-based E3 ubiquitin ligase, CRL4. E3 ubiquitin ligase complexes are regulated by neddylation, the covalent attachment of the small ubiquitin-like protein, Nedd8, to the cullin subunit. The small molecule MLN4924 prevents cullin neddylation. In this study MLN4924 was used to study the mechanism by which SAMHD1 restricts HIV-1.

Methodology: Monocyte derived dendritic cells (MDDC) were incubated with MLN4924 prior to infection with the Vpx-containing HIV-1.GFP reporter virus. The degradation of SAMHD1 was then determined by immunoblot analysis and infectivity was analyzed by flow cytometry. The effect of the neddylation inhibitor was also tested on a cell line that expressed a GFP-SAMHD1 fusion protein that contained only the Vpx-interacting domain of SAMHD1. The cell line allowed measurement of the kinetics and cellular requirements for Vpx-mediated degradation of SAMHD1.

Results: MLN4924 inhibited the neddylation of CRL4, blocking the Vpx-induced degradation of SAMHD1. Incubation of cells expressing the GFP-SAMHD1 fusion with Vpx-containing HIV-1 resulted in a rapid reduction in GFP fluorescence and the reduction was blocked by MLN4924. The neddylation inhibitor maintained SAMHD1-mediated restriction in cells that expressed SAMHD1 when infected with Vpx-containing HIV-1. In cells that did not express SAMHD1 the drug had no effect on infectivity. Removal of the drug several hours post-infection released the block. Similarly, Vpx-containing virus-like particles and deoxynucleosides added to the cells more than 24 h post-infection released the SAMHD1-mediated block.

Conclusions: The block to SAMHD1-mediated restriction of HIV-1 is reversible for several hours, arguing against an exonuclease model and supporting dNTP pool depletion as the primary mechanism of restriction. Virus replication requires the function of various cullin-based E3 ubiquitin ligases. Thus, this class of small molecules may have antiviral activity and at least one is already approved for use in humans.

46 MX2, an Interferon-Induced Inhibitor of HIV-1 Infection

Melissa Kane[1], Shalini S. Yadav[1,2], Julia Bitzegeio[1], Sebla B. Kutluay[1], Trinity Zang[1,2], Sam J. Wilson[1,2], Daniel Blanco-Melo[1], Masahiro Yamashita[3], Theodora Hatziioannou[3], Paul D. Bieniasz[1,2]

[1]The Rockefeller University, New York, NY, United States, [2]Howard Hughes Medical Institute, New York, NY, United States, [3]Aaron Diamond AIDS Research Center, New York, NY, United States

Background: HIV-1 replication can be inhibited by type I interferon (IFN), and the expression of a number of gene products with anti-HIV-1 activity is induced by type I IFN. However, none of the known antiretroviral proteins can account for the ability of type I IFN to inhibit early, preintegration phases of the HIV-1 replication cycle in human cells.

Methodology: Screens of interferon stimulated genes and comparison of gene expression profiles in cell lines that differ in their ability to restrict HIV-1 infection upon exposure to IFN-α revealed MX2 as a potential anti-HIV-1 protein. We examined the the ability of wild type MX2, and mutant forms of lacking GTPase activity, the nuclear localization signal, or leucine rich effector domain to inhibit HIV-1 infection in stably transduced cell lines.

Results: Ectopic expression of MX2 inhibited infection by HIV-1 and a variety of other primate lentiviruses, while knockdown of MX2 expression reduced the anti-viral effect of type I IFN. We found that the The GTPase activity of MX2 was dispensable for inhibition of infection. However, both the N-terminal nuclear localization and C-terminal leucine-rich effector domains were required. HIV-1 reverse transcription proceeded normally in MX2-expressing cells, but 2-LTR circular forms of HIV-1 DNA were less abundant, suggesting that MX2 inhibits HIV-1 nuclear import, or destabilizes nuclear HIV-1 DNA. Consistent with this notion, mutations in the HIV-1 capsid protein that are known, or suspected, to alter the nuclear import pathways used by HIV-1 confered resistance to MX2, whereas preventing cell division increased MX2 potency. Finally, the anti-viral activity of MX2 did not appear to be species-specific, as MX2 proteins from a variety of Old and New World monkey species (rhesus macaque, African green monkey, Owl monkey, and squirrel monkey) were able to inhibit HIV-1 infection.

Conclusions: Our findings demonstrate that MX2 is an effector in the anti-HIV-1 activity of type I IFN, but is not solely responsible for the inhibitory action of IFN-α during the early steps of the HIV-1 replication cycle. The anti-viral activity of MX2 may involve the inhibition of HIV-1 nuclear import, and appears to be conserved among primate species

47 BCA2/Rabring7 Targets HIV-1 Gag for Lysosomal Degradation in a Tetherin-Independent Manner

Ruth Serra-Moreno
Harvard Medical School, Southborough, MA, United States

Background: BCA2 (Breast Cancer-Associated gene 2, Rabring7) is an E3 ubiquitin ligase that was identified as a co-factor in the restriction imposed by tetherin on HIV-1, lacking antiviral activity in the absence of tetherin. Contrary to this model, we found that BCA2 also possesses tetherin-independent antiviral activity, which leads to a reduction in the cellular levels of Gag, and therefore, in the amount of virus particles released from cells.

Methodology: Virus release assays (p24 ELISA) were performed from tetherin-deficient cells transiently transfected with HIV proviral DNA and constructs coding for tetherin, BCA2, or BCA2 mutants. To explore if BCA2 promotes the degradation of Gag, similar assays were performed in the presence of proteasomal (ALLN, clasto-lactacystin-β-lactone) and lysosomal inhibitors (chloroquine, pepstatin, leupeptin, E64). To investigate if BCA2 promotes Gag ubiquitination, cells were engineered to express Gag and BCA2. The levels of Ub-Gag were determined by immunoprecipitation followed by western blotting, using an Ubiquitin-specific antibody. Next, Gag was tested for an interaction with BCA2 by co-immunoprecipitation. The role of endogenous BCA2 in virus release and replication was investigated by shRNA knockdowns. Finally, the effects of BCA2 on the subcellular distribution of Gag were evaluated by confocal microscopy.

Results: Expression of BCA2 in tetherin-deficient cells caused a ~3-fold decrease in virus release. Western blot analyses indicated that this corresponds to a defect in Gag expression, with no effects on the levels of other viral proteins. Our binding and ubiquitination assays showed that BCA2 interacts with Gag through the Matrix region, and that BCA2 promotes Gag ubiquitination. The addition of lysosomal inhibitors to BCA2-expressing cells significantly restored Gag levels and virus release. The targeted depletion of BCA2 resulted in a substantial increase in virus release (5-fold more) and virus replication (10-fold more). Finally, cellular imaging assays revealed that BCA2 induces drastic changes in the subcellular distribution of Gag, which is primarily present in endo-lysosomal compartments.

Conclusions: (1) BCA2 has tetherin-independent antiviral activity; (2) BCA2 promotes the ubiquitination and lysosomal degradation of HIV-1 Gag; and (3) the targeted depletion of BCA2 in tetherin-deficient cells increases virus release and replication, indicating that endogenous BCA2 possesses antiviral activity. These results indicate that BCA2 is an important antiviral factor that promotes the degradation of HIV-1 Gag, thereby, impairing virus assembly.

48 Crystal Structure of APOBEC3F Elucidates HIV-1 Vif Interaction and Dynamic Oligomerization

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Background: Human APOBEC3F is an anti-retroviral ssDNA cytosine deaminase, susceptible to proteasomal degradation mediated by the HIV-1 protein Vif. Elucidating regulation of APOBEC3F and susceptibility to Vif might lead to novel approaches in antiretroviral therapy.

Methodology: We determined the crystal structure of the HIV-1 Vif interacting catalytically active, C-terminal domain of human APOBEC3F and performed dynamic light scattering experiments to investigate the solution state of different APOBEC3F mutants.

Results: The catalytic domain of APOBEC3F shares structural motifs with APOBEC3C, APOBEC2 and the C-terminal domain of APOBEC3G. Residues previously identified as determinants of susceptibility to Vif-mediated degradation fit within a charged contiguous surface on APOBEC3F. Sequence motifs critical for Vif susceptibility and virion encapsidation are shown to be conserved across APOBEC3 family members and between APOBEC3F and Vif. Physiological APOBEC3F activity is dependent on a conversion from high molecular mass complexes of megadalton in size to a low molecular mass form of less than 100 kD. The single domain protein APOBEC3A does not undergo a similar conversion. We show the C-terminal domain of APOBEC3F being capable of forming complexes of high molecular mass in solution which are not observable for APOBEC3A. Interface residues identified from the crystal structure of APOBEC3F are the determinants of APOBEC3F complex formation.

Conclusions: The identification of potential oligomerization interfaces might help elucidate the anti-viral regulatory role of high molecular mass complexes of active APOBEC3 proteins and facilitate approaches utilizing modulation of APOBEC3 activity in novel antiretroviral strategies.

49LB Crystal Structure of a TRIM Coiled-Coil: Implications for HIV-1 Capsid Recognition by TRIM5α

Jacint G. Sanchez[1], Katarzyna Okreglicka[1], Viswanathan Chandrasekaran[2], Jordan M. Welker[1], Wesley I. Sundquist[2], **Owen Pornillos[1]**
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Background: TRIM5α is a cytosolic pattern-recognition receptor that intercepts incoming capsids of retroviruses, including HIV-1. Capsid recognition results in species-specific restriction of viral replication and induction of an innate immune response. The prevailing model is that TRIM5α recognizes the HIV capsid through synergy of at least 3 biochemical activities: direct binding of capsid subunits by a B30.2/SPRY domain, TRIM5α dimerization, and higher-order assembly of the tripartite motif into a hexagonal lattice. A key point is that multiple B30.2 domains in the TRIM5α assembly are positioned to match the spacing of their repeating binding epitopes on the capsid surface, thereby vastly amplifying the avidity of capsid recognition. However, the molecular details of the above biochemical activities remain to be uncovered. The tripartite motif is a series of domains - RING, B-box, and coiled-coil - arranged in that order from the N-terminus. Here, we describe the structure of the coiled-coil, which mediates TRIM dimerization and is required for higher-

order TRIM5α assembly. Our studies reveal how TRIM5α dimerizes, how it positions the B30.2/SPRY domains to bind capsid subunits, and how TRIM5α dimers organize into hexagonal arrays to recognize the capsid lattice and restrict viral replication.

Methodology: Working under the framework that a comprehensive mechanistic model must address how the various TRIM domains are structurally coupled, we initially focused on the coiled-coil, because it specifies dimerization and defines the spatial relationships between the other domains. We used human TRIM25 as a model system since it lacks TRIM5's propensity for higher-order assembly and is therefore more tractable biochemically. We determined the crystal structure of the TRIM25 coiled-coil at 2.6 Å resolution. Based on this structure, we built and experimentally validated a homology model for the TRIM5α coiled-coil.

Results: Our analyses revealed that: 1) the TRIM coiled-coil is an elongated dimer of hairpin-shaped subunits; 2) the coiled-coil dimers form the edges of the TRIM5α hexagon, positioning two C-terminal B30.2 domains at the center of each edge and the N-terminal RING and B-box domains at the vertices; and 3) the "L2" linker between the coiled-coil and B30.2 is integrated with the tripartite motif and participates in dimer formation. We propose that the L2 linker of TRIM5α structurally couples the tripartite motif to its B30.2 domain, thereby orienting the two capsid-binding domains of one TRIM5α dimer on the same side and positioning them with a defined spacing relative to each other.

Conclusions: Our studies support a model wherein TRIM5 proteins recognize retroviral capsids by acting as "molecular rulers" that measure the spacing of the assembled capsid subunits.

50 Global Identification of the RNA Targets of HIV-1 Gag During Particle Genesis

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Background: HIV-1 Gag protein selectively packages two copies of the viral genome, an event thought to be primarily mediated by interactions between the packaging signal (Ψ) on the viral genome and the nucleocapsid domain of Gag. However, the Ψ sequence is defined based only on genetic studies and limited in vitro binding data. To date, no assay has been able to demonstrate a direct and specific interaction between Ψ and Gag protein in a relevant context, i.e. in live cells and in virions. Importantly, deletion of Ψ does not completely abolish genome encapsidation, suggesting that packaging may be more complex than Ψ:Gag interaction, and other regions on the viral genome may contribute. Finally, Gag undergoes several changes in localization, multimerization state and is proteolytically processed during particle genesis, but it is completely unknown how these changes affect RNA-binding properties of Gag. Therefore, we set out to determine globally and at near-nucleotide resolution the RNA targets of Gag during various stages of virion genesis, in cells and in virus particles.

Methodology: To identify the RNA targets of Gag, we adapted a CLIP-seq (crosslinking-immunoprecipitation-sequencing) methodology, which combines immunoprecipitation of covalently crosslinked protein-RNA complexes with high-throughput sequencing. This method globally identifies the RNA molecules associated with an RNA-binding protein of interest in biological settings and provides near-nucleotide-resolution information about the protein-RNA interaction sites.

Results: In addition to determining precisely where within Ψ Gag is bound, we identified several novel sites on the viral genome that are specifically bound by Gag in the cytosol of cells. Mutation of these sites delayed virus replication and we are currently investigating whether this is due to defects in genome packaging. Experiments performed on fractionated cells and in virions indicated that there are major changes in RNA binding specificity during particle morphogenesis: in contrast to cytosolic Gag, Gag associated with the plasma membrane and in virions binds to numerous other regions on, but does not uniformly coat, the viral genomic RNA. We have also globally identified several cellular RNA molecules, such as 7SL RNA, that are specifically bound by Gag in the cytosol and encapsidated into virus particles.

Conclusions: Our studies indicate that Gag selects viral genome for packaging by binding to a few distinct regions on the viral genome and that association with the plasma membrane and particle formation induces significant changes in the RNA-binding properties of Gag. These studies provide the first dynamic, quantitative and high-resolution picture of viral/cellular RNA interactions with Gag in relevant biological contexts.

51 Gorillas Transmitted SIV To Humans: Identification of HIV-1 Group P and O Ancestors

Mirela D'arc[1], Ahidjo Ayouba[2], Amandine Esteban[2], Avelin Aghokeng[2,3], Sabrina Locatelli[2], Lucie Etienne[2], Beatrice Hahn[4], Eric Delaporte[2], Eitel Mpoudi Ngole[5], Martine Peeters[2]

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Background: Western lowland gorillas (G. g. gorilla) are infected with a simian immunodeficiency virus, SIVgor, that is related to HIV-1 groups O and P. Partial SIVgor sequences suggested that gorillas from southwest Cameroon are infected with the ancestor of HIV-1 P, but the origin of HIV-1 O remained unclear. In order to confirm whether gorillas are the reservoir of HIV-1 P and to elucidate the origin of HIV-1 O, we studied more in detail SIVgor in wild gorillas from Cameroon and characterized full-length genomes of new SIVgor strains.

Methodology: Between 09/2009 and 06/2013, we collected 1559 fecal samples from wild gorilla populations at 14 different sites in southern Cameroon. All samples were preserved in RNAlater and then tested for presence of HIV cross-reactive antibodies. We extracted nucleic acids from reactive samples and performed RT-PCR using SIVcpz/SIVgor/HIV-1 consensus and specific primers. We sequenced the full-length genome of two new SIVgor strains. The species and enumeration of individuals were obtained by mitochondrial DNA and microsatellite analyses. We used PhyML for phylogenetic analyses.

Results: SIVgor antibodies were identified in 69/1559 samples from 4/14 sites. Partial viral sequence analyses showed a high genetic diversity, with strains closely related to HIV-1 O and P. The full-length genome sequence of the new SIVgorBP-ID01 strain (9029 bp), from southwest Cameroon, was

most closely related to HIV-1 P across the entire genome. At least two gorilla populations were infected with this SIVgor variant at high rates (54%). Analyses of SIVgorBQ-ID01 (full-length, 9236 bp), from a gorilla from southcentral Cameroon, revealed a recombinant SIVgor strain with 6914 bp of the genome most closely related to HIV-1 O and fragments in pol (470 bp) and env (1850 bp) that were most closely related to other SIVgor strains. To calculate the genetic distances, a modified alignment was completed, and breakpoint information was used to extract the non-group O related regions of the SIVgorBQ-ID01 from the genome alignment. Genetic distances between SIVgorBQ-ID01 / HIV-1 O (0.167) and SIVgorBP-ID01 / HIV-1 P (0.124) were smaller than between SIVcpz and their HIV-1 counterparts, groups M (0.260) or N (0.158).

Conclusions: Gorilla populations from southwest Cameroon are the direct source of HIV-1 P and we show for the first time that SIV sequences closely related to HIV-1 O circulate also in wild gorilla populations. Further studies are needed to identify more in detail the sources of HIV-1 O. Although SIV infection is less widespread in gorillas than in chimpanzees, SIVgor was most likely transmitted to humans on two occasions. These new findings show that we are closer to resolve the origins of all HIV-1 groups and that two ape species are involved in the origin of HIV-1 in humans.

52LB A Gorilla Reservoir for Human T-lymphotropic Virus Type 4 (HTLV-4)

Matthew LeBreton[1,2], William M. Switzer[3], Cyrille F. Djoko[2], Amethyst Gillis[1], Hongwei Jia[3], **Walid Heneine[3]**, Anupama Shankar[3], HaoQiang Zheng[3], Bradley S. Schneider[1], Nathan D. Wolfe[1,4]

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Background: While the primate origins of human retroviruses have been identified by detailed epidemiologic and phylogenetic analyses of isolates from both humans and nonhuman primates (NHPs), of the seven known species of human retroviruses, one, HTLV-4, lacks a known animal reservoir. HTLV-4 was discovered in 2005 in a 48-yr-old male hunter from rural Cameroon who reported hunting monkeys, chimpanzees, gorillas, and other animals and currently represents the only known primate (human or simian) virus in this lineage.

Methodology: 1,107 individual captive and wild NHPs from Cameroon consisting of 21 species were screened for evidence of simian T-cell lymphotropic virus type 4 (STLV-4) infection, the simian origin of HTLV-4, using a real-time PCR assay specific for the detection of HTLV-4-like *pol* sequences. *pol, env, tax* and full genome sequences were obtained by nested PCR from positive samples. Phylogenetic analyses to demonstrate the genetic relatedness of STLV-4 and HTLV-4 and to estimate the possible date of STLV-4 entry into humans using detailed Bayesian phylogenetic analyses were performed.

Results: Of the 1,107 individuals of 21 species tested, samples from only three wild and three captive gorillas were positive. Partial PTLV-4 (primate-T-cell lymphotropic virus type 4) *pol, env* and *tax* sequences were detected for the six gorilla samples and all showed at least 99% nucleotide identity to HTLV-4(1863LE) and to each other. These results were confirmed by phylogenetic analysis of *tax* and *pol* sequences which showed a clustering of all STLV-4 sequences with those from HTLV-4. One gorilla was dually infected with PTLV-1. TMRCA estimates for the PTLV-4 ancestor were 3,300 - 8,400 years suggesting a relatively recent introduction of STLV-4 into humans.

Conclusions: These findings indicate that STLV-4 is endemic to gorillas, and that HTLV-4 recently emerged from a gorilla reservoir, likely through the hunting and butchering of wild gorillas. Our findings shed further light on the importance of gorillas as keystone reservoirs for the evolution and emergence of human infectious diseases and provide a clear course for preventing HTLV-4 emergence through management of contact with gorillas, the development of improved assays for HTLV-4/STLV-4 detection, and the monitoring of STLV-4 among gorillas and for HTLV-4 zoonosis among individuals exposed to gorilla populations.

Session S1 Symposium

4:00 PM – 6:00 PM **Ballroom B/C**

Toward a Cure: A Challenging Game of Hide and Seek

53 Impact of Early ART On HIV Eradication in Children

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Background: Combination antiretroviral therapy (cART) initiated within three months of birth is not only effective in controlling HIV-1 replication and preserving immune function, but also markedly reduces HIV-1 related mortality. Early diagnosis of HIV-1 infected infants and initiation of cART is thus recommended globally. The development of highly sensitive assays has facilitated the characterization of HIV-1 persistence in early-treated infants. Durable suppression of HIV-1 replication is associated with lack of detectable plasma viremia (LOD 2 copies/ml), limited T cell activation, and absent HIV-1 specific immune responses. Under these conditions, proviral and replication-competent reservoirs decline steeply over the first year of therapy; continued reductions result in extremely low levels of proviral DNA and lack of recoverable replication-competent HIV-1 after a decade or more of suppressive therapy. The decay in PBMC HIV-1 proviral DNA and replication-competent HIV-1, in the absence of detectable HIV-specific immune responses, suggest that early cART limits seeding of long-lived cellular reservoirs. This may be particularly true in infants, where primary HIV-1 infection occurs in the context of a developing immune system. Additional support for this hypothesis is provided by a previously reported case of a very early-treated HIV-1 infected child who controlled HIV-1 viremia off therapy after receiving cART between 30 hours and 18 months of age, as well as preliminary data from studies of infected CD4+ T cell subsets.

Conclusions: Early and very early cART restrict the numbers of long-lived CD4+ T cells that harbor HIV-1 DNA and replication-competent virus, which serve as the barrier to cure. Continued refinement of assays to measure and characterize viral reservoirs in early-treated children should further improve our understanding of HIV persistence, define markers predictive of successful control of HIV-1 replication off cART, and lead to the conduct of additional trials aimed at sparing children a lifetime of therapy.

54 T Memory Stem Cells: The Stem Cell Reservoir for HIV?

Mathias Lichterfeld
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Background: Current antiretroviral combination therapy is extremely effective in suppressing HIV-1 viremia, but replication-competent HIV-1 can persist for extremely long-periods of time despite effective treatment with HAART. Defining the cell types that serve as a reservoir for long-term persistence of HIV-1 is critical for designing interventions that may at one point lead to HIV-1 eradication and cure. Stem cells represent the most long-lasting human cells and are maintained by specific molecular programs that induce self-renewal, homeostatic proliferation and resistance against apoptotic cell death. Tissue-specific stem cells, in particular hematopoietic stem cells, have been proposed as long-term reservoirs for HIV-1, but their role for HIV-1 persistence remains controversial. A number of recent observations indicate that molecular stem cell programs are not exclusively active in classical organ-specific stem cells, but also govern developmental programs of cellular immune memory. In fact, recent data suggest that the process of memory T cell development originates from an exquisitely rare population of T cells with stem cell-like properties. These cells, termed T memory stem cells, likely represent the earliest and most immature developmental stage of memory T cells and have recently been described in humans, mice and non-human primates. Functionally, T memory stem cells exceed the proliferative capacity of all known alternative memory T cell subsets, and can differentiate into large numbers of mature effector T cells, while maintaining their own pool size through homeostatic self-renewal. Due to these characteristics, CD4 T memory stem cells may represent a preferred cellular niche for HIV-1 persistence during suppressive antiretroviral therapy.

Conclusions: Our data suggest that CD4 T memory stem cells are susceptible to HIV-1, and harbor high levels of HIV-1 DNA in HIV-1 infected patients treated with suppressive HAART. In addition, we show that HIV-1 DNA levels in these cells remain stable for many of antiretroviral therapy, and that the relative contribution of these cells to the total viral reservoir increases over time. As such, HIV-1 infected CD4 T memory stem cells may represent a stem-cell like reservoir for HIV-1 that has a similar function for maintaining HIV-1 persistence as cancer stem cells have for perpetuating certain oncologic diseases. The increasing understanding of how stem cell-like properties of cellular immune memory support HIV-1 persistence despite HAART may be translatable into improved clinical strategies for inducing HIV-1 eradication.

55 Inflammation as an Obstacle for Remission: Lessons Learned From Non-Human Primate Models

Michaela Müller-Trutwin
Institut Pasteur, Paris, France

Background: Chronic immune activation (IA) during HIV-1 infection persists even in patients with controlled viremia. This residual inflammation might fuel viral replication by creating new target cells and thus could represent an additional obstacle for cure. Early treatment likely has a favourable impact on the reduction of viral reservoirs, and eventually on the inflammatory set point. Non-human primate models allow analyzing the early events after viral infection, exploring the nature of the viral reservoirs in tissues and searching the factors, which initiate chronic immune activation. Several non-human primate models for virological or inflammatory control exist. We have shown previously that natural hosts of SIV (African green monkeys, AGM) are capable to efficiently resolve inflammation by the end of acute SIVagm infection. Based on this observation in AGMs, we had analyzed if the early level of inflammation during HIV-1 infection would predict the disease progression rate. We reported elevated plasma CXCL10/IP-10 levels during primary HIV-1 infection being more robust predictors of rapid progression toward AIDS than viral RNA and CD4 counts.

Conclusions: Here, we show that during acute HIV-1 infection, plasma IP-10 level was a better predictor of rapid disease progression than viral DNA. Moreover, we evaluated whether the plasma levels of IP-10 already before SIV infection and before HIV-1 infection (Amsterdam Cohort Studies) have an impact on the outcome of infection. We quantified the expression of an endogenous antagonist of IP-10 and observed that it's frequency is decreased during primary HIV-1 infection in those patients who rapidly loose their CD4+ T cells (ANRS PRIMO Cohort No6). Finally, we investigated the source of IP-10 in Humans and in non-human primates (rhesus macaques and African green monkeys), probing blood and relevant tissues, notably the gut (in the simian models). The IP-10 expression in intestinal CD4+ cells was associated with IP-10 plasma levels, suggesting that plasma levels can reflect the levels of IP-10 production in the gut and/or that these gut cells represent the major source of systemic IP-10. These studies are in favor of IP-10 as a robust early biomarker for inflammation and of efforts combining viral suppressive therapies with anti-inflammatory strategies.

56 Humanized Mouse Models for Studies On HIV Latency, Reservoirs, and Eradication Strategies

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Background: Humanized mice represent a relatively recent tool in the growing armamentarium of animal models for the in vivo study of HIV and other human hematotropic viruses. These models can be created by transplanting human hematopoietic cells into immunodeficient mice. However, the choice of mouse strain used can have dramatic effects on the reconstitution of key immune organs like the gut. Another important, issue that affects reconstitution and outcomes is the co-implantation of human thymus, used in the bone marrow/liver/thymus (or BLT) model, which can result in bona fide education of human T cells in the context of HLA. Highly relevant to in vivo studies of HIV persistency has been the development and implementation of adequate drug regimens that can suppress peripheral blood viremia. This has been achieved in mouse models using the same antiretrovirals used in humans. Also critical to these efforts, has been the establishment of sensitive and reproducible assays for latency in human T cells obtained from these mice. This has been recently demonstrated in mouse models using the same methodology used to quantitate the number of latently infected cells present in the peripheral blood of humans. Based on this information, BLT humanized mice have more recently been used to establish the systemic distribution of latently infected cells in vivo and to evaluate novel approaches to destroy residual HIV+ cells in tissues. Specifically, we used BLT humanized mice to evaluate the efficacy of envelope targeted immunotoxins to kill HIV infected cells in the tissues of ART suppressed mice.

Conclusions: Our results demonstrate that this approach can be highly effective at killing residual HIV infected cells in vivo. In summary, humanized BLT mice serve as a flexible and accessible platform for the in vivo evaluation of novel approaches for the study of HIV latency, reservoirs and eradication strategies.

Session S2 Symposium
4:00 PM – 6:00 PM Ballroom A
HCV and Beyond

57 HEV: State of the Art

Kenneth E. Sherman
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Background: The hepatitis E virus (HEV) is a small, fecal-orally transmitted RNA virus with a worldwide distribution. There are multiple genotypes which are associated with both host and geographic specificity. In resource-limited regions of the world, large epidemics of acute hepatitis associated with HEV are common during periods of flooding, or with poor sanitation in refugee camps and during military conflict. The endemic nature of the infection in Western countries has not been widely recognized. It seems to be highly associated with exposure to swine and swine products infected with HEV genotype 3. Misclassification of acute hepatitis as drug injury, which was actually attributable to acute HEV infection has been described. Testing for HEV remains problematic. Recent data suggests that HEV is highly prevalent in those with HCV, though the transmission epidemiology of this finding is uncertain. Furthermore, in immunosuppressed hosts, including those with HIV infection, as well as transplant recipients the virus is capable of establishing a chronic infection which can be associated with progressive hepatic fibrosis. HEV viral clearance with ribavirin, interferon, or withdrawal of immunosuppression has been described.

Conclusions: HEV is increasingly recognized as a cause of both acute and chronic liver injury in the United States and other Western countries. Chronic infection can lead to progressive liver injury and cirrhosis in immunosuppressed hosts.

58 HBV Eradication: Similarities To and Differences From HIV

Shyam Kottilil
National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, United States

Background: Chronic hepatitis B virus (HBV) infection is a major public health concern affecting over 500 million people worldwide. HBV is a partially double stranded DNA virus that preferentially infects hepatocytes and causes acute hepatitis. While this acute hepatitis resolves in most patients, a subset of patients progress to chronic hepatitis with development of liver fibrosis. HBV shares several features with HIV that includes similar routes of transmission, development of chronic disease, and use of a reverse transcriptase enzyme to integrate in to the host genome. The latter feature is associated with the difficulties involved in eradicating HBV in chronically infected patients. Current treatment options for HBV include pegylated interferon alfa and nucleotide based therapy. Suppression of HBV replication is achieved in most treated patients, however, similar to HIV infection, discontinuation of therapy is associated with relapse of HBV viremia. Unlike HIV infection, both innate and adaptive immune responses have been associated with resolution of acute HBV infection and development of protective immunity in most adult patients exposed to HBV resulting in resolution of acute HBV infection. However, strategies to replicate this protective immunity in human subjects, which would enable them to stop antiviral therapy, have not yet been successful. Major reasons for our inability to cure HBV in chronically infected subjects include both viral and host factors. Viral factors such as a highly error prone replication system, presence of pre-core mutants, immune escape mutants and host factors that result in a lack of development of adaptive immune responses against HBV underscore the difficulties in our ability to boost HBV specific immunity in vivo. Recently, several strategies to eradicate HBV have been adopted that target the virus (potent directly acting antiviral agents, agents that target release of HBsAg), target innate immune system (toll-like receptor agonists), enhance antiviral immunity (therapeutic vaccinations) and target immunoregulatory mechanisms (PD-1, Tim-3). These approaches are promising, however, the safety profile of targeting key immunoregulatory mechanisms that may be vital for maintenance of physiological homeostasis of host immunity may need to be carefully evaluated.

Conclusions: A combination of targeting the virus and boosting host immunity may be the ideal approach to eradicate HBV. The safety of such an approach chronic hepatitis B patients needs to be evaluated.

59 Humoral Immunity and the Innate Response To HCV

Andrea L. Cox
The Johns Hopkins University School of Medicine, Baltimore, MD, United States

Background: Hepatitis C virus (HCV) infection is a blood born disease with global distribution that affects almost 3% of the world's population and 25% of those with HIV in the United States. In the United States and many other countries, HCV remains the leading cause of liver failure requiring transplantation and of hepatocellular carcinoma. Continuing advances in therapeutic regimens are promising for effecting cures of HCV and may reduce transmission. However, access to therapy is limited for many of those infected given its costs and the fact that HCV often goes undiagnosed. In addition, therapy for HCV does not provide immunity against subsequent reinfection or fully reverse damage already done to the liver, much of which is thought to be immune mediated. Due to the silent nature of most chronic infections, diagnosis of HCV infection before significant damage is done to the liver can be challenging. This is particularly true of those with HIV infection, in whom liver diseases progresses more quickly. Thus, prevention of chronic infection through prophylactic vaccination and development of therapies to reverse damage in those with liver disease remain a priority. Understanding the immune response to HCV is important for development of both.

Conclusions: The host-virus interaction during the earliest stages of HCV infection influences the developing immune response and, ultimately, the outcome of infection. Recently, novel mechanisms of viral recognition utilizing a family of cytosolic pattern-recognition-receptors called the nucleotide-binding oligomerization domain (NOD)-like receptors have been reported. Engagement of NOD receptors activates the inflammasome-complex leading to production of the pro-inflammatory, inflammasome-associated cytokines interleukin (IL)-18 and IL-1β. These cytokines not only amplify the innate antiviral immune response and skew developing adaptive immune responses, but high levels are associated with cardiovascular disease and metabolic syndromes. In following subjects at high risk of HCV infection longitudinally from pre-infection through clinical outcome, we determined that IL-18 was the earliest and the most reliable host response to acute HCV infection measured in blood. IL-18 remains elevated in chronic infection, although at lower levels than in the acute phase of infection. HIV infection is also associated with high IL-18 levels. This talk will present a summary of recent data from multiple groups on the mechanisms by which HIV and HCV induce activation of the inflammasome-complex, modulation of this response in chronic infection, and the effect of the humoral response on this innate sensing. Better understanding of this innate response may increase understanding of protective immunity and pathogenesis.

60 Interferon Alfa-Free Treatment of HCV

Jean-Michel Pawlotsky
Henri Mondor Hospital, University of Paris-Est, Créteil, France

Background: Hepatitis C therapy is living its revolution. Several new anti-hepatitis C virus (HCV) drugs have reached the market and many others, including direct-acting antivirals (DAAs) and host-targeted agents (HTAs), are at the late clinical developmental stage. Several all-oral, interferon-free drug combination strategies are being developed, including nucleotide-based strategies, nucleoside-free strategies based on 3 DAAs with a low barrier to resistance, nucleoside-free strategies based on 2 DAAs including at least one second-generation drug with a higher barrier to resistance. Infection cure rates over 90% can be expected with these new therapies.

Conclusions: A number of unanswered questions and challenges however remain that will need to be addressed, including treatment of special populations, the role of ribavirin in interferon-free regimens, the role of HCV resistance in HCV treatment failures, strategic choices and cost issues, as well as screening and broad access to care in resource-constrained areas.

Session S3 Symposium

4:00 PM – 6:00 PM **Room 304**

PrEP: Use It or Lose It

61 HIV Pre-Exposure Prophylaxis: Clinical Pharmacology Insights

Craig W. Hendrix
The Johns Hopkins University School of Medicine, Baltimore, MD, United States

Background: HIV pre-exposure prophylaxis (PrEP) trials with tenofovir-containing regimens have achieved perfect protection in some sub-populations and no benefit in others. Pharmacological data from all PrEP trials and smaller pharmacokinetically (PK)-intensive studies provide critically useful data to help understand the larger sources of PrEP trial outcome variability, principally, highly variable adherence across studies. There is a clear concentration-response relationship between tenofovir and its protective benefit that indicates PrEP regimens are highly effective, if taken as directed. Clinical PrEP implementation questions remain, especially questions of intermittent or periodic dosing regimens that have not and may not be formally studied in the future. In the absence of prospective randomized trials, clinical pharmacology provides some cautious guidance on the limitations of intermittent or periodic PrEP dosing which may differ in its protective effect for receptive anal and vaginal intercourse. In this regard, animal and *ex vivo*HIV challenge studies may also be useful, but with important caveats. Looking forward, this rich pharmacological datashould inform planning the next generation of PrEP trials.

Conclusions: Clinical pharmacology helps explain PrEP trial outcomes, inform PrEP management in the clinic, and guide the design of the next generation of PrEP candidates.

62 Notes From the Field: Implementing PrEP in Resource Constrained Settings

Nelly R. Mugo
Kenya Medical Research Institute, Nairobi, Kenya

Introduction: Unequivocal evidence from landmark clinical trials has demonstrated that oral tenofovir disoproxil fumarate-based Pre-Exposure Prophylaxis (PrEP) is a highly effective biomedical intervention for preventing acquisition of HIV-1 infection. For the first time we have a much sought HIV prevention tool for vulnerable HIV-uninfected individuals without requiring negotiation of safe sex with partners. We currently have a robust toolbox of evidence-based biomedical and behavioural HIV prevention strategies that can be used in combination to effectively combat the HIV/AIDS epidemic.

However, clinical trial efficacy is only the first step towards public health effectiveness. For high impact public health implementation, we require a delivery package that is both acceptable and accessible to the populations that most need it.

The use of antiretroviral medications both as treatment and prophylaxis in combination with other interventions has shifted the goals of prevention of mother to child HIV transmission towards elimination; similarly, current evidence of PrEP and treatment as prevention in combination with each other and other preventative strategies can shift the goals of prevention of sexual HIV transmission towards zero new infections.

From clinical trial efficacy to public health effectiveness, PrEP requires innovative implementation strategies and unrelenting demand creation. In the absence of these efforts a highly effective and needed HIV prevention intervention will join the pile of effective and underutilized public health interventions as the pool of newly infected individuals continues to rise.

This presentation will discuss current on going activities in resource restrained settings that will inform both science and policy makers on PrEP implementation such as the current on-going 'demonstration projects' and options for successful PrEP delivery.

Conclusion: PrEP implementation is not only possible, but it is required in resource-constrained settings.

63 A Community Perspective On PrEP

Christopher Balthazar and London Dorris
Stroger Hospital of Cook County, Chicago, IL, United States

Background: Following the success of several clinical pre-exposure prophylaxis (PrEP) trials and the approval of FTC/TDF for the prevention of HIV, attention has shifted to the interest and uptake of PrEP as well as the best practices for PrEP implementation. In the United States, young men who have sex with men (YMSM), particularly racial minority YMSM, are an anticipated target population for PrEP interventions. Thus, a better understanding of community knowledge, interest, and attitudes about PrEP is important. The speakers bring extensive experience, both professional and personal, with community outreach and education around PrEP, recruitment and retention across multiple PrEP trials focused on YMSM (ATN 082, ATN 110/113, and iPrEx OLE), and adherence to daily PrEP.

Conclusions: Extensive efforts to engage with and educate adolescent and young adult MSM around PrEP have revealed a dearth of knowledge in community and school settings about this new HIV prevention approach. Within groups that have basic information about PrEP, misinformation is common and misconceptions have allowed PrEP use to quickly become stigmatized. For those who are taking PrEP, daily adherence can be difficult and integrating PrEP into sexual relationships can be challenging. However, for YMSM who are vulnerable to HIV infection, PrEP is a feasible and highly acceptable prevention intervention that can make a difference in their lives.

64 Choosing Populations for Maximal Impact

David V. Glidden
University of California San Francisco, San Francisco, CA, United States

Background: Oral emtricitabine/tenofovir (FTC/TDF)-based pre-exposure prophylaxis (PrEP) has been shown to prevent acquisition of HIV. PrEP is a promising, yet resource-intensive prevention strategy with high drug and monitoring costs. Providers and policy makers need evidence-based guidance to make decision on prioritizing populations for PrEP. This talk will discuss development of optimal strategies for identifying subgroups for which PrEP will have maximum impact.

Conclusions: The efficient prioritization for subgroups tracks with the effectiveness of PrEP as measured by the absolute (rather than relative) difference in HIV incidence rates. Populations for which this difference is maximized have a lowest number of individuals needed to treat (NNT) per infection prevented. Underlying HIV incidence and relative efficacy (and hence adherence) determine the absolute change in HIV rates due to PrEP. Hence, lower adherence in some settings may be offset by higher underlying HIV incidence and need not preclude the efficient delivery of PrEP. The population impact of PrEP prioritization strategies will be largely determined by the concentration of HIV incidence within that subpopulation _ summarized by the population attributable fraction. Additional considerations for deployment include cost, resistance, toxicity and indirect effects on HIV by interrupting HIV transmission networks. We will illustrate these considerations by combining results of published modeling studies with results from the iPrEx trial (Grant et al, 2010) - a randomized study of daily FTC/TDF based PrEP in men who have sex with men.

WEDNESDAY MARCH 5, 2014

Session PL3 Plenary
8:30 AM – 9:00 AM Auditorium

65 B-Cell Responses To HIV Infection: Challenges and Opportunities

Susan L. Moir, *National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, United States*

Background: B cells and the antibodies they secrete play a critical role in the prevention of and recovery from most infectious diseases. HIV remains an exception, both in terms of the inability of the antibody response to control the virus once an individual is infected and the difficulty in developing an antibody-based vaccine to prevent HIV infection. Of note, potent and broadly neutralizing antibodies against HIV can be elicited in 20 percent of untreated infected individuals and occur to varying degrees only after several years of infection. Paradoxically, the virus itself likely contributes to a broadening of the antibody response as it escapes neutralization by sequential mutations, thus explaining at least in part why a neutralizing antibody response provides little benefit to the infected individual. This presentation reviews how B cells that recognize T-cell dependent antigens, such as HIV, are induced in secondary lymphoid tissues and migrate to interact with CD4+ T follicular helper cells. These interactions lead to the formation of germinal centers that generate memory B cells and plasma cells, the latter of which migrate to the bone marrow to become long-lived sources of antibodies that ultimately circulate in the blood. Germinal center and memory B cells, as well as plasma cells, are perturbed in HIV disease, especially in individuals who do not control HIV viremia either naturally or as a result of antiretroviral therapy.

Conclusions: This presentation reviews the virologic and immunologic factors that likely contribute to the ineffectiveness of the early antibody response against HIV and those factors during the chronic phase of infection that likely exacerbate the inadequacy of the HIV-specific antibody response. Finally, recent advances that are providing new opportunities to improve the quantity and quality of HIV-specific antibody responses are discussed, as well as consideration for how passive immunization with such antibodies could be used to treat infected individuals.

Session PL4 Plenary
9:00 AM – 9:30 AM Auditorium

66 NeuroHIV in 2014: Beyond Dementia

Serena S. Spudich, *Yale University, New Haven, CT, United States*

Background: The fact that HIV infection directly impacts the central nervous system (CNS) has been recognized since very early in the global HIV epidemic. However, the emergence of widespread combination antiretroviral therapy (cART) use has dramatically altered the clinical character of neurologic disease observed in HIV, has led to new challenges related to optimization of CNS treatment, and raised a host of questions related to the role of the CNS as a potential barrier to HIV eradication and cure. This presentation will review key issues in this new landscape of clinical and scientific issues facing HIV-infected persons, providers, and investigators in the current era. Potential mechanisms of HIV-related CNS dysfunction observed in patients treated with cART include persistent CNS infection, ongoing immune activation, effect of comorbidities and risk factors including vascular disease, aging, and genetics, antiretroviral drug exposure in the CNS associated with either toxicity or inadequate tissue distribution, and neurologic injury accrued prior to initiation of antiretroviral treatment. Related to issues of persistent clinical CNS abnormality in the face of cART, a unexplored frontier of research has emerged due to isolated reports of successful HIV 'cure' in the systemic field: whether the CNS may provide a reservoir for infection which may be a significant impediment to efforts to eradicate HIV. The pathobiology of this putative reservoir is under active investigation, including studies on the timing of establishment of CNS infection, the potential cells and tissues harboring HIV in the CNS, evidence of independent evolution of HIV in the CNS, and the possibility of autonomous CNS sources of HIV replication in the setting of suppressive therapy.

Conclusions: Potent antiretroviral treatment for HIV has changed the spectrum of issues and questions related to HIV's effects on the nervous system. Although cART treatment can almost always prevent or ameliorate the most severe form of HIV-associated dementia, numerous clinical and laboratory biomarkers suggest that the CNS is not always normal in cART-treated HIV infected individuals. Whether this persistent perturbation of the CNS has deleterious effects on the brain is uncertain; whether it in part reflects a reservoir for HIV within cells of CNS in the setting of apparently successful cART is an essential question of relevance to both treatment and cure strategies.

Session O-5 Oral Abstracts
10:00 AM – 12:15 PM Room 304

Critical Issues in MTCT: Maternal Health and HIV Treatment in Children

67 A 15-Year Review of Maternal Deaths in a Background of Changing HIV Management Guidelines

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Background: While there has been a global decline in maternal deaths, South Africa has seen a reversal in gains with an increase in the maternal mortality ratio in the past decade. Published data up to 2010 indicate that HIV-related infections remain the leading cause of maternal deaths in South Africa. The data do not reflect the impact of increased antiretroviral therapy (ART) coverage, and increase in CD4 threshold for pregnant women to 350 cells/mm^3, since 2010.

Methodology: We assessed trends in maternal deaths over a 15-year period, 1997-2012, in a district referral hospital in Johannesburg, South Africa. The hospital has approximately 22 000 deliveries per annum, with about a third of pregnant women HIV-infected. It is part of a relatively well-functioning prevention of mother-to-child transmission (PMTCT) programme, where transmission rates have decreased to between 2% and 3% in the past decade. Time trends were analysed by comparing the number of maternal deaths; patterns in HIV-related deaths; and diagnosis and management of HIV disease in pregnant women, over four time periods. The periods coincide with major guideline changes in South Africa - Table 1.

Results: During the 15-year period, there were 590 maternal deaths in the hospital. Overall, HIV-related infections were the leading cause of maternal mortality, accounting for 37.8% of all deaths, followed by hypertension (17.5%) and obstetric haemorrhage (13.4%). Of the women who died, 20.5% had not accessed antenatal care, while 11.9% had no documented records of antenatal care. The majority of deaths occurred postpartum - 470/590 (79.7%), and HIV-related deaths increased between 2003 and 2008, and have remained stable around 40%. Out of a total of 284 HIV-infected women who died, 66 (23.2%) had documented initiation of antiretrovirals (ARVs). Of those that had a CD4 count done, 74.6% had a ≤200 cells/mm^3.

Conclusions: In this review up to the end of 2012, HIV-related infections remained the leading cause of maternal deaths, despite the availability of efficacious ARVs. While HIV diagnosis during pregnancy improved, the majority of HIV-infected women who died were ART-eligible, and died without being started on ART. These findings are similar to national reports prior to the widespread availability of ART. In South Africa, gains made in PMTCT are not reflected in maternal mortality rates - targeted antenatal and postpartum interventions are needed if we are to decrease HIV-related maternal deaths.

Trends in HIV-related Maternal Deaths, 1997-2012				
Time period	Maternal deaths	Tested for HIV (%)	CD4 count tests done in HIV+ (%)	HIV-related deaths (%)
*1997-2002 *no PMTCT interventions	184	84 (45.6)	20 (35.1)	58 (31.5)
*2003-2008 *sdNVP for PMTCT *ART from 2003; CD4 threshold 200 cell/mm^3	247	185 (74.9)	88 (66.2)	102 (41.3)
*2009-2010 *AZT for PMTCT *from 2010, CD4 threshold 350	86	73 (84.9)	37 (80.4)	34 (39.5)
*2011-2012 *ART availability within antenatal clinics	73	61 (83.6)	44 (91.7)	29 (39.7)

68 Incidence and Cofactors of Acute HIV During Pregnancy and Postpartum

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Background: Tremendous progress has been made in identifying and treating women with HIV within prevention of mother-to-child HIV transmission (PMTCT) programs. However, PMTCT focuses predominantly on women with chronic HIV infection. Women who are HIV seronegative at antenatal HIV test may be reassured and fail to recognize continued risk for HIV acquisition. We evaluated rates and correlates of acute HIV infection among pregnant and postpartum women in Western Kenya.

Methodology: At two District Hospitals in Western Kenya, pregnant women seeking antenatal care were enrolled if they were HIV negative (by two rapid HIV tests), either at that visit or within the last three months. Consenting mothers completed a questionnaire that assessed sociodemographic characteristics and sexual behavior. Blood was obtained for nucleic acid amplification tests (NAATs) and genital swabs were collected for detection of sexually transmitted infections (STIs) at baseline and serially during 9 month postpartum follow-up.

Results: Between May 2011 and June 2013, 1305 women were enrolled. Median age was 22 years (interquartile range (IQR) 19-26), 1022 (78.3%) were married for a median duration of 4 (IQR 1-8) years and 87 (6.7%) reported prior STIs. Twenty four women had acute HIV infection, of whom 11 (45.8%) had a positive NAAT at enrollment and 13 (54.2%) became infected during follow-up, either later in pregnancy (2) or postpartum (11). Six (29%) women with acute HIV infection had symptoms of primary HIV infection. During 1071 person-years of follow-up, estimated HIV incidence was 2.63/100 person-yrs (95% CI: 0.65-4.82). Shorter duration of marriage (OR=1.15, 95%CI: 1.01-1.32), history of STIs (OR=3.84, 95% CI: 1.4-10.57) and infection with syphilis (OR=9.95, 95% CI: 1.98-46.02) or bacterial vaginosis at enrollment (OR=2.88, 95% CI: 1.28-6.5) were associated with acute HIV infection. Maternal age, marital status, education level and age difference from partner did not differ between women with or without acute HIV infection.

Conclusions: Among pregnant/postpartum women in a high HIV seroprevalence region, risk of HIV incident infection was high and comparable to discordant couples or sex worker cohorts. Almost half of acute HIV infections were detected during pregnancy, suggesting value of repeat HIV testing at delivery. Screening and treatment for STIs, including bacterial vaginosis and syphilis may be useful for HIV prevention, particularly among women with history of STI in shorter duration partnerships. Other HIV preventive options (such as PrEP or partner treatment) should be assessed in this population.

69 Efficacy and Safety of LPV/r Versus EFV in HIV+ Pregnant and Breast-Feeding Ugandan Women

Deborah Cohan[1], Paul Natureeba[2], Albert Plenty[3], Flavia Luwedde Julia Mwesigwa[2], Veronica Ades[4], Edwin Charlebois[3], Tamara Clark Bridget Nzarubara[2], Moses Kamya[5], Pius Okong[6], Diane Havlir[3]

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Background: 2013 WHO ART guidelines recommend EFV-based combination ART (cART) for all pregnant women, though there are limited data on maternal/infant outcomes and alternative ART regimens. We report maternal/infant outcomes of a randomized trial comparing LPV/r to EFV-based cART in rural Uganda.

Methodology: PROMOTE was an open label trial (NCT00993031) enrolling HIV+ cART-naïve pregnant women between 12-28 weeks gestation. Women received AZT/3TC and either LPV/r or EFV at enrollment through 1 year of breastfeeding. LPV/r increased to 600/150 twice daily at 30 weeks. We compared virologic, immunologic and safety outcomes between the 2 arms. All women received cotrimoxazole and infants received ART prophylaxis per Ugandan guidelines.

Results: 389 women enrolled - mean age was 29, median pre-ART CD4 count was 370 and mean pre-ART viral load was 61,611 c/mL. Compared to LPV/r, women on EFV were significantly more likely to achieve viral suppression (<400 copies/mL) by delivery (85.7% [LPV/r] vs. 97.6% [EFV], p <.0001) and 24 weeks post-ART initiation (88.5% vs. 94.3%, p=.04) and maintain suppression throughout breastfeeding (74.3% [LPV/r] vs. 83.8% [EFV],

p=.03). Among the 373 women with virologic suppression, there was significantly more virologic failure in the LPV/r arm (HR: 3.11, 95% CI 1.13 - 8.54, p=.03). Women on LPV/r experienced greater CD4 count recovery by 24 weeks post-ART initiation (+181.5 vs. +109.2, p=.01). There was no difference in grade 3 or 4 adverse events (AEs) (incidence rate [IR] 0.26 per woman-year), though grade 1 or 2 gastrointestinal AEs were significantly more likely for women on LPV/r (IR ratio [IRR] 1.69 (1.41-2.02), p < .0001). HIV transmission rate was 2/374 liveborn infants (.5%, .01-1.9%) - one in-utero and one breastfeeding transmission in LPV/r arm. HIV-free infant survival did not differ between arms (92.9% [LPV/r] vs. 97.2% [EFV] p=.10) and there was no difference in grade 3 or 4 AEs among infants (IR 0.39 per person-year, IRR 1.25 (0.87-1.80), p=.21).

Conclusions: EFV was associated with superior virologic outcomes compared to LPV/r among cART-naïve pregnant and breastfeeding women. Both regimens were extremely effective at preventing HIV transmission during pregnancy and breastfeeding. These data affirm WHO guidelines recommending EFV as first-line cART for Option B+ and support LPV/r as an alternative.

70 Infant Lopinavir/r Versus 3TC To Prevent Postnatal HIV-1 Transmission: The ANRS 12174 Trial

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Background: Strategies to prevent mother-to-child postnatal transmission of HIV-1 in Africa, including infant prophylaxis, have never been evaluated for the entire recommended period of breastfeeding, i.e. 12 months. Beside lamivudine, which proved safe and efficacious during 6 months for this purpose, lopinavir/ritonavir (LPV/r) is a good candidate for infant prophylaxis due to its good safety profile in infants, its potent antiretroviral activity and its high genetic barrier to HIV resistance mutations.

Methodology: The ANRS 12174 study is a randomised controlled trial comparing the efficacy and safety of prolonged infant peri-exposure prophylaxis (PreP) with lopinavir/ritonavir (LPV/r) versus lamivudine (3TC) to prevent postnatal HIV-1 transmission during the full duration of breastfeeding (50 weeks), in children born to HIV-1-infected mothers not eligible for ART (i.e. with CD4 >350 cells/µL). In Burkina Faso, South Africa, Uganda and Zambia, seven days old HIV-uninfected breastfed newborns with birth weight > 2000g were randomised for either drug in a 1:1 ratio. The primary outcome was infant HIV infection until 50 weeks, diagnosed every 3 months by HIV-1 DNA PCR. Secondary outcomes included mortality, HIV-free survival and severe adverse events, including routine biological parameters. Outcomes were analysed using Kaplan-Meier survival methods with an intention-to-treat approach.

Results: Overall, 1273 children were enrolled in the trial, 636 in the LPV/r arm and 637 in the 3TC arm. Baseline infants' characteristics were similar between arms. Antenatal maternal median CD4 count was 529 (IQR: 432-669). At final follow-up (completed in May 2013), 1119 (88.32%) infants had attended the final visit and 115 (9.08%) were lost to follow-up. The median duration of breastfeeding was 42 weeks (IQR:41-42). Overall, 17 HIV infections were diagnosed (of which 8 after 6 months), 8 in the LPV/r arm and 9 in the 3TC arm, and giving HIV infection rates of 1.39% (0.70 - 2.76) and 1.53 % (0.80 - 2.91) at 50 weeks, respectively (p=0.83). Overall, 18 (2.83%) died in the LPV/r arm and 15 (2.35%) in the 3TC arm, respectively (p=0.57). HIV-free survival was similar between arms, at 96.5% (94.6-97.7) and 96.3% (94.4-97.5), respectively (p=0.85). Medical or biological severe adverse events were not different between arms.

Conclusions: Very low rates of HIV-1 postnatal transmission were achieved by using infant prophylactic LPV/r or 3TC for the whole duration of breastfeeding, without difference between the two drugs, which were both well tolerated. Infant PreP is a feasible and effective strategy to eliminate HIV transmission through breastfeeding. Further studies should evaluate the benefit of adding infant PreP to WHO option B/B+ in order to prevent residual breastfeeding transmission.

71 Lower Newborn Bone Mineral Content Associated With Maternal Use of Tenofovir Disoproxil Fumarate

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Background: The impact of maternal tenofovir disoproxil fumarate (TDF) use on infant bone mass has not been well studied.

Methodology: Two groups of HIV-exposed, uninfected newborns >36 weeks gestational age [GA] were enrolled in this substudy of the US multisite Pediatric HIV AIDS Cohort Study. The TDF group included infants whose mothers used ≥8 weeks of TDF in the 3rd trimester; the nonTDF group included infants whose mothers used no TDF during the pregnancy. Within 4 weeks of birth, a whole body (WB) dual-energy X-ray absorptiometry (DXA) scan was obtained to measure WB bone mineral content (BMC) with head (WBWH) and less head (WBLH). Standardized analysis of scans was performed centrally. Maternal demographic/clinical data were prospectively collected. Infant weight/length were measured within 72 hours of birth. Target sample size was 75 (63 evaluable) per group to detect WBWH BMC difference between groups of 7% or 0.5 standard deviation (SD) with 80% power. Differences in covariates by TDF group were evaluated by Chi-square and Wilcoxon test. Linear regression models were fit to evaluate BMC by TDF group, adjusted and unadjusted for potential confounders.

Results: 74 TDF and 69 nonTDF group infants from 14 sites had evaluable DXA scans. Maternal TDF use varied by site (p<.001). Compared to the nonTDF group, TDF group mothers were more likely to be married (31% vs 22%, p=.035) and use boosted protease inhibitors (bPI) (86% vs 64%, p=.005); the groups were similar on demographics, infant weight (p=.159) and length (p= .21) z-scores and GA (p=.60). Among mothers with values available in 3rd trimester for CD4 (63 in TDF;44 in nonTDF) and viral load [VL] (62 in TDF; 50 in nonTDF), similar proportions of TDF and nonTDF group mothers had CD4 ≥ 250 (94% and 93%, respectively) and VL < 400 copies/mL (90% and 90%, respectively). The unadjusted mean infant WBWH BMC was significantly lower in the TDF group (56g vs 64g, p=.002, 12.2%, 0.5 SD) as was the mean WBLH BMC (33 g vs 36g, p=.038, 8.3%, 0.3 SD). These differences persisted after adjusting individually for site; maternal bPI use, age, smoking, and pre-pregnancy body mass index; and infant GA, race/ethnicity, age at DXA and length. Maternal CD4 and VL during the 3rd trimester were not correlated with WBWH BMC (p=.44 and p=.13, respectively) or WBLH BMC (p=.29 and p=.34, respectively). Adjusted for site, maternal bPI use, age, and smoking, and infant body length, race/ethnicity and age at DXA, the mean WBWH BMC and mean WBLH BMC were lower in the TDF group than in the nonTDF group by 6.3g (p = .004) and 2.6 g (p = .056), respectively.

Conclusions: Maternal TDF use is associated with a significant reduction in neonatal BMC that persists after adjustment for other factors. The duration and clinical significance of this finding merit evaluation in longitudinal studies.

72 Virologic Control by 1 Year of Age Significantly Reduces HIV-1 Reservoirs in Perinatal Infection

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Background: Reducing proviral reservoir size is an important prerequisite for achieving HIV-1 remission for which antiretroviral therapy can be discontinued without viremic rebound. The extent to which proviral reservoir size can be substantially reduced with long-term, early combination antiretroviral therapy (cART) for perinatally HIV-infected (PHIV+) children is unknown.

Methodology: We quantified with droplet digital PCR proviral load in peripheral blood mononuclear cells (PBMCs) from 144 PHIV+ children enrolled in the Pediatric HIVAIDS Cohort Study/Adolescent Master Protocol (PHACS/AMP) who were receiving cART for a median of 10 years. Proviral burden, HIV serostatus, 2-LTR circles, and immune activation markers (soluble CD14, CD163, IFN-γ, IL-6, and IL-1β) were compared by age at virologic control (less than 1 vs. 1-5 vs greater than 5 years of age). Immune activation markers were also compared to perinatally-HIV-exposed, uninfected (PHEU) children. Proviral burden was also correlated with HIV serostatus and 2-LTR circles.

Results: When studied at 8-20 years of age, the proviral load of PHIV+ children who achieved virologic control by one year of age was significantly lower than that of PHIV+ children who suppressed between 1-5 years and after age 5 (p<0.001, Table 1); 46% of PHIV+ children who suppressed by one year of age had an undetectable proviral reservoir at <4 copies/million PBMCs compared to 11% of those who suppressed after age 1 (p=0.01). Lower proviral burden was associated with undetectable 2-LTR circles (p<0.001) and HIV-1 seronegative/indeterminate status (p<0.001). Plasma concentrations of soluble CD14, CD163, IFN-γ, and IL-1β were similar across the three age groups of virologic control (Table 1) but sCD14 and IL1 β levels were significantly higher in PHIV+ children than in PHEU (p<0.001 and p=0.004 respectively).

Table 1	Age at virologic control among PHIV+			p-value	PHEU (N=10)	p-value (PHIV+ vs. PHEU)
	<1 year (N=14)	1-5 years (N=53)	>5 years (N=77)			
Age at analysis (years)	12.6 (11.1, 14.0)	12.7 (10.4, 15.4)	15.8 (13.8, 17.2)	<0.001	--	--
Age at cART initiation (months)	2.4 (1.7, 3.1)	22.6 (9.8, 39.6)	67.6 (25.7, 111.2)	<0.001	--	--
cART duration (years)	12.4 (11.0, 13.7)	10.9 (8.5, 12.7)	8.3 (6.0, 12.0)	<0.001	--	--
Proviral Burden* (copies/million PBMCs)	4.2 (2.6, 8.6)	19.4 (5.5, 99.8)	70.7 (23.2, 209.4)	<0.001	--	--
HIV serostatus (%) Positive Indeterminate/Negative	14% 86%	81% 19%	97% 3%	<0.001	--	--
Plasma soluble CD14 (x 10^b pg/ml)	1.9 (1.6, 2.3)	1.8 (1.5, 2.0)	1.8 (1.5, 2.1)	0.41	1.3 (1.1, 1.5)	<0.001
Soluble CD163 (ng/ml)	449 (291, 554)	481 (393, 695)	510 (386, 633)	0.20	376 (307, 550)	0.17
IFN-γ (pg/ml)	4.0 (3.0, 7.9)	4.1 (3.7, 7.9)	4.2 (3.7, 7.9)	0.88	3.7 (3.7, 8.9)	0.95
IL-6 (pg/ml)	2.5 (2.1, 3.0)	2.3 (1.2, 4.0)	3.0 (1.5, 5.2)	0.38	2.5 (1.2, 3.5)	0.56
IL-1β (pg/ml)	2.0 (0.9, 3.7)	3.3 (1.1, 6.9)	3.7 (1.8, 9.2)	0.17	1.1 (1.1, 1.1)	0.004

Presented as Median (IQR) except HIV serostatus.
p-values from Kruskal-Wallis and Fisher's exact tests.
*Values below the limit of detection reset to the limit of detection.
PHIV+: perinatally HIV-infected youth, PHEU: perinatally HIV-exposed but uninfected youth.

Conclusions: Achieving virologic control by one year of age in perinatal infection leads to significantly smaller proviral reservoirs in those with HIV-negative or indeterminate serostatus and absent 2-LTR circles. It does not reverse immune activation. These findings emphasize the benefits of early therapy in perinatal infection with implications for a viro-immunologic profile for HIV cure-related clinical trials.

73 Virologic Efficacy of Efavirenz Maintenance Therapy in Nevirapine Prophylaxis-Exposed Children

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Background: Ritonavir-boosted lopinavir (LPV/r)-based therapy is recommended as first-line for young children in low resource settings in part to circumvent drug resistance selected following nevirapine (NVP) prophylaxis. Whether prophylactic NVP exposure precludes later use of efavirenz (EFV) among children initially suppressed on LPV/r is unknown.

Methodology: NEVEREST 3 was designed as a randomized clinical trial to test whether transition to EFV maintenance therapy has equivalent virologic efficacy to standard continuation of LPV/r-based therapy in children infected despite exposure to NVP-containing prophylaxis. At Rahima Moosa Mother & Child Hospital in Johannesburg, South Africa, 298 children, exposed to NVP prophylaxis and aged 3-5 years were enrolled in a non-inferiority trial. All initiated LPV/r-based therapy <24 months of age and were suppressed <50 copies/ml (cpm) at enrollment. Children were randomized to switch to EFV or to continue on LPV/r. Children were followed with regular viral load, CD4 and other laboratory tests, growth measurements and clinical assessments to 48 weeks. Two primary endpoints were defined: 1) non-suppression i.e. RNA >50 cpm ever and 2) viral failure i.e. RNA >1000 cpm confirmed. The study was powered to rule out a difference between arms in virologic efficacy of ≥10%.

Results: Children were an average of 4.1 years of age, had initiated therapy at a mean of 9 months and had been on therapy for a mean of 3.5 years at the time of randomization. 150 children were randomized to switch to EFV and 148 to stay on LPV/r. Retention was 98%, there were no deaths and 2 children in the EFV and 3 children in the LPV/r arms were hospitalized during the course of follow-up. Both primary virologic endpoints were found to be non-inferior in the EFV arm relative to the LPV/r arm. In the EFV arm, 18% had non-suppression >50 cpm by 48 weeks vs. 28% in the LPV/r arm (delta=10; 95% CI:-0.4, 19.9). In the EFV arm 2.8% had viral failure (>1000 cpm confirmed) vs. 2.2% in the LPV/r arm (delta -0.6; 95% CI: -3.1, 4.3). Sleep difficulties were reported among 26% 4 weeks after the EFV switch but declined to < 1% thereafter. There were no differences by arm in behavioral problems assessed by the Strengths & Difficulties Questionnaire (SDQ). CD4% and weight- and height-for-age remained in the normal range, similar by arm. Laboratory abnormalities and other complications were rare.

Conclusions: Children exposed to NVP prophylaxis who are initially suppressed on LPV/r-based therapy can safely transition to EFV-based maintenance therapy without increased risk of viral rebound. There are several advantages of the switch to EFV, including assisting adherence, simplifying tuberculosis treatment, preserving second-line options, avoiding metabolic toxicities, and reducing cost.

74LB Final Results of Koncert: A Randomized Noninferiority Trial of QD Vs BD LPV/r Dosing in Children

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Background: Evidence for the efficacy of once daily (QD) ART for HIV-1 infected children/adolescents is limited. Lopinavir/ritonavir (LPV/r) is approved for use in adults once or twice daily, but twice daily (BID) in children.

Methodology: KONCERT was a randomized, non-inferiority PENTA trial in Europe, Thailand, Argentina and Brazil. Children (<18 yrs, ≥15kg) on LPV/r-containing ART with HIV-RNA (VL)<50 c/mL for ≥24 weeks were randomized to continue LPV/r BID or switch to QD dosing, according to FDA approved body weight-based dosing. Children were followed for minimum 48 weeks, visits at weeks 0, 4, 8, 12 then 12 weekly. The primary outcome was the percentage with confirmed VL≥50 c/mL by 48 weeks, estimated using the Kaplan-Meier method (12% non-inferiority margin). 26 children (on LPV/r 100/25mg pediatric tablets) in the QD arm had LPV/r pharmacokinetic (PK) measurements at weeks 0 (BID) and 4 (QD). Within-subject ratios for QD versus BID of AUC_{0-24}, C_{max} and C_{min} were calculated. PK analyses were per-protocol, all others intention-to-treat.

Results: 173 children were randomized to QD (86) or BID (87): 46% male, median age 11 (IQR 9-14) years; 25% white, 27% black, 35% Asian; 29% CDC stage C, median time on ART 7.2 years. Median baseline CD4% was 32% (IQR: 27, 36) QD vs 34% (28, 40) BID. Although all children had VL<50c/mL at screening, 12 (14%) QD vs 4 (5%) BID had baseline VL≥50 c/mL (IQR: 66, 239). By week 48 (1 QD child lost at week 4), 97% and 98% of time was spent on QD and BID respectively. 12 QD vs 7 BID children had confirmed VL≥50 c/mL within 48 weeks; the estimated percentage with VL rebound was 14% QD vs 8% BID: difference 6% (90% CI -2, 14; p=0.2); reducing to 4% (-4, 11) after adjustment for baseline CD4% and VL in a post-hoc analysis. No child died or had a new CDC C event. Two children (BID) had a major PI mutation at VL rebound (L90M, M46I+V82A); 3 QD vs 2 BID children had M184V, 2 QD vs 2 BID developed TAMs. Changes from baseline to week 48 in CD4%, CD4 count, biochemistry, hematology and lipids were similar between arms, as were the number of children with grade 3/4 AEs (10 QD vs 7 BID, p=0.6). 14 (4%) QD vs 6 (2%) BID children/carers reported missing a dose within 3 days of any clinic visit (p=0.2). For the 26 QD children in the PK substudy, the geometric mean ratio (GMR) (90% CI) of AUC_{0-24} was 0.72 (0.61, 0.85) falling outside the 80-125% limits for bioequivalence. GMR for C_{max} was 1.13 (0.99, 1.28) and for C_{min} was 0.18 (0.11, 0.29).

Conclusions: Non-inferiority for VL suppression on QD versus BID LPV/r dosing was not demonstrated in this trial and LPV daily drug exposure was lower with QD dosing. Resistance and safety data were similar in both arms. Although the results can be partly explained by chance VL imbalance at baseline, they do not support the routine use of LPV/r QD in children and adolescents.

75LB Very Early Combination Antiretroviral Therapy in Perinatal HIV Infection: Two Case Studies

Deborah Persaud[1], Audra Deveikis[2], Hannah Gay[3], Jagmohan Batra[2], Tempe Chen[2], David E. Michalik[2], Kaitlin Rainwater-Lovett[1], Carrie Ziemniak[1], Katherine Luzuriaga[4], Yvonne Bryson[5]

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Background: Combination Antiretroviral treatment (cART) by 31 hours of age led to HIV remission in the Mississippi Child where cART cessation did not lead to rebound viremia. We report follow-up virologic and immunologic markers at 21 months off ART in the Mississippi Child and in a second perinatally-infected infant who started cART similar to that of the Mississippi Child (by four hours of age) and remains on cART through age 8 months.

Methodology: Standard HIV DNA and RNA tests were used to confirm infection and assess virologic responses to cART. HIV-specific immune responses were assessed by ELISA, western blot and cytotoxic T-cell responses. CD4+ and CD8+ T cell percentages were enumerated by flow cytometry. Droplet digital PCR (DDPCR) was used to quantify proviral burden in peripheral blood mononuclear cells (PBMCs), resting CD4+ T cells, activated CD4+ T cells and monocytes. Replication-competent proviral genomes were identified using a limiting dilution viral outgrowth assay. Non-induced proviral genomes were quantified by DDPCR of culture-negative wells.

Results: The Mississippi Child has remained in remission with undetectable plasma viremia (<20 copies/mL) and normal CD4+ and CD8+ T cell counts at 39 months of age, 21 months after stopping cART. Trace proviral DNA is persistently detectable in PBMCs but replication competent HIV is not; non-induced proviruses were not detected in culture-negative wells. HIV-specific immune responses remain undetectable.

A second infant with high-risk exposure to HIV was started on cART at four hours of age. HIV infection was confirmed by positive peripheral blood HIV DNA PCR at four hours of life and HIV RNA of 217 copies/mL at 36 hours of age. HIV RNA was detected in CSF at 32 copies/mL on DOL#6. Plasma HIV RNA was undetectable on DOL#11 and remained undetectable through age 8 months. HIV DNA testing was negative by DOL#6, and remained undetectable at DOL#47 and 67. Replication-competent HIV was not recovered from resting CD4+ T cells at 1 and 3 months of age; non-induced proviral genomes were detected by DDPCR, in culture-negative wells, at one month but not age three months. At age 3 months, HIV antibody is indeterminate (western blot reactivity to gp160). CD4+ T cell percentages remained normal for age.

Conclusions: Very early cART in an HIV-infected infant led to sustained HIV remission through 39 months of age, 21 months after stopping cART. In a second infant, cART by four hours of life led to rapid clearance of replicating virus and an undetectable proviral DNA by clinical assays within 6 days of life, supporting restriction of HIV spread with very early cART. Development of sensitive laboratory markers and standardized approaches will be necessary to guide the optimal management of very early HIV treated infants in order to achieve remission.

Session O-6 Oral Abstracts
10:00 AM – 12:00 PM **Room 312**
HIV/SIV Pathogenesis

76 Pyroptosis Drives Both CD4 T Cell Death and Chronic Inflammation in HIV-Infected Lymphoid Tissues

Gilad Doitsh[1], Nicole Galloway[1], Xin Geng[1], Kathryn Monroe[1], Zhiyuan Yang[1], Orlando Zepeda[2], Peter Hunt[2], Hiroyu Hatano[2], Stefanie Sowinski[1], Warner C. Greene[1]

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Background: The progressive loss of CD4 T cells in HIV-infected individuals is the over-arching cause of AIDS. Apoptosis is the mechanism by which productively infected CD4 T-cells die. In contrast, very little is known about how "bystander" resting CD4 T cells die in lymphoid tissues. These cells are refractory to productive HIV infection yet they account >95% of the CD4 T cell losses occurring in many lymphoid tissues like tonsil and spleen.

Methodology: Human lymphoid aggregated cultures (HLACs) were prepared using tonsil and spleen tissue; lymph nodes from consenting HIV-infected volunteers not on antiretroviral therapy were surgically excised and used in immuno-histological staining studies.

Results: Our finding demonstrate that productive HIV infection in activated CD4 T cells from tonsil and spleen (95%) leads to by caspase-1-mediated pyroptosis, an intensely inflammatory form of programmed cell death. In the pyroptotic death pathway, cytoplasmic contents and pro-inflammatory cytokines including IL-1β, are released into the extracellular space. Surprisingly, lymphoid CD4 T-cells, but not CD8 T cells or B cells in the same tissue, are primed to mount proinflammatory death responses as reflected by high-level expression of pro-IL-1beta. These events combine to create a vicious pathogenic cycle where dying CD4 T-cells release inflammatory signals that attract more cells to become abortively infected and die by pyroptosis causing more inflammation. Cell-to-cell transmission of HIV is obligately required to elicit this pyroptotic death response-cell free virions are ineffective Pyroptosis is efficiently blocked by VX-765, a small-molecule inhibitor of caspase-1 that has been shown to be safe in humans. Analysis of lymph nodes from HIV-infected subjects confirms caspase-1 dependent pyroptotic death of bystander CD4 T cells and release of IL-1beta.

Conclusions:

1. CD4 T-cell death in HIV-infected lymphoid tissues is principally controlled by caspase-1-mediated pyroptosis, an intensely inflammatory form of programmed cell death.
2. Pyroptosis provides a new and exciting nexus between CD4 T-cell death and inflammation with strong implications for HIV pathogenesis and disease progression.
3. Small-molecule inhibitors of caspase-1 could form a promising new "anti-AIDS" therapy that complements current treatment strategies by altering the detrimental host innate immune response to the virus rather than the virus itself.

77 Early ART Initiation Prevents Disruption of the Mucosal Barrier and Subsequent T-Cell Activation

Alexandra Schuetz[1], Yuwadee Phuang-Ngern[1], Rungsun Rerknimitr[2], Eugene Kroon[1,3], Nitiya Chomchey[3], Praphan Phanuphak[3], Merlin Robb[4], Jerome Kim[4], Mark de Souza[3], Jintanat Ananworanich[2,3], on behalf of the RV254/SEARCH 010 and RV304 StudyGroups

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Background: Chronic HIV-infection is associated with damage of the intestinal epithelium partly by disrupting the Th17/Treg balance and contributing to systemic immune activation, a marker for disease progression. The initiation of anti-retroviral treatment (ART) early during acute HIV-infection (AHI) might represent an opportunity to intervene and limit destruction of the mucosal barrier.

Methodology: 38 subjects in Fiebig stages I to III were enrolled and underwent sigmoid biopsy at baseline, 6 months (29/38) and 24 months (17/38) post initiation of ART. Ten gender- and age-matched HIV uninfected (HIV-) and 5 ART-naïve chronically HIV+ subjects (CHI), 6 to 12 month post infection, served as controls. Mucosal mononuclear cells were isolated and subsequently stained for multi-parameter flow cytometry.

Results: At baseline, subjects were Fiebig stage: I (13), II (4) and III (21). A significantly lower frequency of Th17 cells was observed in FIII compared to FI/II (Median 7.1% vs. 13.2%, p=0.03). No difference was seen between FI/II and HIV- (Median 13.2% vs. 14.5%, p=NS), while FIII had lower Th17 cells compared to HIV- (Median 7.1% vs. 14.3%, p=0.01). Subjects who started ART in FI/II maintained frequencies of Th17 cells at 6 months (Median 13.5%) and 24 months (Median 12.7%) comparable to HIV-, while Th17 cells were depleted in (CHI) (Median 1.1%, p<0.001). Initiation of ART at FIII prevented further loss of Th17 cells, but did not reconstitute Th17 frequencies to the level of HIV- (Median baseline: 7.1%, 6 months: 9.2%, 24 months: 8.1%, HIV- 14.5%). At 24 months subjects treated at FI/II and at FIII maintained higher frequencies of Treg compared to HIV- (Median FI/II 6.7%, p=0.001 and FIII 7.7%; p=0.003 vs. HIV- 3.1%), but never increased to levels seen in CHI (Median 20.6%). Additionally, FIII subjects showed significantly increased CD8 T cell activation before ART compared to HIV- as measured by HLA-DR/CD38 expression (Median 12.7% vs. 4.7%, p<0.001). However, at 6 and 24 months CD8 T cell activation decreased to frequencies similar to HIV- with 4.5% and 5.1%, respectively. FI/II subjects did not show an initial significant increase in CD8 T cell activation compared to HIV- (Median 6.9% vs. 4.7%, p=NS) and maintained low levels of immune activation at 6 and 24 months (Median 5.5% and 4.9%).

Conclusions: FI/II subjects exhibit levels of Th17 cells and CD8 T cell activation similar to HIV- subjects and maintain those levels under ART. Early initiation of ART may prevent the loss of Th17 cells and subsequent CD8 T cell activation thus contributing to the integrity of the mucosal barrier.

78 Characterizing the IFNα Resistance of Transmitted Founder HIV-1

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Background: Elucidating the host innate effector mechanisms that control HIV-1 replication at the site of entry during the earliest stages of infection could be instrumental in the development of an effective AIDS vaccine. We reported previously that transmitted founder (TF) viruses are more resistant to the antiviral effects of interferon α (IFNα) than viruses that predominate during chronic infection. Here, we used matched pairs of TF and 6-month (6-mo) consensus infectious molecular clones (IMCs) to identify genetic determinants of IFNα resistance.

Methodology: Single genome sequencing (SGS) was used to infer the full-length TF sequence as well as consensus sequences at 45 days, 85 days and 6-mo post-seroconversion from one patient (CH58). In addition, TF and 6-mo genome sequences were derived from 11 longitudinally followed patients (8 subtype C and 3 subtype B). IMCs were synthesized and viral replication was assessed in human CD4+ T-lymphocytes in the presence and absence of IFNα.

Results: To characterize the decline in IFNα resistance over time, we analyzed sequential IMCs from a single patient, CH58. In the absence of IFNα, all four viruses replicated with similar kinetics. However, when target cells were pretreated with IFNα, the TF, d45 and d85 viruses replicated nearly 10-fold more efficiently than the corresponding 6-mo virus (p<0.001). To determine whether loss of IFNα resistance was a common phenotype, we compared the replication potential of matched TF/ 6-mo pairs from 11 additional patients. In each case, TF viruses replicated more efficiently than the corresponding 6-mo viruses in the presence of IFNα. This difference was statistically significant (p<0.05) throughout the 11-day replication time course, with the greatest replication increase observed at day 7 post-infection (range 2.3- 10.2 fold). This phenotype was reproduced in CD4+ T-lymphocytes from multiple human donors. Interestingly, we identified two distinct IFNα sensitivity profiles by varying the duration of pretreatment of target cells. For ten pairs, differential replication was observed when cells were pretreated from 4- 24 hours prior to infection, while two pairs only showed differential replication up to 16 hours of pretreatment, and not beyond. IFNα resistance mapped to nucleotide changes in different genes in two pairs.

Conclusions: These data demonstrate that antiviral genes up-regulated by IFNα exert significant selective pressure on the transmitted HIV-1 pool, resulting in the establishment of infection by variants that are relatively IFNα resistant. This IFNα resistance declines within 6 months of infection and is subtype independent. Multiple IFNα -stimulated genes likely contribute to this phenotype.

79LB Identification of IFI16 as HIV Restriction Factor

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Background: Antiretroviral restriction factors are encoded by genes that are under strong positive selection pressure, induced in HIV-1 infection, and frequently interacting with viral proteins. Here, we used evolutionary genomics, transcriptomics, and protein interaction data to identify additional human genes showing these features and to characterize new restrictions factors.

Methodology: We first performed a genome-wide screen for genes under positive selection pressure in primates. The output was assessed in the context of orthogonal sets of transcriptome and protein interaction data. A cell-based assay was used to determine the impact of candidates on HIV-1 gene expression, virus production and virion infectivity. We monitored HIV-1 Gag and Env protein expression in the cells and in the culture supernatants by western blot analysis. Detailed analysis of the γ-interferon-inducible protein 16 (IFI16) included knockdown in primary cells, assessment of counteraction with viral accessory proteins and use of primate orthologs and a panel of viral strains and isolates. Silencing of IFI16, cGAS and STING was performed to distinguish between immune sensing activity and direct restriction.

Results: We identified 30 genes showing the signature of restriction factors. Overexpression of a strikingly high proportion of them inhibited transcription or translation of HIV-1, while a small subset impaired viral infectivity. Analysis of IFI16 demonstrated that this immune sensor of viral DNAs strongly reduces the production of infectious HIV-1 by interfering with LTR activity and Gag processing. This antiviral activity is conserved across different primate species, dependent on a nuclear localization signal, and counteracted by the viral Vpr protein. Silencing of IFI16 but not of other factors in the innate DNA sensing pathway, such as STING or cGAS, increased infectious virus production.

Conclusions: The number of human genes sharing the characteristics of known host restriction factors is very limited. The screen allowed the identification of IFI16 as an innate immunity factor that restricts HIV-1 independently of its DNA sensing activity.

80 Central Memory and Effector Memory CD4 T Cells From HIV Controllers Harbor Distinct HIV Strains

Eli Boritz[1], Luke Swaszek[1], Rebecca Hoh[2], Jeffrey Martin[3], Steven Deeks[2], Daniel Douek[1]

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Background: The distinct immunologic functions performed by CD4 T cells of central memory (CM) and effector memory (EM) phenotypes require distinct gene expression programs that could differentially affect HIV replication. We tested the difference between CM and EM cells as HIV hosts in vivo by quantifying and sequencing HIV genomes from these cellular subsets in a group of HIV-infected donors with spontaneous control of plasma HIV-1 RNA levels to <1,000 copies/mL in the absence of cART.

Methodology: CM and EM cells were sorted from PBMC of 6 HIV controllers by FACS. RNA genomes were extracted from plasma virions and reverse-transcribed. *Env* gene fragments were quantified and cloned from cell-associated DNA or virion cDNA using a novel, high-throughput single-genome amplification method termed fluorescence-assisted clonal amplification (FCA). Clonal sequences were checked for hypermutation using the Hypermut algorithm. Coreceptor specificities of clonal sequences were predicted using the Geno2pheno algorithm. Maximum-likelihood phylogenetic trees were reconstructed from alignments of non-hypermutant clonal sequences using the general time-reversible model of substitution with gamma distribution. Compartmentalization was assessed by Slatkin-Maddison testing.

Results: Levels of HIV genomic DNA were indistinguishable in CM and EM cells from HIV controllers. By contrast, *env* DNA sequences from these two subsets diverged markedly, with genetic compartmentalization between CM and EM in all 6 controllers studied. No clonal sequence from any controller was predicted to be X4-tropic, and few sequences were hypermutant (CM median 3.9% of all sequences per donor, range 0-22.7%; EM median 2.15%, range 0-9.5%). Sequences from CM cells were more closely related to sequences from plasma virions than were sequences from EM cells, with CM/plasma compartmentalization in 3/6 controllers and EM/plasma compartmentalization in 6/6. Average genetic distances between groups of clonal sequences were smaller between CM and plasma than between EM and plasma. Phylogenetic trees from controllers but not from two untreated subjects with viral loads >20,000 copies/mL showed large clusters of matching sequences, often separated by large genetic distances. Several large clusters represented HIV clones with truncations in gp120, suggesting non-viable proviruses amplified by T cell clonal expansion.

Conclusions: The population of productively infected CD4 T cells in HIV controllers is very small. This is particularly true in the EM subset, where most cells harboring HIV DNA appear to have expanded from a few non-productively infected precursors. The key focus of ongoing HIV replication in controllers may be a tissue site containing CM-like cells.

81 Accelerated Viral Load Increase and CD4 Decline in HIV-1 Superinfected Women

Keshet Ronen[1], Barbra Richardson[1], Susan Graham[2], Kishor Mandaliya[3], Walter Jaoko[4], Scott McClelland[2], Julie Overbaugh[1]

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Background: HIV superinfection (SI) has been detected at a substantial rate in several settings, but its impact on disease course remains poorly characterized. Understanding the consequences of SI has important implications for counseling HIV-infected individuals, as well as estimating transmission risk in epidemic modeling. Prior studies have suggested that SI may lead to a transient increase in viral load (VL) and sustained acceleration in VL increase

over time, however these studies were small (analyzing 2-12 cases of SI) or did not distinguish between coinfection and SI. We recently screened a cohort of HIV-infected high-risk women in Mombasa, Kenya, for superinfection. Among 145 women singly infected at baseline, 21 acquired SI during follow-up.

Methodology: Detailed clinical and laboratory data collected at quarterly intervals were used to compare disease progression between superinfected and singly infected women from the Mombasa cohort. Linear mixed effects models were used to compare post-acute VL and CD4 counts over time. Cox proportional hazards analysis was used to determine the effect of SI on time to clinical progression (CD4 < 200, ART initiation or death).

Results: Overall, 124 singly infected and 21 superinfected women contributed 925 person-years of follow-up, during which 1788 VL and 1532 CD4 counts were collected and 91 progression events occurred. VL increased more rapidly following SI than during single infection (increasing at 0.14 vs. 0.08 log10 copies/ml/year respectively, p=0.04). Conversely, CD4 counts decreased more rapidly in SI cases than singly infected women (at 1.57 vs. 0.97 √CD4+cells/ml/year respectively, p=0.05). Prior to SI acquisition, there was a trend for ultimately superinfected women having lower setpoint VL than singly infected women (-0.37 log10 copies/ml, p=0.09). Adjustment for viral subtype, genital infection at HIV acquisition and HLA alleles reported to modify HIV progression had negligible effect on the results. We did not detect a significant effect of SI on time to clinical events, though this may have been due to limited statistical power. We also did not detect transient changes in VL or CD4 at the time of SI detection, though sampling was not optimal for this analysis.

Conclusions: This is the largest study to date examining the effect of SI on HIV progression. Our findings suggest that SI may accelerate disease progression and, through elevated VL, increase infectivity, arguing for greater awareness among clinicians and patients of the consequences of SI. Additionally, the observation that VL setpoint may be lower pre-SI than in women who remain singly infected suggests that low initial viral replication may be associated with SI, prompting further investigation of viral fitness and immune responses in the setting of SI.

82 Selection for Active SAMHD1 Antagonism in Natural Infections of SIVagm

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Background: The restriction factor SAMHD1, an effector of the innate immune response to viral pathogens, blocks retroviral reverse transcription in myeloid cells and resting CD4+ T-cells. Many retroviruses, including HIV-2 and other related Simian Immunodeficiency Viruses (SIVs), encode accessory genes that serve to counteract host SAMHD1 restriction by inducing the degradation of this antiviral factor. The viral accessory protein Vpr is responsible for SAMHD1 degradation in some lineages of lentiviruses, while in others, the related protein Vpx assumes this task. However, HIV-1 has no SAMHD1 degradation capability, leading to questions about whether or not there is a selective advantage to this activity.

Methodology: We used an evolutionary approach to examine the importance of SAMHD1 antagonism for viral fitness by studying adaptation to host in the context of natural SIV infections. Though African Green Monkeys (AGMs) comprise four related species, each population is infected with a distinct subtype of SIVagm, providing a unique opportunity to study the evolutionary forces governing virus-host interactions. We sequenced SAMHD1 from 50 AGMs representing four host species to identify SAMHD1 polymorphism which could alter Vpr specificity. We then determined how Vpr proteins from different SIVagm subtypes are capable of mediating degradation of each of the different AGM SAMHD1 variants.

Results: We found multiple SAMHD1 haplotypes in AGMs which are differentially sensitive to degradation by Vpr from SIVagm subtypes. SIVagm Vprs are capable of inducing the degradation of the major SAMHD1 alleles found in their host population, but are often incapable of degrading SAMHD1 found in other populations. The specificity of Vpr for SAMHD1 involves both the N- and C-terminal regions of SAMHD1 and this specificity has evolved independently from adaptations of other Vpr proteins for their host SAMHD1.

Conclusions: We conclude that SIVagm has adapted to the SAMHD1 polymorphisms of the AGM population in which it is found. Evidence of viral adaptation to host restriction indicates that SAMHD1 antagonism is actively maintained in natural infections and that this function must be advantageous to viral fitness, despite its absence in HIV-1.

83 Probiotic and IL-21 Treatment Promotes Th17 Cell Recovery in ARV-Treatment of Pigtail Macaques

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Background: Loss of GI tract-resident, IL-17/IL-22-producing lymphocytes correlates inversely with HIV disease progression and often persists despite prolonged antiretroviral (ARV) therapy. Recent findings have indicated that incomplete immunological reconstitution following ARV-treatment stems from a persistent dysbiosis of commensal microbiota, which directly inhibits Th17 differentiation and maintenance. We have previously demonstrated that oral probiotics promote increased intestinal CD4+ T-cell reconstitution, but not Th17 recovery, during ARV treatment in a non-human primate model of HIV infection. In this study, we sought to promote Th17 cell recovery by administering IL21 to ARV-treated, probiotic-supplemented, SIV-infected macaques.

Methodology: We treated 11 SIVmac239-infected, pigtail macaques (PTM) at day 90 post-infection with the ARVs L'812, PMPA and FTC and with or without probiotic (VSL#3) and IL21. We evaluated treatment efficacy by tracking SIV viremia by RT-PCR and systemic immune function by multi-parameter flow cytometry, ELISA and immunohistochemistry.

Results: Probiotic and IL21-supplementation of ARVs in SIV-infected PTMs promoted intestinal B-cell expansion, CD4+ T-cell reconstitution, and led to increased Th17 frequency and polyfunctionality. Our treatment was not associated with increased viral load nor was there evidence of increased immune activation. Importantly, treatment resulted in significantly fewer subclinical opportunistic infections and ARV-associated complications as compared to ARV-only control animals.

Conclusions: Our results are the first to demonstrate in vivo Th17 recovery in a non-human primate model of progressive HIV infection. By directly targeting microbial dysbiosis and defective Th17 differentiation, probiotic and IL21 supplementation to ARV treatment improved GI tract immunological functionality. Probiotic and IL21 supplementation of ARV treatment was well tolerated and further associated with reduced disease incidence as compared to ARV-only animals. We propose that combining ARVs with therapeutics aimed at restoring intestinal stasis will significantly improve disease prognosis of ARV-treated, HIV-infected, individuals.

Session O-7 Oral Abstracts

10:00 AM – 12:15 PM **Ballroom B/C**

Randomized Controlled Trials and Antiretroviral Resistance

84LB First-Line RAL + DRV/r Is Non-Inferior To TDF/FTC + DRV/r: The NEAT001/ANRS143 Randomised Trial

François Raffi[1], Abdel G. Babiker[2], Laura Richert[3], Jean-Michel Molina[4], Elizabeth C. George[2], Andrea Antinori[5], Jose Arribas[6], Stefano Vella[7], Geneviève Chêne[3], Anton L. Pozniak[8], NEAT001/ANRS143 Study Group

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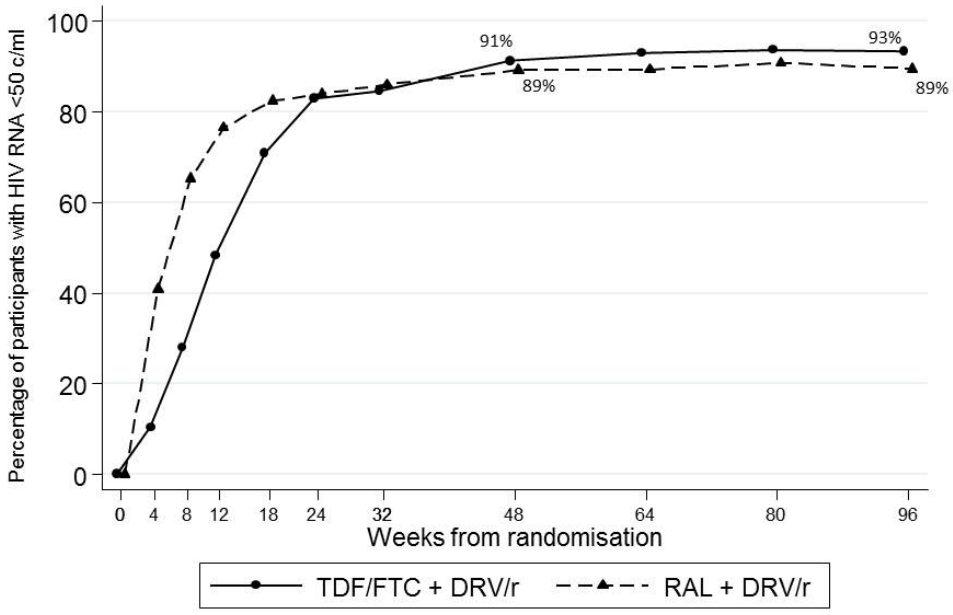
Background: NEAT001/ANRS143 is a randomised, open-label, non-inferiority study comparing efficacy, safety and tolerability of darunavir/ritonavir (DRV/r) plus either raltegravir (RAL) or tenofovir/emtricitabine (TDF/FTC) in antiretroviral (ARV) treatment-näive HIV-infected adults. We present the final results from the trial, which involved 78 clinical sites from 15 countries.

Methodology: Primary outcome was time to first occurrence of failure defined as virologic (change of treatment before W32 because of HIV RNA viral load (VL) drop < 1 $\log_{10}$ copies/mL (c/mL) by W18 or VL ≥ 400 c/mL at W24, or confirmed VL ≥ 50 c/mL at or after W32) or clinical (death, AIDS, serious non-AIDS events) by W96. The pre-defined non-inferiority margin was an absolute difference of at most 9% for the failure rate of RAL vs TDF/FTC in the intent-to-treat (ITT) analysis estimated by Kaplan-Meier methods. Major secondary endpoints included safety, changes in CD4 and HIV RNA, and genotypic resistance.

Results: There were 805 patients (88% men), with median age 38 years, VL 4.77 $\log_{10}$ c/mL, CD4 333 cells/µL, and 123 weeks' follow-up. Outcomes (RAL [n=401] vs TDF/FTC [n=404]) were as follows: 17.4% vs 13.7% met the primary endpoint (difference: 3.7%, 95% CI: -1.1%, 8.6%); 23.0% vs 19.8% either met the primary endpoint or stopped the randomised regimen for any reason (difference: 3.2%, 95% CI: -1.8, 8.2%); no significant difference in terms of serious adverse events (SAE) or grade 3 or 4 AE or treatment modifying AE (9.8 vs 8.0 per 100 person-years (py), log rank p=0.17; 9.5 vs 7.0 per 100 py, p=0.16; 4.1 vs 4.1 per 100 py, p=0.84, respectively). Percentage of participants achieving HIV RNA <50 c/ml over time from randomisation (ITT) is shown in the figure. Median CD4 increases at W96 were +267 (RAL) and +266 (TDF/FTC) cells/µL (p=0.92). Mean changes in creatinine clearance from baseline at W96 were +1.3 vs -4.1 mL/minute, p=0.004, and changes in total cholesterol/HDLc ratio were 0.0 vs 0.0, respectively (p=0.67). Treatment-emergent resistance was seen in 5/28 (RAL) vs 0/13 (TDF/FTC) patients with available genotype at failure.



N tests available	W0	W12	W24	W32	W48	W96
TDF/FTC+DRV/r	404	389	385	387	388	374
RAL + DRV/r	401	385	377	382	376	356

Conclusions: The nucleotide/nucleoside-sparing regimen RAL + DRV/r was non-inferior to TDF/FTC + DRV/r in terms of W96 virological/clinical efficacy, with similar immunological reconstitution, safety and tolerability, in first-line ARV therapy.

85 Efficacy and Tolerability of Atazanavir, Raltegravir, or Darunavir With FTC/Tenofovir: ACTG 5257

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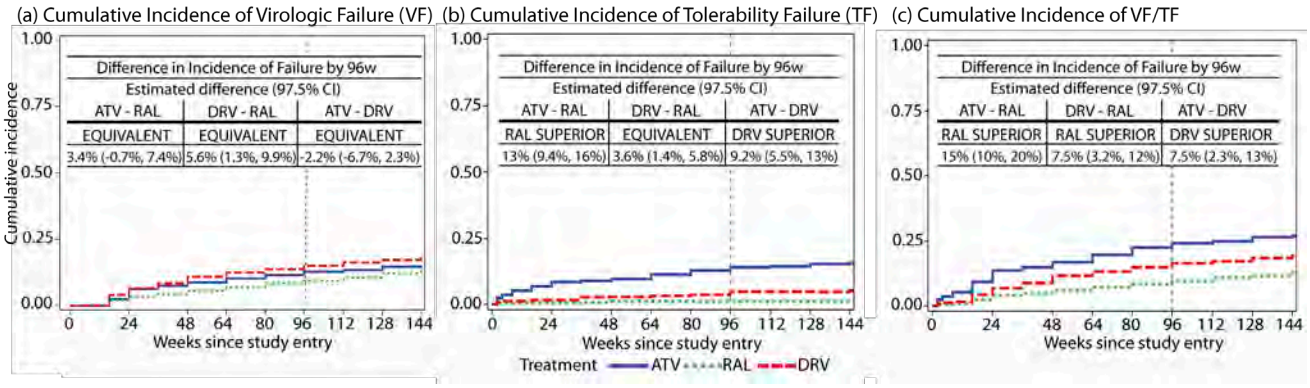
Background: Non-nucleoside reverse transcriptase inhibitor (NNRTI) based antiretroviral therapy (ART) is not suitable for all HIV-infected persons. A5257, a randomized, open label trial, was designed to provide rigorous evaluation of virologic efficacy and tolerability of three NNRTI sparing preferred initial ART regimens.

Methodology: ART naïve persons ≥ age 18 years with HIV-1 RNA (VL) >1000 copies/ml (c/ml) without study regimen resistance were eligible. Subjects were randomized 1:1:1 to ATV (atazanavir 300 mg QD + ritonavir 100 mg QD [RTV]), RAL (raltegravir 400mg BID) or DRV (darunavir 800mg QD + RTV) ; all subjects received FTC/tenofovir QD. Subjects were followed until the last enrolled reached 96 weeks (w). The primary objective was to demonstrate regimen equivalence with regard to virologic efficacy and tolerability over 96w. The virologic endpoint was time to virologic failure (VF), defined from study entry to confirmed VL >1000 c/ml (w16 to before w24) or >200 c/ml (≥w24); time to tolerability failure (TF) was from entry to discontinuation of ATV, RAL or DRV for toxicity. 600 subjects per arm provided 90% power to show equivalence in pairwise comparisons. Equivalence was defined as a 2-sided 97.5% confidence interval (CI) on the difference in 96w cumulative incidence of VF entirely within ±10%; comparisons of TF and composite VF/TF were similarly defined. If equivalence was not shown, superiority was assessed by exclusion of 0 from the CI (pre-planned).

Results: 1809 eligible subjects enrolled: 34% non-Hispanic white, 42% non-Hispanic black, 22% Hispanic. 24% were women. Mean entry VL was 4.6 log10 c/ml; 69% had VL <100,000 c/ml. Mean baseline CD4 cell count was 308/mm3; CD4 was <200/mm3 for 30%. 92% of subjects completed 96w on study. ATV, RAL and DRV were equivalent with respect to VF (Fig a); VL was ≤50 c/ml in 88%, 94% and 89% for ATV, RAL and DRV, respectively at 96w (intent to treat). 14%, 1% and 5% discontinued ATV, RAL and DRV, for toxicity largely due to clinical jaundice and hyperbilirubinemia with ATV; other discontinuations were similarly distributed across arms. In comparisons of TF, ATV was inferior to RAL and DRV (b). For the composite VF/TF endpoint, RAL was superior to ATV and DRV; DRV was superior to ATV (c).

Conclusions: High and equivalent rates of virologic control were attained for all regimens. RAL was superior to both ATV (largely due to elevated bilirubin) and DRV (driven by both virology and differences in gastrointestinal toxicity) when considering TF and VF together.



86 Attachment Inhibitor Prodrug BMS-663068 in ARV-Experienced Subjects: Week 24 Analysis

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Background: New antiretrovirals (ARVs) are needed for treatment-experienced (TE) HIV+ patients due to the development of resistance and the long-term safety and tolerability issues observed with existing agents. BMS-663068 is a prodrug of BMS-626529, an attachment inhibitor that binds directly to HIV-1 gp120, preventing the initial interaction between virus and host cell. This study is investigating the safety, efficacy and dose-response of BMS-663068 versus atazanavir/ritonavir (ATV/r) in TE HIV-1 infected subjects.

Methodology: AI438011 is an ongoing Phase 2b, randomized, active-controlled trial, blinded to BMS-663068 dose. TE adults (≥1 week exposure to ≥1 ARV) with viral loads (VL) ≥1,000 c/mL and susceptibility to all study drugs (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. A lead-in monotherapy substudy was performed in approximately 10 subjects per BMS-663068 arm. The primary endpoints were the proportion of subjects with HIV-1 RNA <50 c/mL at Week 24 and the frequency of SAEs and AEs leading to discontinuations through Week 24.

Results: Overall, 254 subjects were randomized and 251 were treated across all arms. The median age was 39 years and 60% were male. The median VL was 4.85 $\log_{10}$ c/mL (43% of subjects had VL > 100,000 c/mL) and the median CD4 count was 230 cells/mm^3 (38% had < 200 CD4 cells/mm^3). Across

all arms, 20-40% had baseline NRTI/NNRTI resistance. Subjects electing to undergo 7 days of BMS-663068 monotherapy (n = 32) showed average VL reductions of 0.7 to 1.5 $\log_{10}$ c/mL at Day 8 (Table). Through Week 24, 69-80% of BMS-663068-treated subjects and 75% of ATV/r-treated subjects had HIV-1 RNA <50 c/mL (Table, modified Intent-To-Treat [mITT] FDA Snapshot). Similarly, 78-87% of subjects in the BMS-663068 arms had HIV-1 RNA <50 c/mL at Week 24 compared with 86% of subjects on ATV/r in the observed analysis (Table). All BMS-663068 doses were well tolerated and no SAEs or AEs leading to discontinuation were related to BMS-663068.

Conclusions: In a TE population, the attachment inhibitor BMS-663068, in combination with RAL and TDF, showed favorable safety and tolerability profiles, with similar efficacy in both mITT and observed analyses in comparison with ATV/r through Week 24. These results support the continued development of BMS-663068.

Monotherapy Substudy and Week 24 Primary Study Results					
	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	
Monotherapy Substudy, N	7	5	10	10	NA
Day 8 mean change from baseline in plasma HIV RNA ($\log_{10}$ c/mL)	-0.7	-1.4	-1.2	-1.5	NA
Primary Study mITT, N (FDA SnapShot algorithm)	50	49	51	50	51
HIV RNA <50 c/ml, n (%)	40 (80)	34 (69)	39 (77)	36 (72)	38 (75)
HIV RNA <400 c/ml, n (%)	46 (92)	39 (80)	46 (90)	40 (80)	42 (82)
Primary Study Observed, N (Subjects with data within Week 24 window)	46	42	50	43	44
HIV RNA <50 c/ml, n (%)	40 (87)	34 (81)	39 (78)	36 (84)	38 (86)
HIV RNA <400 c/ml, n (%)	46 (100)	39 (93)	46 (92)	40 (93)	42 (95)
ATV/r, ritonavir-boosted atazanavir; mITT, modified intent-to-treat; TDF, tenofovir disoproxil fumarate; RAL, raltegravir					

87 Sensitive Screening Reveals Widespread Underestimation of Transmitted HIV Drug Resistance

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Background: Our previous studies using sensitive testing to better assess transmitted HIV drug resistance were limited to a few large urban areas. Here we applied sensitive resistance screening on a population drawn from broader geographic regions and population densities in the United States.

Methodology: We used validated allele-specific PCR assays to screen 1070 de-identified plasma specimens collected in 2009-2011 within 3 months of HIV diagnosis from persons with no reported evidence of antiretroviral drug use. We focused on five RT mutations as sentinel markers of transmitted drug resistance, comprised of the historically frequently transmitted mutations, M41L, K103N, Y181C, and M184V, and a rare but clinically important mutation, K65R. The screening assays are capable of detecting resistant minority variants above random quasispecies noise at levels 10-100-times below what conventional bulk genotyping can detect. We determined the prevalence of transmitted resistance by demographic characteristics and used chi-square tests to compare percentages.

Results: Transmission prevalence of the five mutations with sensitive testing (16.6%) was 2.1-times that detected by conventional sequencing (7.9%) ($p<0.0001$). The increase was least for K103N (7.0% to 8.4%, 1.2-times), and greatest for K65R (0% to 1.7%). One-third of the K65R mutations were in samples with ≥1 of the other four mutations screened. The study population was 54% black, 29% white, 71% men who have sex with men (MSM), 14% female, and the major age group was 20-29 years (40%). By race/ethnicity, the prevalence of transmitted resistance by sensitive screening for whites (16.4%) and blacks (14.9%) were both significantly higher than for Hispanics/Latinos (6.4%) ($p=0.005$ and 0.013, respectively). By age, resistance prevalence was highest (23.1%) in those 13-19 years (85% were black) followed by 50-59 years (17.7%). Additionally, the 14.3% drug resistance prevalence identified in women (72% were black) was nearly the 15.1% prevalence observed for MSM (47% were black). Transmitted resistance prevalence in population densities of <50,000, 50,000-499,999, and ≥500,000 was 16.4%, 16.3%, and 13%, respectively ($P=0.13$).

Conclusions: The majority of transmitted resistance in this population was not detected by conventional testing. HIV transmission involving resistant virus was similar across genders and population densities. A substantial drug resistance burden was identified in the <20 year olds, who were predominantly black. The findings highlight the importance of sensitive testing for accurate drug resistance screening and underscore the importance of prevention efforts for at-risk youth.

88 Transmitted HIV-1 Drug Resistance Between Partner-Pairs

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Background: Population-based studies suggest that drug resistant HIV-1 is less likely to be transmitted than drug-susceptible viruses. We aimed to evaluate the likelihood of transmission of HIV-1 drug resistance between confirmed partner-pairs.

Methodology: Persons with primary HIV-1 infection have enrolled in an observational cohort at the University of Washington Primary Infection Clinic (PIC) since 1992. We attempted to identify sex partners of PIC enrollees. Partial gp120 env sequences were generated from transmitting and recipient partners, and relationships were confirmed by phylogenetic linkage and genetic distance analysis. Drug resistance mutations in pol encoding Pro and RT regions were assessed by pyrosequencing of >100 viral templates from plasma RNA and PBMC DNA from partner-pairs enrolled after 1995. We considered a mutation to be present if found in >1% of pyrosequences.

Results: Since 1992, 36 (72%) of 50 partner-pairs have had genetically linked infections. Plasma RNA and PBMC DNA specimens for pyrosequencing were obtained from 31 male recipient partners a median of 23 (IQR 18-40) and 29 (IQR 21-52) days after infection, respectively. Plasma and PBMC specimens from the 30 male and one female transmitter were obtained a median of 22 (IQR 2-66) and 29 (IQR 2-94) days after the estimated date of HIV-infection of the recipient. 13 (42%) transmitters had 1-4 drug resistance mutations (total=25) detected at a median frequency of 6.0% (IQR 1.5-98.6%, range 1.0-99.5%). 11 of these 25 mutations were present in the HIV-1 population of the transmitter at a frequency >95%; 100% of these majority variants were detected in the recipient. 14 mutations were present as minority variants in the transmitter, ranging from 1.0-11.8% of the viral population; 2 (14%, 95% CI 1.8-42.8%) were detected in PBMCs of the recipient at levels above 1%. If drug resistance does not impact "transmission fitness" and if drug resistant variants are transmitted independently, then the probability of transmission would be dependent on the frequency of the variant in the viral population of the transmitter. In this case, the likelihood that two or more of the minority variants would have been identified in recipient partners is 5.3%, which is less than our point estimate but falls within the 95% CI. Requiring further investigation, 10 recipients had 12 mutations identified in PBMCs at a median of 2.0% (IQR 1.3-4.0, range 1.1-99.6%) that were not detected in plasma or PBMCs of the transmitter.

Conclusions: Drug-resistant HIV-1 variants are more likely to be transmitted when present as majority variants compared to those present as minority variants. This study does not support crude population-level data that HIV-1 drug resistance reduces "transmission fitness" compared to drug-susceptible viruses.

89 Silent Mutations in HIV-1 Subtype B Reverse Transcriptase Selected by ART Restore Viral Fitness

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Background: Most mutations selected during antiretroviral therapy (ART) are non-synonymous (i.e. result in an amino acid change). However, silent mutations, K65K and K66K, in HIV-1 reverse transcriptase (RT) occur in over 35% of highly experienced patients and are among the most commonly selected mutations in subtype B strains. K65K/K66K are associated with thymidine analogue mutations (TAMs) including D67N+K70R and interrupt a homopolymeric nucleotide region introduced by D67N; however their impact in the context of HIV-1 replication is unknown. We hypothesise that silent mutations alleviate viral fitness defects conferred by D67N+K70R.

Methodology: The impact of K65K/K66K in the HIV-1 subtype B clone NL4.3 harboring the TAMs D67N+K70R on drug resistance and fitness was determined using in vitro drug susceptibility and growth competition assays. The mechanism of the fitness advantage conferred by K65K/K66K was assessed by analyzing virions produced by transfection and single-cycle infection assays, qPCR quantitation of intracellular reverse transcription products, and evaluation of cDNA synthesis efficiency by recombinant HIV-1 RT from RNA templates with D67N+K70R +/- K65K or K66K using a quantitative product enhanced reverse transcription (qPERT) assay.

Results: K65K/K66K did not alter susceptibility to zidovudine (ZDV), tenofovir (TFV), abacavir or nevirapine in MT-2 cells ($p>0.05$, $n=4$) or the infectivity of virus (normalized to p24) produced by transfection or from single-cycle infection assays. However, we found that K65K/K66K alleviated fitness defects conferred by D67N+K70R following multiple rounds of replication in the absence or presence of ZDV and TFV in MT-2 and in peripheral blood mononuclear cells. TAMs and silent mutations did not affect virion-associated RT activity or steady-state RT levels in virions produced by HIV plasmid transfection of MT-2 cells. No impact of K65K/K66K on early and late intracellular reverse transcription products in a single-cycle assay was detected. In contrast, using a highly sensitive qPERT assay, D67N+K70R in the RNA template resulted in an 8% decreased synthesis of a 111 nucleotide cDNA product compared to wild-type (WT) RNA ($p=0.028$, $n=4$) and this defect was restored by either K65K or K66K to WT levels.

Conclusions: Silent mutations in HIV-1 subtype B RT selected during ART alleviate fitness defects caused by TAMs and have no direct impact on drug susceptibility. The fitness advantage conferred by K65K/K66K is likely due to their ability to alleviate pausing by RT at homopolymeric stretches of nucleotides introduced by TAMs. Our study provides an explanation for why silent mutations are strongly selected in drug-treated individuals and supports their role as novel compensatory mutations in vivo.

90 Reduced In Vivo Replicative Capacity of Drug-Resistant SHIV During Acute Infection

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Background: Drug resistance mutations reduce replicative fitness *in vitro* but this impact remains poorly defined *in vivo*. To better understand the *in vivo* replicative capacity of drug resistant viruses we used a macaque SHIV model and compared multiple viral markers of acute infection with either wildtype (WT) or drug-resistant SHIV containing the K65R or M184V resistance mutation.

Methodology: We measured plasma RNA (copies/ml) and proviral DNA (copies/10^6 cells) during 10 consecutive weeks following peak viremia in macaques infected with site-directed SHIV162p3 mutants containing the M184V (n=4) or K65R (n=6) mutations associated with resistance to emtricitabine or tenofovir. Levels were compared with those seen in macaques infected with WT SHIV162p3 (n=6). Proviral DNA was quantified using a double-stranded primer assay coupled with co-amplification of RNase P gene as an internal PBMC control. Plasma RNA was quantified by an RT-PCR assay containing an internal normalizer. The correlation between $\log_{10}$ transformed RNA and DNA levels was determined using the Pearson correlation coefficient. The slopes of the linear regressions were used to infer the ability of the viruses to initiate and spread infection. The effect of K65R and M184V on replicative capacity was evaluated *in vitro* using a competition assay with WT SHIV.

Results: $SHIV_{K65R}$ and $SHIV_{M184V}$ were rapidly outcompeted by WT SHIV *in vitro* with a decay half-life of 1.3 and 2.2 days, respectively. RNA and DNA levels correlated well during acute WT (r=0.98; p<0.0001), K65R (r=0.95; p<0.0001), or M184V (r=0.85; p=0.004) infections. Peak RNA but not DNA levels were significantly lower in K65R and M184V infections compared to WT infections (p<0.05). Viral RNA to proviral DNA ratios for K65R (1.8±0.2 $\log_{10}$) and M184V (1.6±0.4 $\log_{10}$) infections were also reduced by 90% and 93.7% relative to WT (RNA/DNA ratio of 2.8±0.2 $\log_{10}$; p=0.006 and p=0.017, respectively).

Conclusions: In this well-controlled macaque model we show that measurement of viral RNA to proviral DNA ratios during acute infection reveals the *in vivo* effect of drug resistance mutations on virus fitness. Our findings documenting reduced acute replication of M184V and K65R mutants suggest that infection with these viruses has the potential to alter acute virus dynamics and influence disease progression.

91LB 744 and Rilpivirine as Two-Drug Oral Maintenance Therapy: LAI116482 (LATTE) Week 48 Results

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Background: GSK1265744 (744) is an HIV integrase inhibitor (INI) under development as both an oral tablet and long-acting (LA) injectable. LATTE was designed to select an oral dose of 744 and to evaluate a two drug ART regimen with rilpivirine (RPV), as suppressive maintenance therapy. A separate study to evaluate 744 LA + RPV LA is planned.

Methodology: 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 744 10 mg, 30 mg, 60 mg or efavirenz (EFV) 600 mg with TDF/FTC or ABC/3TC through W24, followed by a two drug oral maintenance regimen of 744 + RPV 25 mg through W96 (ongoing).

Results: 243 patients (Pts) were randomized and treated (ITT-E): 96% male, 38% non-white, 16%>100,000 c/mL HIV-1 RNA, 61% TDF/FTC. Plasma HIV-1 RNA declined rapidly across all 744 doses with no differences by NRTI. 744 Pts with a VL <50 c/mL immediately prior to W24 discontinued NRTIs and began RPV 25 mg; no change was made to the EFV arm. 207 Pts were treated in the ITT-Maintenance Exposed (ITT-ME) population. At W48, 82% of 744 + RPV Pts and 71% of EFV Pts were <50 c/mL by Snapshot (ITT-E). Amongst Pts who began 744 + RPV at W24, 93% were <50 c/mL by Snapshot at W48 (ITT-ME), with similar response rates for all 744 doses. Three virologic failures occurred during Maintenance (744 10 mg, 744 30 mg , EFV). One Pt on 744 10 mg + RPV, with very low 744 and RPV drug exposures, developed virologic failure at W48 with treatment-emergent INI (Q148R) and NNRTI (E138Q) resistance mutations. Drug-related AEs ≥ Grade 2 were reported by 14% and 19% of 744 and EFV Pts, respectively. Drug-related AEs ≥ Grade 2 during Maintenance were uncommon, 744 (4%) and EFV (4%). SAEs occurred in eleven 744 Pts (none related); and three EFV Pts (one related - suicide attempt). Fewer 744 Pts withdrew due to AEs (3%), than EFV Pts (13%). Treatment emergent max lab abnormalities ≥ Grade 3 occurred in 21% (744) and 31% (EFV) of Pts through W48. Rates of any graded ALT elevations were 17% (744) and 21% (EFV).

Conclusions: Oral 744 + NRTIs was well tolerated with good antiviral activity at all doses through W24. When used as maintenance therapy in virologically suppressed Pts, the two drug regimen 744 + RPV provided similar antiviral activity to EFV+NRTIs through the W48 primary analysis. 744 + RPV was safe and well tolerated across all 744 doses. These data support further development of 744 and the planned evaluation of 744 LA + RPV LA as an injectable regimen for HIV treatment.

	744 10 mg (n=60)	744 30 mg (n=60)	744 60 mg (n=61)	744 Subtotal (n=181)	EFV control (n=62)
Mean baseline HIV-1 RNA (log_{10} c/mL)	4.42	4.27	4.43	4.37	4.29
%<50 c/mL at W24 Snapshot (ITT-E) (95% CI)	52 (87%) (78%,95%)	51 (85%) (76%,94%)	53 (87%) (78%,95%)	156 (86%) (81%,91%)	46 (74%) (63%,85%)
%<50 c/mL at W48 Snapshot (ITT-E) (95% CI)+	48 (80%) (70%,90%)	48 (80%) (70%,90%)	53 (87%) (78%,95%)	149 (82%) (77%,88%)	44 (71%) (60%,82%)
%<50 c/mL at W48 Snapshot (ITT-ME) (95% CI)+	48/52 (92%) (85%,100%)	48/5 (91%) (83%,98%)	53/55 (96%) (91%,100%)	149/160 (93%) (89%,97%)	44/47* (94%) (87%,100%)
Median Baseline CD4+ cells/mm^3 (change from Baseline at W48)+	415 (+203)	404 (+235)	420 (+240)	412 (+219)	417 (+227)

*EFV Pts with a W24 visit (n=47)
+W48 represents a 24 Week Induction Period followed by a 24 Week Maintenance Period
Intent to Treat-Exposed (ITT-E) and Intent to Treat-Maintenance Exposed (ITT-ME)

92LB Safety and Antiviral Effect of MK-1439, A Novel NNRTI (+FTC/TDF) in ART-Naive HIV-Infected Patients

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Background: MK-1439 is an investigational NNRTI active in vitro against both wild type HIV and most common NNRTI resistant variants at concentrations achieved with once daily (qd) dosing.

Methodology: Double-blind, randomized, dose-ranging study to examine the safety, tolerability and efficacy of 4 MK-1439 dose levels (25, 50, 100 and 200 mg qd) vs efavirenz (EFV) 600 mg qhs, each in combination with qd emtricitabine/tenofovir (FTC/TDF) in ART-naïve HIV-1 infected patients (pts) with baseline vRNA > 1000 c/mL, stratified by vRNA ≥ or <100,000 c/mL. The primary efficacy endpoint is the proportion of pts with vRNA <40 c/mL at week 24.

Results: Of 210 pts randomized, 208 were treated (n=40-43 per treatment group) and were of mean age 37 years, 91% male and 74% white; 12% had AIDS. Baseline vRNA was >100,000 c/mL in 28% of pts (median 4.6 log_{10} c/mL) and mean CD4 cell count was 417 cells/μL. Main week 24 results are shown below.

			Proportion of Patients with Virologic Response (95% CI)		Mean CD4 Change from Baseline (95% CI)
Treatment† (mg)		N	vRNA < 40 c/mL	vRNA < 200 c/mL	cells/μL
MK-1439 qd	25	40	80.0 (64.4, 90.9)	85.0 (70.2, 94.3)	158 (119, 197)
	50	43	76.2 (60.5, 87.9)	85.7 (71.5, 94.6)	116 (77, 155)
	100	42	71.4 (55.4, 84.3)	92.9 (80.5, 98.5)	134 (100, 167)
	200	41	78.0 (62.4, 89.4)	90.2 (76.9, 97.3)	141 (96, 186)
Efavirenz qhs	600	42	64.3 (48.0, 78.4)	81.0 (65.9, 91.4)	121 (73, 169)
Missing data approach:			Non-completer = Failure		Observed Failure

†In combination with FTC/TDF

Clinical adverse events (AEs) were reported by 135 (81%) of the 166 pts who received MK-1439 (any dose) and by 34 (81%) of the 42 pts who received EFV, and were considered drug-related (DR) in 35% and 57%, respectively. Serious AEs were reported in 3% and 7%, respectively; none were considered DR. The most common DR clinical AEs were abnormal dreams (9% of all MK-1439 pts; 7% of EFV pts), dizziness (3%; 24%), nausea (8%; 2%), fatigue (7%; 5%), and diarrhea (5%; 10%), and generally mild to moderate. The following DR AEs led to discontinuation in 2% of pts receiving MK-1439 (all doses) and 5% of pts receiving EFV: stupor, abdominal pain/nausea/insomnia, sleep disorder, and hallucinations (1 pt each) for MK-1439, and right-sided dysesthesia and hallucinations (1 pt each) for EFV. By week 8, CNS AEs (all causality) were seen in 18%, 35%, 14% and 15 %, in the 25mg, 50mg, 100mg, and 200mg MK-1439 groups (20% overall), and 33% in the EFV group. Grade 1 elevations in AST, ALT, LDL and total cholesterol were more common for EFV vs. any MK-1439 group.

Conclusions: In ART-naïve, HIV-1 infected pts, MK-1439 25, 50, 100, and 200 mg qd in combination with FTC/TDF demonstrated potent antiretroviral activity as compared with EFV, and was generally well tolerated at 24 weeks. No dose-response trend was observed for MK-1439; all MK-1439 dose groups had numerically greater virologic response rates than EFV. All groups showed increased CD4 counts. Safety and tolerability appeared comparable among the MK-1439 dosing groups, with fewer DR AEs compared with EFV.

Session O-8 Oral Abstracts
10:00 AM – 12:00 PM **Ballroom A**
TB and Other Coinfections

93 A Phase 2 Trial of a Rifapentine Plus Moxifloxacin-Based Regimen for Pulmonary TB Treatment

Marcus B. Conde[1], Solange C. Cavalcante[2,3], Margareth Dalcolmo[4], Fernanda Mello[1], Rafael Duarte[5], Carla Loredo[5], Valeria Rolla[4], Betina Durovni[2,3], Silvia Cohn[6], Richard E. Chaisson[6], **Susan E. Dorman**[6]

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Background: Potent combination chemotherapy may allow reduction in duration of treatment required for drug-susceptible pulmonary TB. In the mouse model of TB treatment, intensive phase regimens containing rifapentine plus moxifloxacin have robust sterilizing activity. We assessed the antimicrobial activity, safety, and tolerability of a dual-substitution regimen containing rifapentine substituted for rifampin plus moxifloxacin substituted for ethambutol during the first 8 weeks (intensive phase) of pulmonary TB treatment.

Methodology: Adults with sputum smear-positive pulmonary TB were randomly assigned to an investigational regimen of rifapentine 7.5 mg/kg/day plus moxifloxacin 400 mg/day plus isoniazid and pyrazinamide (PMHZ), or a control regimen of rifampin 10 mg/kg/day plus ethambutol plus isoniazid and pyrazinamide (REHZ). Directly-observed treatment was administered 7 days/week for 8 weeks. Sputum was collected weekly for culture on solid Lowenstein Jensen (LJ) and liquid MGIT media. Outcomes were treatment discontinuations, adverse events, and stable culture conversion at the end of intensive phase. A modified intention-to treat (MITT) group was comprised of participants with drug-susceptible TB, and a per-protocol group was comprised of MITT participants who in addition completed assigned treatment in ≤71 days and had an evaluable end-of-intensive phase culture.

Results: 121 participants were enrolled (69% male, 76% with cavitation on chest x-ray). Proportions of participants who discontinued assigned treatment for any reason were 9/62 (15%) in the PMHZ arm vs. 8/59 (14%) in the REHZ arm (p=0.88). Discontinuations due to toxicity were 4/62 (6%) in the PMHZ arm vs. 2/59 (3%) in the REHZ arm (p=0.44). A grade 3 or higher adverse event attributed to study treatment occurred in 6/62 (10%) in the PMHZ arm vs. 7/59 (12%) in the REHZ arm (p=0.70). Gastrointestinal, hepatic, and hematological toxicity did not differ between arms. In the MITT group, proportions with stable culture conversion at end of intensive phase on LJ medium were 51/60 (85%) in the PMHZ arm vs. 44/51 (86%, p=0.85) in the REHZ arm; and in MGIT medium were 39/46 (85%) in the PMHZ arm vs. 29/42 (69%, p=0.08) in the REHZ arm. In the per-protocol group, proportions with stable conversion at end of intensive phase in MGIT medium were 34/36 (94%) in the PMHZ arm vs. 27/37 (73%, p=0.01) in the REHZ arm.

Conclusions: The PMHZ regimen was well-tolerated and safe. The PMHZ regimen was more active than the REHZ regimen based on the surrogate endpoint of stable MGIT culture conversion at end of intensive phase. These results support evaluation of regimens containing rifapentine plus moxifloxacin for TB treatment shortening.

94 Tuberculosis Infection in Early Childhood in Uganda and the Influence of HIV Exposure

Carina Marquez[1], Gabriel Chamie[1], Jane Achan[2], Anne F. Luetkemeyer[1], Mary Kyohere[3], Grant Dorsey[1], Moses R. Kamya[2], Edwin D. Charlebois[1], Diane V. Havlir[1]

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Background: In high tuberculosis (TB) burden countries a significant proportion of the latent TB reservoir is established by age five; however, data on TB acquisition before age five is limited. Additionally, the risk of TB infection in HIV-exposed un-infected children (HEU), a growing group of children with a higher rate of mortality and impaired immune responses to infection compared to HIV-unexposed un-infected children (HUU), is unknown. We sought to address two knowledge gaps in the epidemiology of TB infection in early childhood: (1) the prevalence of TB infection in rural Uganda using an interferon gamma release assay (IGRA) and (2) the odds of TB infection in HEU vs. HUU children.

Methodology: We recruited children under 72 months from two well-characterized cohorts in Tororo, Uganda. We measured TB infection with the Quantiferon Gold in Tube IGRA (QFT-IT) and a tuberculin skin test (TST). A positive TST was defined as an induration greater than or equal to 10mm. Measurements were obtained from 450 children, 48% with HIV-infected mothers. The association between HIV exposure and TB infection in HIV-uninfected children was assessed using logistic regression controlling for age; this regression was restricted to the 254 children whose HIV-status was available due to their participation in the clinical cohorts.

Results: The children's median age was 35.3 months (IQR: 14.1 -39.5). 76% of children had a BCG scar, and there was no difference when stratified by HIV-exposure. 21% of children had a positive TST, 7% had a positive QFT-IT, and 2% had an indeterminate QFT-IT. Discordance was high between TST and QFT-IT, κ=0.14. The proportion of TST positive children decreased with age (p=0.03): 32% among children under 12 months, 21% among children 12-35 months, and 13% among children 36 to 72 months. QFT-IT positivity was not detected in children less than 11 months. QFT-IT positivity was 3% among children under 12 months, 12% among children 12-35 months, and 6% among children 36 to 72 months. HEU had a higher risk of TB infection as defined by positive TST or QFT-IT (OR 2.6 p=0.02) compared to HUU.

Conclusions: HEU had an increased risk of TB infection compared to HUU. We detected positive QFT-IT results as early as 11 months, suggesting TB acquisition is detectable with this assay in early childhood. These data support intensified prevention efforts in early childhood, especially for HEU children.

95 Effect of Xpert MTB/RIF On Early Mortality in Adults With Suspected TB: A Pragmatic Randomized Trial

Gavin Churchyard[1], Kerrigan McCarthy[1], Katherine L. Fielding[2], Wendy Stevens[3], Violet Chihota[1], Mark Nicol[4], Norbert Ndjeka[5], Alison D. Grant[2], David Mametja[5]

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Background: South Africa has phased in Xpert MTB/RIF, replacing sputum smear microscopy in laboratories, as the first-line diagnostic test for tuberculosis (TB). In a pragmatic cluster randomized trial, we evaluated the effect of Xpert on early mortality in persons with suspected TB.

Methodology: 20 laboratories in 4 provinces were randomized to intervention (immediate Xpert implementation) or control (microscopy, with Xpert implementation deferred) arms. At 2 primary health clinics served by each laboratory, a systematic sample of adults with suspected TB, identified by clinic staff, was invited to participate; demographic and clinical data relevant to TB and mortality risk were collected. Vital status after 6 months was determined by interview of participants or relatives and using the National Vital Status Register. The intervention effect on mortality risk was estimated using methods appropriate for cluster randomized trials with small number of clusters. An adjusted analysis was conducted to control for baseline differences of individual-level factors by study arm.

Results: Between June to November 2012, 4,972 persons with suspected TB were screened for the study. 4,712 (94.8%) were eligible and 4,665 (99.0%) contributed to the analysis. Of 4,665 participants (median age 36 years, 62% female, 93% South African), 76% (3,551) knew their HIV status, 62% (2,212/3,551) reported being HIV positive with a median self-reported CD4 count of 311 cells/mm^3, 33% of whom reported ever being on ART, all similar by study arm. Participants in the intervention vs. control arm had lower socioeconomic indicators and were more likely to be asymptomatic (7.5% vs. 4.3%). Among 4,665 participants, 4,617 (99.0%) had known vital status at 6 months, with 208 deaths (4.5%). The 6 month mortality risk in the intervention and control arms were 3.9% (91/2,326) and 5.0% (117/2,339) respectively (risk ratio [RR] 0.86, 95% CI: 0.58, 1.27, p=0.42). After adjusting for age, sex, BMI, HIV status and factors imbalanced at baseline, the adjusted RR was 1.08 (95% CI: 0.73, 1.61; p=0.67). The 6 month mortality risk for self-reported HIV positive vs. -negative participants was 5.6% (124/2,212) and 1.9% (26/1,339) respectively (RR 2.63 (95%CI: 1.68, 4.12, p<0.001); and for HIV positive participants on vs. not on ART was 4.1% (30/730) and 6.3% (94/1,482) respectively (RR 0.63, 95% CI: 0.41, 0.97, p=0.03).

Conclusions: HIV prevalence and all-cause mortality were high among people with suspected TB, and mortality was not reduced by Xpert replacing smear microscopy in laboratories. Our data suggest that a sensitive diagnostic test needs to be supported by systems linking to appropriate care, particularly ensuring that people know their HIV status and those eligible, start ART promptly.

96LB Xpert as the First-Line TB Test in South Africa: Yield, Initial Loss To Follow-Up, Proportion Treated

Katherine L. Fielding[1], Kerrigan M. McCarthy[2], Helen Cox[3], Linda Erasmus[4], Sibuse Ginindza[2], Anna Vassall[1], Lindiwe Mvusi[5], Chris Dye[6], Alison D. Grant[1], Gavin J. Churchyard[2]

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Background: South Africa has phased in Xpert MTB/RIF, replacing sputum smear microscopy in centralised laboratories, as the first-line test for tuberculosis (TB). In a pragmatic cluster-randomized trial, we evaluated the effect of Xpert implementation on yield, initial loss to follow-up and proportion treated.

Methodology: 20 laboratories in 4 provinces were randomized to intervention (immediate Xpert implementation) or control (microscopy; Xpert deferred) arms. At 2 primary health clinics per laboratory, a systematic sample of adults with suspected TB, identified by clinic staff, was enrolled. Laboratory results were obtained from the National Health Laboratory Service database, and TB treatment start dates from clinic registers or participant interview. Yield was defined as the proportion with a positive index Xpert or smear result. Initial loss to follow-up among participants with a positive index result was defined as not starting TB treatment within 28 days. The intervention effect was estimated using methods appropriate for cluster-randomized trials. An adjusted analysis controlled for baseline differences in individual-level factors.

Results: From June-November 2012, 4972 persons were screened, and 4656 (93.6%) enrolled (median age 36yrs, 62% female). More participants in the intervention vs. control arm were asymptomatic (7.4% vs. 4.3%) and fewer had BMI<18.5 (8.7% vs. 12.3%). Among 4412 participants (94.8%) with a laboratory test result available, the yield was greater in the intervention vs. control arm (9.2% (200/2176) and 7.8% (174/2236) respectively, (adjusted prevalence ratio 1.49 [1.00-2.23), p=0.05). Among 374 participants with a positive index test result, initial loss to follow-up was similar by study arm (intervention: 17% (34/200), control: 14.9% (26/174); adjusted risk ratio [aRR] 0.96, 0.48-1.93). Among 4656 participants, the proportion starting TB treatment by 6 months was similar by study arm (intervention vs. control: 10.8% (250/2324) vs 12.5% (291/2332) respectively, aRR 1.04 (0.76-1.43)).

Conclusions: Xpert increased the yield of TB by 49% but did not increase the proportion treated overall or reduce initial loss to follow-up. The increased yield has potential to be cost saving, and economic analyses are in progress. This analysis does not assess time to treatment rifampicin-resistant TB, which is a limitation. Maximising the benefit of Xpert scale-up requires strengthened health systems, particularly ensuring that people with positive test results start treatment promptly.

97LB 14 Day EBA Study of PA-824, Bedaquiline, Pyrazinamide and Clofazimine in Smear-Positive TB Patients

Andreas Diacon[1], Rodney Dawson[2], Christo Van Niekerk[3], Jane Hutchings[3], Stephen Murray[4], Robert Schall[5], Divan Burger[6], Dan Everitt[4], Carl Mendel[4]

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Background: Bedaquiline (B) and PA-824 (PA) have demonstrated potent bactericidal and sterilizing activity in combination with clofazimine (C) and pyrazinamide (Z) in murine models of TB. C is currently in use for multi-drug resistant TB, but its efficacy has not been established in controlled clinical trials. This study evaluated the 14 day early bactericidal activity (EBA) of C and Z alone and in combination with B and PA.

Methodology: This prospective, randomized, open label trial randomized subjects with newly diagnosed smear positive pulmonary DS-TB into 7 parallel treatment arms of equal size: 1) Isoniazid, rifampicin, pyrazinamide and ethambutol (H-R-Z-E); 2) C; 3) Z; 4) PA-B-Z; 5) PA-B-Z-C; 6) PA-B-C; 7) B-Z-C. C was administered as 300 mg/day x 3d, then 100 mg/d X 11d. Subjects were evaluated

through daily overnight sputum collections. Sputum was cultured on solid agar (CFU) and in liquid culture (TTP). The primary endpoint was the EBA_{CFU}(0-14) as determined by the rate of change in logCFU per ml sputum over days 0 - 14 and the secondary endpoint was the rate of change in log TTP over days 0-14, both analyzed by a Joint Bayesian Non-linear Mixed Effects Regression Model (JB-NLME). Minimum inhibitory concentrations (MIC) for B, PA and C were determined by microtiter assay on isolates from baseline sputum samples. The time over MIC (TMIC) was determined using day 14 pharmacokinetic (PK) data with and without correction for plasma protein binding.

Results: 105 subjects (11 HIV+) were enrolled. H-R-Z-E had bactericidal activity similar to prior studies, with an EBA_{CFU}(0-14)/day of 0.151, 95% CI [0.070; 0.231]. The PA-B-Z combination had an EBA_{CFU}(0-14)/day of 0.167, 95% CI [0.078; 0.256]. C had no EBA by CFU or TTP and did not add to the bactericidal activity of the studied combinations. The MIC_{90} of the isolates from baseline were similar to prior reports, with B = 0.029 ug/mL in all arms, PA = 0.06-0.125 ug/ml and C = 0.125 - 0.25 ug/ml. The TMIC, calculated both with and without taking into account plasma protein binding for B and PA was 100% for the majority of patients. The TMIC for C, calculated without taking into account plasma protein binding was 100%, but taking into account plasma protein binding was 0%, for the majority of patients.

Conclusions: The PA-B-Z combination had robust EBA and will be taken in to a trial of longer duration. C did not have demonstrable EBA alone or in combination over 14 days of therapy. These results are consistent with the finding that the TMIC was nearly 100% for all subjects across arms for B and PA, but was 0% for most subjects for C, when plasma protein binding was accounted for.

98 CTX Prophylaxis Discontinuation Among ART-Treated Adults: A Randomized Non-Inferiority Trial

Christina S. Polyak[1], Krista Yuhas[2], Benson Singa[3], Monica Khaemba[3], Judd Walson[2], Barbra Richardson[2], Grace John-Stewart[2]

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Background: Cotrimoxazole (CTX) prophylaxis is recommended by the WHO for all HIV-infected individuals in settings with high prevalence of HIV and infectious disease. These guidelines were developed prior to scale-up of antiretroviral therapy (ART). Following ART, the threshold for CTX discontinuation after ART initiation remains undefined in resource-limited settings. We conducted a randomized clinical trial among adults on ART to determine whether discontinuation of CTX was non-inferior to continued CTX prophylaxis in decreasing morbidity.

Methodology: From February 2012 to September 2013, we conducted a non-blinded non-inferiority randomized clinical trial of CTX prophylaxis cessation versus continuation among HIV-infected adults who had been on ART for >18 months and had CD4 >350mm3 (Clinical trials registration NCT01425073). The study was conducted in a large HIV Treatment Program in Homa Bay, Western Kenya, a region with endemic malaria. Participants were randomized to continue or discontinue CTX using block randomization and followed 3-monthly for 12 months with systematic ascertainment of malaria, diarrhea and pneumonia morbidity. Malaria was defined as rapid diagnostic test (RDT) or smear positive with fever. Primary endpoint was a composite of morbidity (malaria, pneumonia, and diarrhea) and mortality. A secondary endpoint was severe adverse events (SAEs) grade 3 or higher. Incidence rate ratios (IRRs) were estimated using Poisson regression with robust error variance. Analyses were intent-to-treat.

Results: Of 538 adults screened, 500 were eligible, enrolled and randomized; 250 to each arm. Median age was 40 years, 361 (72%) were women, and 442 (88%) of participants reported bednet use. Median enrollment CD4 count was 595 cells/mm3 and median ART duration was 4.5 years. These baseline characteristics did not significantly differ between arms. Retention was high with 245 (98%) participants completing 12-month follow-up in each group. Combined morbidity/mortality was significantly higher in the CTX discontinuation arm (IRR=2.27, 95% CI: 1.52-3.38; p<0.001), driven by malaria morbidity. There were 34 cases of malaria, 33 in the CTX discontinuation arm (IRR=33.02, 95% CI: 4.52-241.02; p=0.001). Diarrhea and pneumonia rates did not differ significantly between arms (IRR=1.36, 95% CI: 0.82-2.27, and IRR=1.43, 95% CI: 0.54-3.75, respectively). Rates of SAEs ≥Grade 3 did not differ significantly between arms (IRR=2.00, 95% CI: 0.90-4.44), with limited power to detect a difference.

Conclusions: CTX discontinuation among ART-treated adults in a region with endemic malaria results in increased incidence of clinical malaria but not pneumonia, diarrhea or combined severe SAEs compared to those who continue CTX.

Session O-11 Oral Abstracts
4:00 PM – 6:00 PM Room 312
Malignancies and Pharmacology

99 HIV and Elevated Cancer-Specific Mortality Following Cancer Diagnosis in the United States

Anna E. Coghill, Meredith S. Shiels, Eric A. Engels
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Background: HIV-infected individuals remain at increased cancer risk, despite advances in HIV treatment. In fact, prolonged life expectancy due to effective HIV treatment has resulted in greater numbers of HIV-infected persons reaching ages where cancer incidence is elevated. The combination of this increased opportunity to develop cancer at older ages as well as the established etiologic link between HIV and cancer incidence has resulted in an increasing number of individuals diagnosed with both diseases. This warrants examination of the role HIV may play in altering cancer patient survival, a question inadequately answered to date.

Methodology: We identified cancer cases from 5 U.S. cancer registries participating in the HIV/AIDS Cancer Match Study. HIV status of cancer patients was determined through linkage with HIV registries. We assessed cancer-specific mortality by HIV status, with survival time calculated from cancer diagnosis to either cancer death, censoring due to death from other causes, or last date of registry follow-up. Cox models included HIV as a time-varying covariate and adjustment for age, gender, year of cancer diagnosis, and cancer stage.

Results: The number of cancer cases with HIV infection ranged from 137 for kidney cancer to 2,884 for non-Hodgkin lymphoma (Table 1). Following cancer diagnosis, cancer-specific mortality was significantly elevated in HIV-infected compared to HIV-uninfected patients for most cancers. This adverse association was present for AIDS-defining cancers, i.e. non-Hodgkin lymphoma (hazard ratio=1.25) and cervical cancer (1.36), as well as for commonly diagnosed non-AIDS-defining cancers, i.e. colorectum (1.41), lung (1.24), breast (3.75), and prostate (2.50).

Conclusions: HIV-infected cancer patients experienced higher cancer-specific mortality than HIV-uninfected cancer patients, a trend observed across multiple cancer types, independent of cancer stage. HIV infection could affect cancer mortality through biological effects on the tumor environment. Additionally, HIV-infected individuals may receive sub-optimal cancer treatment. As the number of HIV-infected patients diagnosed with cancer continues to increase, whether HIV results in excess cancer mortality is an increasingly relevant question. Our study was the largest and most comprehensive investigation of HIV and cancer mortality to date and suggests that future research into this relationship is warranted.

Table 1. Association between HIV Infection and Cancer-specific Mortality

Cancer Type	Exposure Category	Total (N)	Crude Cancer-specific Mortality Rate (per 1,000 Person Years)	Cancer-specific Hazard Ratio
NHL	HIV-infected HIV-uninfected	2,884 106,867	57 66	1.25 (1.12-1.39) Referent
Cervix	HIV-infected HIV-uninfected	216 22,829	58 45	1.36 (1.01-1.82) Referent
Oral Cavity/Pharynx	HIV-infected HIV-uninfected	229 42,345	81 45	1.81 (1.30-2.53) Referent
Colorectum	HIV-infected HIV-uninfected	334 198,496	91 74	1.41 (1.13-1.76) Referent
Anus	HIV-infected HIV-uninfected	578 5,540	40 50	1.13 (0.87-1.48) Referent
Liver	HIV-infected HIV-uninfected	282 23,943	627 479	1.23 (1.03-1.46) Referent
Lung	HIV-infected HIV-uninfected	907 240,163	574 435	1.24 (1.14-1.36) Referent
Breast	HIV-infected HIV-uninfected	270 292,518	82 22	3.75 (2.91-4.84) Referent
Prostate	HIV-infected HIV-uninfected	417 295,057	14 11	2.50 (1.59-3.92) Referent
Kidney/Renal Pelvis	HIV-infected HIV-uninfected	137 59,060	48 57	1.03 (0.65-1.64) Referent
HD	HIV-infected HIV-uninfected	470 12,936	17 19	0.88 (0.59-1.31) Referent

100 Impact of Kaposi Sarcoma On Survival in HIV-Infected African Adults On Antiretroviral Therapy

Stephen B. Asiimwe[1,2], Miriam Laker-Oketta[1,3], John Bennett[1], Adrienne Mocello[1], David Glidden[1], Jessica Haberer[4], Mwebesa Bwana[1], Peter Hunt[1], David Bangsberg[4], Edward Mbidde[1], Jeffrey Martin[1]

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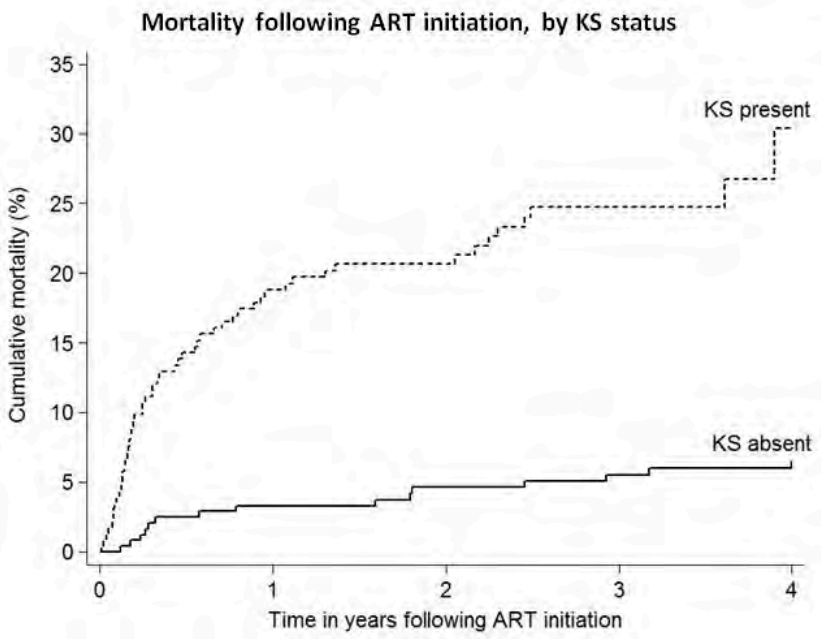
Background: In sub-Saharan Africa (SSA), Kaposi's sarcoma (KS) remains one of the most common malignancies amongst HIV-infected adults. In resource-rich areas, we now know that survival after KS diagnosis has markedly improved in the ART era, and, in fact, ART alone is often initiated for KS in the absence of immediately life-threatening complications. In SSA, ART alone is also often administered for persons with KS, but we know little of the effectiveness of this strategy.

Methodology: We performed a cohort analysis of HIV-infected adults initiating ART in Uganda from 2007 to 2011. Subjects with KS were derived from the Antiretrovirals for Kaposi's Sarcoma clinical trial, which enrolled ART-naïve patients with biopsy-confirmed KS who did not urgently require chemotherapy. The comparator group was subjects without KS from the Uganda AIDS Rural Treatment Outcomes Cohort, based in Mbarara, Uganda; these were consecutive patients initiating ART for indications other than KS. Measurements on both groups were obtained using the same questionnaires and laboratories. Observation was from ART initiation to either death, loss to follow-up, or administrative closure at 4 years.

Results: We evaluated 467 subjects (224 with KS/243 without). Median values for the combined population at the time of ART initiation were: age 34 years (IQR: 28-40), CD4+ T-cell count 135/mm^3 (IQR: 59-230), and plasma HIV RNA 147,993 copies/ml (IQR: 52,164-352,420). Subjects were observed for a median of 3.6 years (IQR 1.9-4.0) with 6.9% lost to follow-up. In an unadjusted analysis, cumulative mortality at 4 years was 30% in the KS group compared with 6.5% in the non-KS group (Figure). In proportional hazards regression models adjusting for age, sex, socio-economic status, mental and physical health status, history of opportunistic infections, body mass index, hemoglobin, CD4 count, and plasma HIV RNA level at ART initiation, patients with KS had a 4.0-fold (95% CI: 1.6-9.7; p =0.003) higher rate of death in the first year after ART and a 2.8-fold higher rate (95% CI: 0.92-8.2; p = 0.07) thereafter.



Conclusions: Among HIV-infected adults initiating ART in Uganda, those with KS experienced substantially higher mortality than those without KS, indicating that treatment with ART alone for all comers with KS is suboptimal. The findings call for improved prognostic staging, and increased access to potent chemotherapy, or development of new adjunctive therapy for KS in resource-poor settings.

101 Prospective Characterization of Kaposi Sarcoma Herpesvirus Inflammatory Cytokine Syndrome

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Background: Kaposi sarcoma herpesvirus (KSHV) is the cause of Kaposi sarcoma (KS), primary effusion lymphoma (PEL), and a form of multicentric Castleman disease (MCD), each associated with HIV. Recently a novel KSHV-associated inflammatory syndrome distinct from KSHV-MCD was described: KSHV inflammatory cytokine syndrome (KICS). We report characteristics of the first ten patients prospectively studied with KICS, separate from the original six, and compare them with control cohorts.

Methodology: We evaluated adults with clinical abnormalities potentially due to KICS, including FDG-PET/CT and biopsy to exclude alternate explanations such as KSHV-MCD. Those meeting the protocol case definition were followed and compared with two prospectively characterized control cohorts: 20 HIV/KSHV-coinfected adults and 20 HIV-infected adults not known to be KSHV-infected, each stratified by HIV viremia (10 with HIV VL ≤50copies/mL and 10 with >10,000 in each). Comparisons were made by Wilcoxon rank-sum for continuous parameters and Cochran-Armitage for symptom severity; given multiple comparisons $p<0.005$ was taken as significant and $0.005<p<0.05$ trend toward significance. Study registered as NCT1419561.

Results: All 10 KICS subjects were HIV infected males; median (range) age 36 (22-60); HIV VL 72copies/mL (<50-74375; <50 in 5/10), CD4 88/μL (7-1308); KS in 10/10; PEL in 2/10. Number clinical abnormalities present 8 (6-11), worst symptom CTC grade 3 (2-4). Symptoms included: gastrointestinal (present in 9/10); edema (9/10); respiratory (6/10); effusion (5/10); adenopathy (4/10); neurologic (3/10); fever (2/10). Lab abnormalities included anemia (all); hypoalbuminemia (all); thrombocytopenia (6/10); leukopenia (4/10) and elevated CRP (all). None developed MCD over 2-36 months; 6 died (4 of KSHV-associated tumors), 4 remitted with therapy. KICS subjects compared with both HIV stratifications within each control group had more severe symptoms; lower hemoglobin and albumin; higher CRP; elevated KSHV VL; and elevated IL-6 and IL-10 (see table).

Conclusions: KICS subjects demonstrated diverse severe clinical abnormalities, a high rate of intercurrent KSHV-associated tumors, and high mortality. KSHV VL and an IL-6/IL-10 cytokine signature were elevated even compared with HIV viremic controls. KICS may be an important unrecognized cause of morbidity and mortality, including some symptoms previously ascribed to HIV, and warrants further exploration of KSHV-directed therapy.

KICS Subject Characteristics Compared With Control Groups					
Parameter	KICS (n=10) Median (range)	KSHV/HIV Coinfected, HIV Viremic (n=10). Median, P vs KICS; ns=not significant	KSHV/HIV Coinfected, HIV Suppressed (n=10). Median, P vs KICS	HIV Infected, HIV Viremic (n=10). Median, P vs KICS	HIV Infected, HIV Suppressed (n=10). Median, P vs KICS
Worst Symptom (CTCAE Grade)	3 (2-4) P<0.0001	0 (0-2) P<0.0001	0 (0-1) P<0.0001	0 (0-2) P<0.0002	0 (0-1) P<0.0001
Hemoglobin (g/L)	9.0 (6.5-10.2)	14.1 P=0.0001	14.3 P=0.0001	13.3 P=0.0009	14.2 P<0.0001
Platelets (x10e9/L)	138 (27-371)	204 ns	211 ns	194 ns	244 ns
Albumin (g/dL)	2.4 (1.6-3.1)	3.8 P=0.0002	3.9 P<0.0001	3.7 P=0.0002	4.0 P<0.0001
C-reactive Protein (mg/dL)	37.8 (4.9-185.0)	1.2 P=0.0003	1.1 P<0.0001	2.0 P<0.0001	1.9 P<0.0001
KSHV VL (copies/10e6 PBMCs)	1569 (0-90909)	0 P=0.0001	0 P=0.0002	0 P=0.0001	0 P=0.0001
Human IL-6 (pg/mL)	14.6 (3.6-330.3)	2.3 P=0.0028	1.9 P<0.0001	2.0 P<0.0001	1.5 P<0.0001
IL-10 (pg/mL)	36.5 (4.6-2357.2)	7.4 P=0.0021	3.8 P<0.0001	9.9 P=0.023	4.7 P=0.0005
IFN-γ (pg/mL)	4.0 (1.1-26.0)	2.4 ns	0.96 P=0.0003	5.1 ns	2.2 ns
TNF-α (pg/mL)	11.4 (6.4-25.5)	11.5 ns	8.0 ns	14.0 ns	6.6 ns
IL-12p70 (pg/mL)	2.1 (0.6-7.7)	2.7 ns	2.3 ns	1.9 ns	0.6 P=0.006

102 Quadrivalent HPV Vaccine Demonstrates Immune Memory in HIV-1-Infected Men

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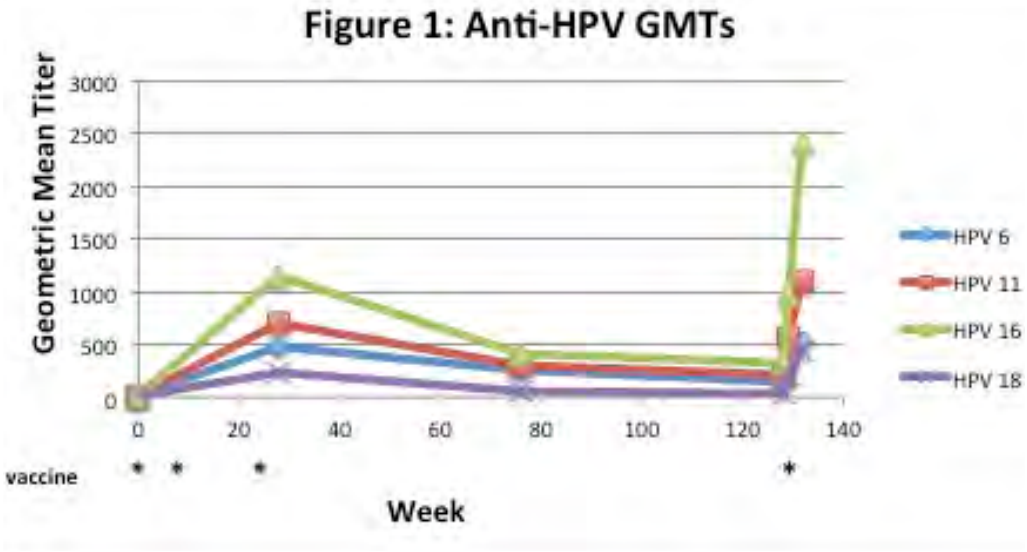
Background: HIV-1-infected men are at a highly increased risk of HPV-related cancers. Prior studies have shown that HPV vaccination is safe and immunogenic in this population. The duration and quality of the immune response in the setting of HIV is unclear. Immune memory from a vaccine is a vigorous immune response upon re-exposure to the relevant antigen. This confers long-term protection against the pathogen.

Methodology: 103 HIV-1-infected adult men received a standard 3-dose series of the quadrivalent HPV vaccine at weeks 0, 8 and 24. 73 participants consented to an extension protocol and received a 4th vaccine dose at week 128. Serum neutralizing antibody concentrations were measured using a competitive Luminex assay at week 0, week 28 (4 weeks after completing 3-dose series), week 76, week 128 (just prior to 4th dose), week 129 and week 132.

Results: The median age of participants was 45 years (interquartile range [IQR] 37-51). 63% were White, 17% Hispanic, 13% Black, 5% Asian. 84% were receiving ART; 83% had a plasma HIV RNA <200 copies/mL; the median CD4 was 517 cells/mm3 (IQR 423-68). Antibodies to HPV types 6, 11, 16, and 18 were detected in 39%, 30%, 26% and 18% prior to the first HPV vaccine increasing to 97%, 98%, 99%, and 96% at week 28. The seropositivity declined to 95%, 96%, 95% and 63% over the next two years. Four weeks after the 4th vaccine dose, antibodies were detected in 100%, 100%, 100% and 94%, and the geometric mean titers (GMT) were significantly higher than those of week 28 for HPV 16 and 18 (P=.002 and P=.001, respectively) suggesting a strong anamnestic immune response. Anti-HPV GMT titers during study follow-up are shown in Figure 1.



Conclusions: The quadrivalent HPV vaccine induces an anamnestic response in HIV-1-infected men. Antibody concentrations declined for two years after completing vaccination, but responded quickly after a challenge of a repeat vaccination. This suggests the development of immune memory, which often correlates with long-lasting protection for other vaccines.

103 HIV-1 Infection Alters Intestinal Expression of Antiretroviral Drug Transporters and Enzymes

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Background: HIV-1 infection is associated with intestinal tissue pathology and inflammation, which may alter the functional expression of drug transporters and metabolic enzymes known to be involved in antiretroviral drug disposition and intestinal absorption. This study investigated the effect of HIV-1 infection and/or chronic antiretroviral therapy on the expression of intestinal drug transporters and metabolic enzymes.

Methodology: Human intestinal biopsy tissues were obtained from i) HIV+ patients receiving atazanavir-based antiretroviral treatment (viral load &lt 50 copies/mL), N=7; ii) HIV+ patients, therapy-naïve (VL &gt 10,000 copies/mL, CD4+ &lt 500 cells/µL), N=7; and iii) age-matched healthy individuals, N=7. Expression of intestinal drug transporters, such as P-glycoprotein (Pgp), multidrug-resistance associated proteins (MRPs), breast cancer resistance protein (BCRP), and organic anion transporting polypeptides (OATPs), as well as cytochrome P450 enzymes (CYP3A4, CYP2B6) was examined by real-time qPCR, immunoblotting, and immunohistochemistry analysis.

Results: Compared to uninfected subjects, antiretroviral-naïve HIV+ patients had significantly lower mRNA expression (2-4 fold) of CYP3A4, MRP2 (ABCC2), and OATP2B1 (SLCO2B1) genes. Several other genes (e.g., Pgp (ABCB1), BCRP (ABCG2)) also showed a trend towards downregulation. In antiretroviral-treated group, CYP3A4, Pgp, MRP2, and BCRP expression was partially restored to healthy levels; however, high inter-individual variability in expression was observed in this group. Immunohistochemistry analysis of CYP3A4 and MRP2 expression in paraffin-embedded tissue slices confirmed downregulation of these genes in HIV-1-infected patients.

Conclusions: Expression of drug-metabolizing enzymes and drug transporters differs between antiretroviral-naïve HIV+ patients and uninfected subjects. These findings are in agreement with studies reporting regulation of these drug transporters and drug-metabolizing enzymes by HIV-1 associated pathogenesis and inflammation in other organs and blood-tissue barriers. Since many antiretroviral drugs are substrates of CYP3A4 (PIs, NNRTIs, maraviroc), Pgp (PIs, NRTIs, integrase inhibitors, maraviroc), MRPs (PIs, NRTIs), and BCRP (NRTIs, raltegravir), these data suggest that the pharmacokinetics of these drugs may differ in HIV-infected patients when compared to healthy volunteers. Overall, antiretroviral pharmacokinetics data and drug-drug interactions assessed in healthy volunteers should be interpreted with caution as they may not reflect antiretroviral drug disposition in HIV-1 infected patients. This study is supported by the Canadian Foundation for AIDS Research.

104 Tenofovir-Emtricitabine Directly Observed Dosing: 100% Adherence Concentrations (HPTN 066)

Craig W. Hendrix[1], Adriana Andrade[1], Angela D. Kashuba[2], Mark Marzinke[1], Peter L. Anderson[3], Ayana Moore[4], Vanessa Elharrar[5], Lei Wang[6], Kenneth H. Mayer[7], Kristine B. Patterson[2]

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Background: Oral pre-exposure prophylaxis trials have yielded disparate efficacy results attributed largely to variable adherence. Objective adherence benchmarks are needed. HPTN 066 was conducted to establish drug concentrations associated with 100% adherence by using directly observed tenofovir (TFV) disoproxil fumarate (TDF)/emtricitabine (FTC) dosing with variable frequency.

Methodology: Healthy, HIV- men and women were randomized 1:1:1:1 to 4 oral TDF 300 mg/FTC 200 mg regimens: 1 tab daily, 2 tabs twice weekly, 1 tab twice weekly, or 1 tab weekly, each for 5 weeks with all doses observed. Trough plasma TFV and FTC, peripheral blood mononuclear cell (PBMC) TFV-diphosphate (TFV-DP) and FTC-triphosphate (FTC-TP) were assessed by UPLC-MS/MS from blood collected prior to the 2nd dose, weekly for 5 weeks, and 2 weeks after the final dose. Tissue biopsies for TFV, FTC, TFV-DP, and FTC-TP concentrations were collected on week 5 and 7 in half the participants.

Results: Thirty-nine participants were evaluable. Steady-state concentrations (Table, median [interquartile range]) were achieved with the 2nd dose for plasma TFV/FTC and by 7 days for PBMC TFV-DP/FTC-TP. Colon tissue concentrations were greater than vaginal tissue concentrations for all moieties and arms except for FTC-TP. Two weeks following the final dose: only PBMC TFV-DP was detected in blood from weekly and twice weekly arms; all drug moieties were detected in blood in most participants in the daily arm; in tissue, detection of any drug moiety was rare except for the daily regimen and in colon tissue. Steady-state weekly-dose-adjusted concentrations did not demonstrate dose-proportionality for TFV-DP and FTC-TP (ANOVA $p<0.05$). Steady-state daily dosing inter- and intra-subject coefficient of variation (CV%) ranged from 33% - 63% and 14% - 34%, respectively, across all drug moieties and increased with less frequent dosing.

Conclusions: Steady-state TFV-DP concentration was established earlier than predicted and dose-proportionality was not demonstrated in the phosphorylated moieties. Steady-state plasma TFV concentrations from daily dosing were consistent with concentrations reported in the Partners, TDF2 and Thai IDU PrEP studies (high levels of HIV protection); higher than in iPrEX (moderate protection), and far higher than in FEM-PrEP and VOICE (no protection). Therefore, HPTN 066 data can be used to benchmark adherence estimates in oral TFV PrEP trials, and assist in interpreting clinical outcomes.

	Plasma		PBMC		Vaginal Tissue				Colorectal Tissue			
	TFV	FTC	TFV-DP	FTC-TP	TFV	FTC	TFV-DP	FTC-TP	TFV	FTC	TFV-DP	FTC-TP
LLOQ	0.3 ng/mL	0.3 ng/mL	0.5 fmol/M	0.02 pmol/M	0.05 ng/mg	0.05 ng/mg	5 fmol/mg	10 fmol/mg	0.05 ng/mg	0.05 ng/mg	5 fmol/mg	10 fmol/mg
1 tab 1x/wk	0.5 (0.5-0.6)	0.8 (0.4-0.9)	2 (0-3)	0.1 (0.1-0.1)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0.01 (0.01-0.06)	0.01 (0-0.01)	16 (0-21)	0 (0-0)
1 tab 2x/wk	4 (3-4)	5 (4-6)	9 (6-11)	0.4 (0.2-0.5)	0 (0-0)	0 (0-0.02)	0 (0-0)	0 (0-0)	0.11 (0.02-3)	0.02 (0-0.16)	27 (13-762)	0 (0-0)
2 tabs 2x/wk	6 (5-6)	7 (5-8)	19 (14-20)	0.6 (0.5-0.6)	0 (0-0)	0.01 (0.01-0.01)	0 (0-0)	-	0.76 (0.09-1)	0.05 (0.01-0.08)	186 (163-209)	0 (0-0)
1 tab Daily	52 (49-56)	71 (68-82)	36 (29-39)	2 (2-3)	0.03 (0.01-0.04)	0.16 (0.15-0.17)	21 (0-41)	39 (39-39)	2.71 (0-12)	1.03 (0-3)	206 (0-595)	0 (0-0)

105 Efavirenz Pharmacokinetics in HIV+ Persons Receiving Rifapentine and Isoniazid for TB Prevention

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Background: AIDS Clinical Trials Group (ACTG) Study A5279 is a phase III clinical trial (N=3000) comparing 4 weeks (wk) of daily rifapentine + isoniazid (RPT/INH) to 9 months of daily INH for the prevention of active TB in HIV-infected individuals. RPT is a known CYP inducer, while EFV is a CYP substrate leading to concern for decreased EFV exposure and risk of virologic failure. The pharmacokinetics (PK) of this combination have not been evaluated. An objective of A5279 was to evaluate the effect of RPT/INH on EFV PK in the first 90 participants who enrolled on a stable EFV-containing regimen.

Methodology: Participants receiving ART containing EFV (600mg PO QD) randomized to the weight based RPT/INH (RPT, ≈ 10mg/kg; INH, 300mg) treatment arm of A5279 were evaluated. Mid interval plasma samples were collected at wk 0 (pre-RPT/INH) and wks 2 and 4 during concomitant RPT/INH. EFV apparent oral clearance (CL/F) was modeled using Bayesian estimation (ADAPT). Wk 2 and 4 EFV concentrations were combined to estimate EFV CL/F on RPT/INH. EFV PK were evaluated in real time. The geometric mean ratio (GMR) and 90% confidence interval (CI) of the pre and during RPT/INH EFV CL/F values were calculated. EFV PK data were to be judged acceptable if >80% of participants had EFV concentrations ≥1 mg/L.

Results: Demographic and baseline data from the 86 evaluable participants were: female, 47 (55%); Black Non-Hispanic, 47 (55%); median age, 35y (13-61); median BMI, 23.2; 78 (93%) had undetectable HIV-1 RNA at randomization; median CD4+ count, 500 cells/mm3 (164-1570). The table gives EFV PK data. The GMR (90% CI) for EFV CL/F was 1.04 (0.98-1.11). The numbers of participants with EFV concentrations ≥ 1 mg/L were: wk 0, 84 (98%); wk 2, 80 (93%); wk 4, 77 (90%); wks 2 and 4, 74 (86%). Median (IQR) RPT concentrations were 9.18 mg/L (6.21-12.7 mg/L).

Efavirenz Pharmacokinetic Data (n=86)	
	Median (IQR)
EFV (mg/L)	
Pre-RPT/INH	2.59 (1.83-3.88)
Week 2	2.46 (1.46-3.87)
Week 4	2.53 (1.44-3.69)
EFV CL/F (L/hr)	
Pre-RPT/INH	9.2 (6.38-13.17)
On RPT/INH	9.8 (7.06-15.66)

Conclusions: Overall, the CL/F of EFV with and without RPT/INH was equivalent, as judged by the GMR and 90% CI. A decrease in the percentage of participants with EFV concentrations ≥ 1 mg/L during RPT/INH therapy suggests induction of EFV CL/F, presumably from RPT. Importantly, the proportion did not cross below the pre-specified threshold of >80%. Assessments of plasma HIV-RNA levels post RPT/INH are ongoing. These drug-drug interaction data provide support that RPT/INH for 4 weeks can be co-administered with EFV-containing ART, and provide the necessary PK evidence for continuing the efficacy assessment of RPT/INH ultra-short therapy for the prevention of TB in HIV-infected individuals.

106 Pharmacokinetic Variability in TB Therapy: Associations With HIV and Effect On Outcome

Derek J. Sloan[1], Alessandro Schipani[2], David Waterhouse[3], Lisa Stone[3], Henry C. Mwandumba[1], Anthony E. Butterworth[4], Robert S. Heyderman[1], Elizabeth L. Corbett[1], Saye H. Khoo[2], Geraint R. Davies[1]

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Background: Inter-individual variability in exposure to anti-tuberculous drugs is well-described during therapy. However, relationships between pharmacokinetic parameters and clinical outcomes are poorly understood, particularly in HIV-endemic regions of southern Africa. Clinical pharmacokinetic-pharmacodynamic (PK-PD) studies are required to evaluate these associations and inform the development of shorter treatment regimens.

Methodology: Adults with a first presentation of smear '++' or '+++' pulmonary TB were treated with standard 6 month therapy. HIV status, CD4 count and prior ART were documented at baseline. Plasma was sampled at 0, 2 and 6 hours post-dose on day 14 or 21 to assay concentrations of all four first-line anti-TB drugs. Mixed effects modelling of liquid culture Time to Positivity (TTP) and Serial Sputum Colony Counting (SSCC) data was used to generate individual patient estimates of the bacillary elimination rate during the first 8 weeks. Patients were followed until 1 year post-treatment and final outcomes were defined as favourable (sustained cure) or unfavourable (failure/relapse). Relationships between PK parameters and PD measurements of treatment response were assessed by logistic regression.

Results: 75/133 (56%) patients were HIV-infected (median CD4 count: 166 [range 6-783] cells/μl) and 24 (18%) were on ART. Although 95% patients reported excellent adherence, 98/113 (87%) had a low rifampicin Cmax, 59/118 (50%) had a low isoniazid Cmax, 46/118 (39%) had a low pyrazinamide Cmax and 24/104 (23%) had a low ethambutol Cmax compared to published reference ranges. HIV associated factors did not explain inter-individual variability in the PK parameters of any first-line drug, although there was a trend towards a lower Cmax of rifampicin amongst those who were HIV-infected (p=0.09). A low AUC0-6h of isoniazid was associated with slower bacillary clearance in TTP and SSCC models (p=0.038 and 0.040 respectively), a lower likelihood of 2 month sputum culture conversion (p=0.045) and a higher likelihood of unfavourable final outcomes (p=0.035).

Conclusions: The frequent finding of a low rifampicin Cmax advocates for acceleration in the conduct of rifamycin dose escalation studies in HIV-endemic populations. The association between low isoniazid exposure and all PD measures of treatment response has not been previously described and highlights the importance of clinical PK-PD studies in unravelling the determinants of early and late TB outcomes.

Session S4 Symposium

4:00 PM – 6:00 PM **Ballroom B/C**

TB: Looking To the Future: Resistance, Persistence, Monitoring, and Control

107 The Genetics and Pathogenesis of MDR and XDR TB Drug Resistance

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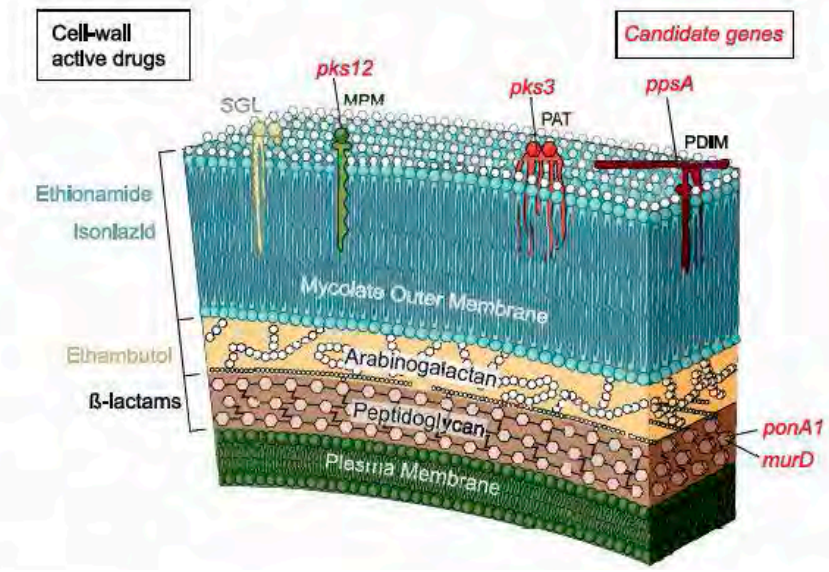
Background: The evolution and spread of drug-resistant tuberculosis threatens to undermine TB control programs. Resistance in MTB arises through serial acquisition of point mutations in genes encoding drug-activating enzymes or drug targets. Current molecular diagnostics amplify and detect known drug resistance mutations, and their performance depends on identification of a comprehensive catalog of these loci. Although known mutations explain much resistance, mutations have not been identified in 10-40% of clinically resistant isolates. In addition to classical drug resistance genes (encoding the protein target of the drug or a drug-metabolizing enzyme), mutations in other classes of genes may confer a selective advantage in the presence of drugs. For example, mutations that reduce cell wall permeability or increase the activity of drug efflux pumps may increase the MICs of drugs, potentially providing an early step toward full-blown drug resistance.



We developed methods to use whole genome sequences of MTB strains to identify biomarkers of drug resistance in a rapid unbiased manner. This approach identified 39 genetic loci newly associated with resistance, 5 of which were associated with cell wall permeability

phenotypes. The unique mycobacterial cell wall contains unusual, complex lipids which contribute to the permeability barrier that underlies the intrinsic antibiotic resistance of most mycobacteria. Multiple tuberculosis drugs target cell wall structures, and many known resistance genes code for enzymes in cell wall lipid pathways. Two of the newly identified genes (murD and ponA1) contribute to the biosynthesis and homeostasis of the cell wall component peptidoglycan. Functional analysis of PonA1 mutants demonstrated an in vitro growth advantage in the presence of the drug rifampicin.

Conclusions: Three of the five genes (ppsA, pks12 and pks3) participate in the biosynthesis and translocation of surface-exposed lipids. Previous work showed that MICS are reduced in pks12-deficient M. avium and that targeted pks12 deletion in BCG leads to increased ethidium bromide uptake and antibiotic sensitivity. Recently, we used an unbiased metabolomics approach to analyze a set of progressively resistant strains from a human patient who developed high level drug resistance, identifying 96 molecules whose intensity changed coincident with the acquisition of resistance.Among these was the lipid product of Pks12, which increased consistent with a gain of function phenotype.

108 Is Latent TB Infection Really Latent?

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Background: Global tuberculosis (TB) eradication efforts are hampered by the vast reservoir of persons with latent TB infection (LTBI). Although the lifetime risk of reactivation is 5-10% among immune competent persons, HIV-infected persons have a ~10% annual risk of reactivation. For this reason, it is recommended that those with HIV infection are tested for LTBI and treated if positive. However, currently available regimens are lengthy (daily isoniazid for 9 months) or pose significant drug-drug interactions with antiretroviral therapy (rifampin for 4 months). Therefore, new strategies to treat LTBI, especially in the setting of HIV co-infection, are urgently needed. A major obstacle to this end is our limited understanding of how Mycobacterium tuberculosis (Mtb) is able to persist in the infected host for years or even decades, exhibiting tolerance to anti-TB drugs. The traditional view is that LTBI represents a paucibacillary population of non-replicating organisms with reduced metabolism, likely as an adaptive response to the unfavorable milieu within caseous granulomas. Several regulatory pathways, including the stringent response, have been implicated in bacillary growth arrest and phenotypic drug tolerance. Challenging this classical paradigm, recent studies using clinically relevant animal models have reported accumulation of Mtb mutations during LTBI, suggesting continued bacillary replication, while other studies have highlighted the importance of bacterial efflux pumps in mediating mycobacterial antibiotic tolerance.

Conclusions: LTBI does not refer to a single entity, but rather represents an array of microbiological and immunohistological findings giving rise to a clinical spectrum spanning LTBI and active TB. An improved understanding of the host-pathogen interactions underlying LTBI is expected to yield: 1) Novel potential drug targets for persistent bacilli, with the goal of shortening the duration of TB chemotherapy; 2) Novel diagnostic markers specific to the latent stage of infection and to reactivation disease; and 3) Novel attenuated vaccine candidates with an inability to reactivate, which is particularly important in the setting of HIV/AIDS.

109 Quantifying TB Treatment Response Using PET/CT

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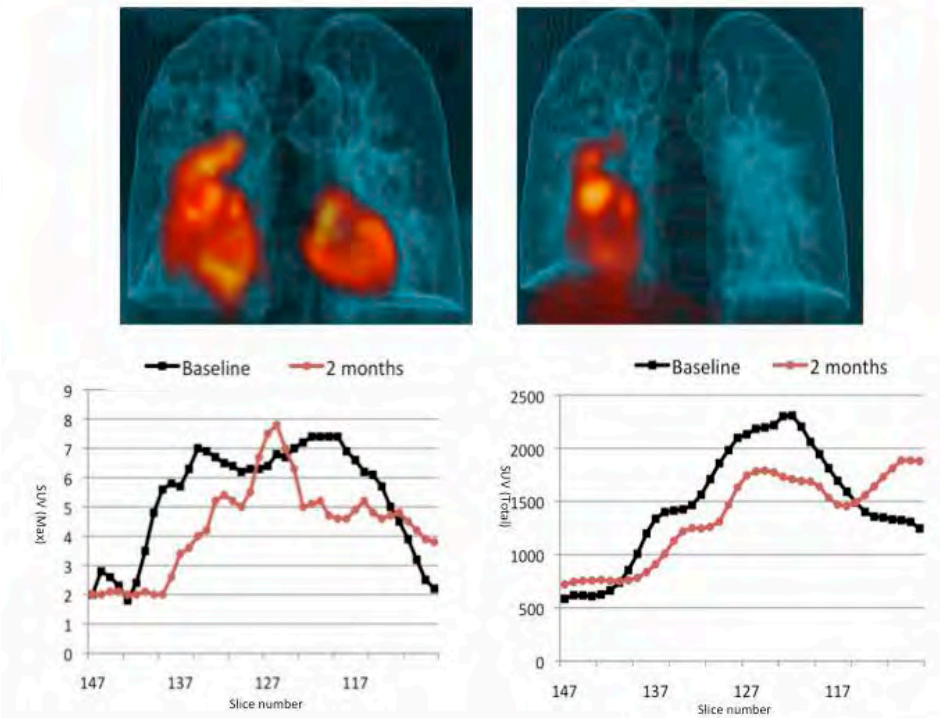
Background: Definitive clinical trials of new chemotherapy for tuberculosis (TB) treatment require following subjects until at least six months after they discontinue taking medicine to assess durable cure, making these trials expensive and lengthy. Surrogate endpoints relating to treatment failure and relapse are currently limited to sputum microbiology, which is neither very sensitive nor very specific.

Conclusions: In this study we prospectively assessed radiographic changes using positron emission tomography (PET) and computed tomography (CT) at two (PET and CT) and six (CT only) months in a cohort of subjects with multidrug-resistant (MDR) TB who were treated with second-line TB therapy for two years and then followed up for an additional six months. CT scans were read semi-quantitatively by radiologists and computationally evaluated using custom software to provide volumetric assessment of TB-associated abnormalities. CT scans assessed by readers were predictive at six months but not two months and changes in computed abnormal volumes were predictive at both time points. Quantitative changes in FDG uptake two months after starting treatment were found to be highly predictive



of long-term outcome. These radiologic markers were all more predictive than conventional sputum microbiology in distinguishing successful from unsuccessful treatment. Lesions on CT with higher radiodensity were most predictive of long-term outcome for subjects in this study. These results support the potential of radiologic biomarkers ("radiomarkers") as possible surrogate endpoints in clinical trials of new TB drug regimens.

110 Population-Level Control of HIV-Related TB

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Joint United Nations Programme on HIV/AIDS (UNAIDS), Geneva, Switzerland

Background: TB is still among the most common causes of death of people living with HIV (PLWH). TB remains out of control in Southern Africa where rates can be more than 1000/100,000 population per year (compared to less than 10 in some high income countries).

Conclusions: To control HIV-related TB we need social, structural and programme actions that: reduce the burden of HIV at the population level; reduce the susceptibility of PLWH to develop TB and reduce transmission of TB. Despite exciting breakthroughs in HIV prevention over the past decade, 2.3 million people were infected with HIV in 2012. Both antiretroviral therapy (ART) and isoniazid preventive therapy (IPT) reduce the risk of TB. ART also reduces the transmission of HIV. However, PLWH on ART continue to have raised rates of TB compared to the general population and the increased longevity achieved with ART expansion and the challenges in maximising and maintaining immune restoration may even increase the burden of TB over the next decades.

Interrupting transmission of TB thus remains crucial. Our understanding of the HIV epidemic relies on a battery of tools that include increasingly reliable markers of recent infection as well as burden and progression of disease. In stark contrast, existing tools present a major challenge to our understanding of TB transmission dynamics. Molecular epidemiology is only available for those who progress from infection to culture positive disease. Infection assays are cumbersome, expensive, or inaccurate, and give information on cumulative infection unless individuals are followed over time. Recent studies have attempted to document contact patterns in population settings and to use markers of "shared air" as proxies for transmission risk.

The large scale community randomised trials and associated studies conducted by CREATE confirmed that IPT works well to reduce the risk of TB in the individual and, in Rio, led to benefits to the whole community of PLWH using routine services. Widescale use of IPT to both HIV-positive and -negative South African gold miners did not reduce incidence or prevalence of TB. A community based approach to enhance case-finding and treatment was inadequate to alter the epidemiology of TB in Zambian and South African communities. However, a household-based approach aimed to reduce HIV transmission, susceptibility of PLWH to TB, and TB transmission probably had a useful impact on both population level transmission of TB and prevalence of TB.

Population-based control of HIV-related TB requires ongoing quality assured expansion of ART and IPT combined with greater investment in the full range of HIV prevention approaches. However it also requires refocus on TB as an infectious disease and to understand the transmission dynamics and interrupt it.

Session S5 Symposium

4:00 PM – 6:00 PM **Ballroom A**

Visualizing the Virus

111 An Ingenious Cloak for Subterfuge: The HIV Capsid Structure

Angela M. Gronenborn
University of Pittsburgh, Pittsburgh, PA, United States

Background: HIV and other retroviruses use a Trojan horse style of infection, taking advantage of a cloak that shields its genome till the time is ripe to open the shield. Once HIV gets inside the cell, it takes over the cellular machinery, turning it into a factory for its own reproduction. This entails first to derail the normal host defense pathways, rendering HIV resistant to cell-mediated destruction responses.

Conclusions: In mature HIV-1 particles a conical-shaped capsid encloses the viral RNA genome. Previous structural analysis of two- and three-dimensional arrays provided a molecular model of the capsid protein (CA) hexamer and revealed three interfaces in the lattice. Using the high-resolution NMR structure of the CA C-terminal domain (CTD) dimer and in particular the unique interface identified, it was possible to reconstruct a model for a tubular assembly of CA protein that fit extremely well into the cryoEM density map.A novel CTD-CTD interface at the local three-fold axis in the cryoEM map was confirmed by mutagenesis to be essential for function. More recently, the cryo-EM structure of the tube was solved at 8Å resolution and this cryo-EM structure allowed unambiguous modeling and refinement by large-scale molecular dynamics (MD) simulation, resulting in all-atom models for the hexamer-of-hexamer and pentamer-of-hexamer elements of spheroidal capsids. Furthermore, the 3D structure of a native HIV-1 core was determined by cryo-electron tomography (Cryo-ET), which in combination with MD simulations permitted the construction of a realistic all-atom model for the entire capsid, based on the 3D authentic core structure.

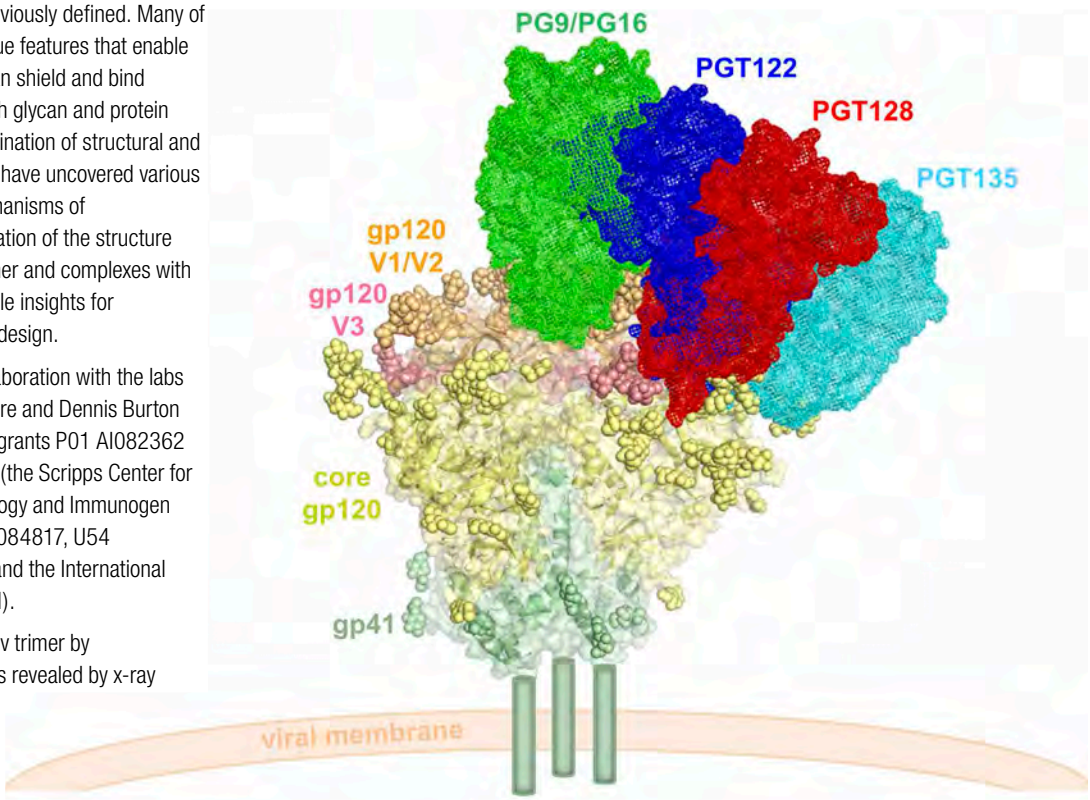
112 Structure of a Soluble, Cleaved HIV-1 Env Trimer and Its Interaction With Broadly Neutralizing Antibodies

Ian A. Wilson
The Scripps Research Institute, La Jolla, CA, United States

Background: The discovery and isolation of highly potent, broadly neutralizing human antibodies (bnAbs) that recognize a broad diversity of HIV-1 isolates has opened up tremendous opportunities for enhancing our understanding of how HIV-1 can be neutralized. However, it has not been possible until recently to map these antibody responses onto the three-dimensional structure of the HIV-1 Envelope glycoprotein (Env), which enables viral entry into cells, as it has been extraordinarily challenging to produce stable soluble Env trimers with near native antigenicity. Such structural information is essential for rational design of HIV-1 vaccine candidates.

Conclusions: We have recently determined the x-ray structure of a soluble cleaved Env trimer that enabled greater understanding of its function in receptor binding and membrane fusion. Furthermore, mapping of the key neutralizing epitopes in the context of the Env trimer has shown that they are much larger and more complex than previously defined. Many of these antibodies have unique features that enable them to penetrate the glycan shield and bind epitopes that consist of both glycan and protein components. Using a combination of structural and biophysical techniques, we have uncovered various modes of binding and mechanisms of neutralization. Thus, elucidation of the structure and function of the Env trimer and complexes with bnAbs now provides valuable insights for structure-assisted vaccine design.

This work was done in collaboration with the labs of Andrew Ward, John Moore and Dennis Burton and was supported by NIH grants P01 AI082362 (HIVRAD), UM1 AI100663 (the Scripps Center for HIV/AIDS Vaccine Immunology and Immunogen Design (CHAVI-ID), R01 AI084817, U54 GM094586 (PSI:Biology) and the International AIDS Vaccine Initiative (IAVI).



Recognition of the HIV-1 Env trimer by glycan-dependent bnAbs as revealed by x-ray crystallography. (image created by Jean-Philippe Julien, The Scripps Research Institute)

113 Imaging the Molecular Dance of Single HIV-1 Env Molecules

Walter H. Mothes
Yale University, New Haven, CT, United States

Background: The HIV-1 envelope (Env) spike is a type-I viral fusion machine that mediates viral entry into host cells. HIV-1 Env is comprised of three gp120 and three gp41 subunits and successfully evades recognition by most antibodies by favoring a neutralization-resistant ground state conformation in which a dense array of N-linked glycans covers most of its outer surface. Interaction with CD4 on the surface of host cells activates Env by inducing gp120 structural rearrangements, which lead to the formation of a site for coreceptor binding. Subsequent interaction with the coreceptor triggers additional Env refolding, with gp41 rearranging to form a stable six-helix bundle, and facilitating fusion of virus and host-cell membranes. While static images of HIV-1 Env in various conformations have been obtained, real-time motions have not been characterized.

Conclusions: Here we introduced fluorophores into the variable regions V1, V4, and V5 of gp120 to enable single-molecule fluorescence resonance energy transfer (smFRET) imaging of Env conformations within the context of the native trimer on the surface of HIV-1 virions. Our data reveal that HIV-1 Env is structurally dynamic, with gp120 transitioning between three distinct prefusion conformations. These were identified through mutational substitution or ligand stabilization as ground-state, CD4-stabilized, and CD4/coreceptor-stabilized conformations. Transition analysis indicated the CD4-stabilized conformation to be a preferred intermediate. Broadly neutralizing antibodies VRC01, PG16, PGT145, and 2G12 stabilized Env in its ground-state conformation. Together the results provide insight into the conformational mobility of unliganded HIV-1 Env and provide a temporal framework for understanding how broadly neutralizing antibodies impede the activation of Env required for virus entry.

114 Kill HIV by Starvation: SAMHD1 as a Potent Viral Restriction Factor and a Master Regulator of Cellular dNTP Metabolism

Yong Xiong
Yale University, New Haven, CT, United States

Background: SAMHD1, a deoxyribonucleoside triphosphate triphosphohydrolase (dNTPase), prevents the infection of blood cells by retroviruses, including HIV, by depleting the cellular dNTP pool available for viral reverse transcription. SAMHD1 is a major regulator of cellular dNTP levels in mammalian cells. Mutations in SAMHD1 are associated with the autoimmune condition Aicardi Goutières Syndrome (AGS), whose clinical manifestations resemble congenital viral infection. The catalytic activity of SAMHD1 is regulated by allosteric binding of dGTP, which enables SAMHD1 monomers/dimers to assemble into the catalytically active tetrameric form.

Conclusions: We have determined the crystal structure of the tetrameric human SAMHD1-dGTP complex. The structure reveals an elegant allosteric mechanism of activation via dGTP-induced assembly of the tetrameric complex from two inactive dimers. Intriguingly, GTP can also activate SAMHD1, and

our data further show the binding promiscuity of other dNTPs at the allosteric site. These findings suggest an intricate regulation system that may have a profound effect on the balancing of cellular dNTP pools. These results provide the basis for a mechanistic understanding of SAMHD1 function in HIV restriction, the pathogenesis of AGS, and regulation of cellular dNTP levels.

Session S6 Symposium

4:00 PM – 6:00 PM Room 304

Know Your Epidemic: From Data To Action

115 Population Surveys: What Do They Show?

Peter D. Ghys

Joint United Nations Programme on HIV/AIDS (UNAIDS), Geneva, Switzerland

Background: Since 2001, a large number of national surveys with measurement of HIV status have been conducted, most of them in sub-Saharan Africa (35 countries), but also in selected countries in Asia (2 countries) and in the Caribbean (2 countries). Many of these surveys are conducted within the Demographic and Health Survey programme, others are conducted as AIDS Indicator Surveys supported by international or national organisations. Typical surveys have been limited to the 15-49 year age range for women and 15-54 or 15-59 for men.

Conclusions: Population surveys provide many advantages over traditional surveillance systems. These include that they include men as well as women, and that they are nationally representative and in recent years also designed to inform at subnational level (typically state or province). Their representative design has been critical for adjusting biases in estimated prevalence from antenatal clinic data. For example Ethiopia and the Democratic Republic of the Congo revised their national prevalence dramatically down on the basis of national surveys which showed much lower prevalence than the ANC surveillance data. The HIV prevalence information from surveys has informed epidemiological patterns used in the estimation of national epidemics, including for the sex and age pattern of prevalence, and to adjust prevalence levels from antenatal clinics in countries without survey.

Another important benefit from population-based surveys is the ability to link HIV status with socio-demographics and behaviours, allowing cross-sectional bivariate and multivariate analyses of determinants and impacts. Examples of how this has changed our understanding of HIV include the ability to map HIV prevalence to wealth status, geographic location, and behaviours.

Limitations include the possibility of biased estimates of HIV prevalence related to survey participation, their infrequent conduct (often once every 5 years), and their relatively high cost (several million USD).

Recently, the inclusion of novel laboratory methodologies is starting to enable direct estimates of HIV incidence (while validation of the optimal assay algorithms is ongoing, and confidence intervals are large) and exposure to antiretroviral treatment (ART). In the future, surveys may be also be used to assess community-based viral load and to inform the epidemiology of small geographic areas of particular interest. Expanding the age range of the sampled population, surveys can provide additional information on the HIV epidemiology among children (to date few surveys have included children) and among people over 50 years of age.

116 MSM in the UK: Prevention Effects of ART in Perspective

Andrew Phillips

University College London, London, United Kingdom

Background: Rates of new HIV infection in men who have sex with men (MSM) have in the UK and elsewhere increased in recent years, despite high levels of ART coverage and the majority of people on ART having a suppressed viral load to very low levels. It has been suggested that the beneficial effects of ART on HIV transmission have likely been counter-acted by a small but significant increase in overall levels of condom-less sex in MSM in general. A further factor which needs to be considered is that a high proportion of new infections probably arise from people undiagnosed with HIV, many of whom are in primary infection. Clearly, one challenge for realization of the maximum benefits of ART in preventing transmission is to be able to diagnose people sufficiently early after infection, and ideally while in the acute stage of infection. It is not intuitively clear how high rates of HIV diagnosis and ART coverage, and how limited any increases in condom-less sex need to be, in order to bring down rates of new infections to a very low level.

The talk will mainly consist of presentation of insights into these questions from the UK MSM HIV Synthesis model, an individual-based simulation model of the epidemic in MSM in UK. The fit of the model to the UK epidemic is informed by data on sexual behaviour, HIV testing, HIV diagnoses, AIDS, death, CD4 count at diagnosis, recent infection at diagnosis, viral load and CD4 count profile of treated people, and levels of drug resistance. The model was used to reconstruct the epidemic in order to study the potential effects of future increases in HIV testing, changes in eligibility criteria for ART initiation, and changes in overall levels of condom-less sex. These results will be compared to those obtained from other MSM epidemics. Areas of uncertainty in model parameters for which additional information is required will be highlighted. These include the individual health benefits of very early ART initiation, changes in levels of condom-less sex induced by HIV diagnosis, and the effect of ART-induced viral suppression on reducing transmission through anal sex.

Conclusions: Antiretroviral treatment and condom use are both exerting a substantial limiting effect on the HIV epidemic in MSM in the UK and elsewhere and we should seek appropriate ways to maximise these effects. In particular, it is critical that the importance of condom use is continuously emphasized as a key element of prevention, with information made widely available on the specific circumstances in which risk of transmission of HIV and other infections is sufficiently low to consider lack of condom use.

117 Understanding Networks of HIV Transmission

Stéphane Helleringer
Columbia University, New York City, NY, United States

Background: HIV is transmitted through sexual or drug injection networks that connect the members of a population. The extent, structure and timing of such networks are thus important determinants of epidemic dynamics and the success of preventive interventions. In this presentation, I describe approaches to collecting network data; I provide a brief overview of the key concepts of network analysis (i.e., mapping, measuring and analyzing patterns of relationships between individuals at risk of HIV infection), and I review recent and ongoing work on HIV risks and transmission networks. In doing so, I focus on studies of heterosexual networks in HIV endemic settings of eastern and southern Africa. In such populations, networks are often characterized by a low average number of partnerships. Nonetheless, dense and decentralized networks still emerge from the formation and dissolution of multiple and possibly concurrent partnerships. Coupled with high infectivity during acute infection, these networks often expose large numbers of individuals to the risk of acquiring HIV.

Conclusions: I identify two gaps in our understanding of HIV transmission networks:

1. A narrow understanding of the complex interactions between network dynamics and the scale-up of biomedical HIV prevention;
2. Limited data on key network parameters that are not easily captured in standard sexual behavior surveys.

Finally, I describe emerging opportunities to learn about HIV transmission networks through sociocentric network studies, data routinely collected by health services during partner notification, or phylogenetic studies.

118 From Evidence To Policy: Experience From Swaziland

Velephi J. Okello
Swaziland National AIDS Programme, Mbabane, Swaziland

Background: The use of evidence to inform health policy is vital. However, generation of such evidence is frequently challenging as low and middle income countries (LMIC) are unable to fund in-country research. As a result, policies are frequently developed based on assumptions, often resulting in failure of policies to achieve desired impact on population health. However, opportunities exist to utilize available epidemiologic data as well as data generated from international settings to inform policy in LMIC. The effectiveness of evidence in informing policies relies on the capacity of the policy makers to cull available the evidence and to adapt it to real-life settings.

Conclusions: Evidence from surveillance and research studies can be utilized to identify issues for policy action and to determine types of actions. Policy makers should partner in the process of evidence generation, in prioritizing research topics and in interpretation of findings. Researchers should focus on questions relevant to key policy issues. Policy makers at the same time need to balance the many social and economic factors that influence adoption of new policies.

Sources of Evidence and Policies Developed		
Evidence Source	Issue identified	Policies Developed
SDHS, 2006	39% of women and men aged 15-49 years are aware of their HIV status	Routine offer of HIV testing and counselling in all health facilities (PIHTC)
SDHS, 2006	About 9% discordance among couples	Couple Testing and Disclosure counselling
SHIMS, 2012	25% of 18-49 year olds who need ART (CD4 350) are not on ART	Linkages to Care and treatment after HTC
SHIMS, 2012	50% of those who knew HIV+ status were on ART	Linkages to Care and Treatment and Enrolment of all HIV+ into Pre-ART Care; Increased CD4 Eligibility to 500
SHIMS, 2012	Knowledge of status and not being on ART was associated with having a high viral load	Implementation of PMTCT B+ Pilots and Immediate ART/Test and Treat Pilots, with Introduction of Routine Viral Load monitoring
HPTN 052, 2010	96% reduction in HIV transmission in discordant couples with early ART initiation	Initiation of Treatment as Prevention Pilots, Partner testing to identify discordant couples

THURSDAY MARCH 6, 2014

Session PL5 Plenary

8:30 AM – 9:00 AM **Auditorium**

119 HIV-1 Infection and Type-1 Interferon

Michael H. Malim
King's College London, London, United Kingdom

Background: The type-1 interferons (IFNs) are pro-inflammatory cytokines that are effective suppressors of HIV-1 replication, are produced at elevated levels during acute HIV-1 infection, and are associated with increased viral loads during chronic infection. This presentation will review the biology of type-1 IFN and its interplay with HIV-1 infection in humans. Drawing upon data gleaned from assorted virus infections, the following subjects will be discussed:

the pathways of IFN induction in response to infection, the mechanisms by which IFN mobilises an anti-viral state, strategies used by viruses to evade IFN-mediated inhibition, and the processes that may be affected by IFN to provoke inflammation and immunopathology.

Session PL6 Plenary
9:00 AM – 9:30 AM Auditorium

120 PEPFAR/Global Fund at 10 years: Past, Present, and Future

Stefano M. Bertozzi
University of California Berkeley School of Public Health, Berkeley, CA, United States

Background: The presentation will review the achievements and major lessons learned from the implementation of *President's Emergency Plan for AIDS Relief* (PEPFAR) and the *Global Fund to Fight AIDS, Tuberculosis and Malaria* over the past ten years. It will explore in greater detail the question "are we getting our money's worth?" and look at the evolution of the efficiency of the AIDS response in both treatment and prevention over the past decade. It will discuss areas for future improvement and options for how they might be addressed.

Session O-9 Oral Abstracts
10:00 AM – 12:15 PM Room 312

Interferon and Antibody at the Interface of Innate and Adaptive Immunity To HIV

121 Cryo-EM Structures of the HIV-1 Env Trimer Reveal the Full Extent of Neutralizing Antibody Epitopes

Andrew B. Ward[1], Dmitry Lyumkis[1], Natalia de Val[1], Jean-Philippe Julien[1], Albert Cupo[2], Per Johan Klasse[2], Rogier Sanders[3], John Moore[2], Ian Wilson[1]
[1]Integrative Structural and Computational Biology, The Scripps Research Institute, La Jolla, CA, United States, [2]Weill Cornell Medical College, New York, NY, United States, [3]Academic Medical Center, Amsterdam, Netherlands

Background: The Envelope glycoprotein (Env) on the surface of HIV-1 mediates cell entry and is the sole target for the adaptive immune system. Broadly neutralizing antibodies (bNAbs) that recognize Env and disarm HIV-1 provide hope that passive treatment or active vaccination strategies can be used to combat this disease. While X-ray crystallography has generated a molecular understanding of how bNAbs interact with Env, studies have been conducted mainly on minimal monomeric gp120 constructs or gp120 outer domain alone. Thus, these studies provide an incomplete picture of the interaction that occurs on native trimeric Env.

Methodology: We used cryo-electron microscopy to determine structures of the cleaved, soluble SOSIP gp140 trimer alone and in complex with bNAbs at sub-nanometer resolution. The combination of this work with additional biophysical studies of the SOSIP trimer, including isothermal titration calorimetry, reveals a detailed picture of Env recognition by bNAbs.

Results: The cryo-EM reconstructions illustrate the secondary structure elements of the Env trimer in relationship to various broadly neutralizing antibodies, while a 5.8 Å structure enabled building of a near complete model of the trimer. This model illustrates for the first time the relationship of the variable loops between gp120 protomers, the gp120/gp41 interface, and the fold of gp41. We find that the Env trimer is stabilized by extensive interactions between gp41, which is a three-helix bundle in the middle of the trimer, as well as inter-protomer contacts in the variable loops. Our model of the Env trimer is consistent with a wide body of Env literature and provides insights into the mechanism of receptor engagement and the conformational changes associated with viral fusion.

Conclusions: Our structural studies provide the first models of intact Env trimer at sub-nanometer resolution, revealing extensive details about the relative arrangement of gp120 and gp41 subunits. Our models also provide a full description of the quaternary nature of bNAb epitopes, the complexity of which were not appreciated from previous studies with monomeric gp120. The models can now be used to directly design new Env antigens for testing as HIV-1 vaccines as well as potentially improve existing bNAbs to be used for passive vaccination strategies.

122LB Immunogenicity of Cleaved, Soluble BG505 SOSIP.664 Native-Like Trimers in Rabbits

John P. Moore
Microbiology/Immunology, Weill Medical College, New York, NY, United States

Background: An HIV-1 Env vaccine should induce broadly neutralizing antibodies (bNAbs). One approach is to create soluble mimics of the native Env trimer that expose multiple bNAb epitopes, while occluding non-NAbs epitopes. The cleaved SOSIP.664 gp140 trimers based on the subtype A founder virus, BG505, closely approximate the desired antigenicity properties. These trimers are also highly stable and homogeneous, closely resemble native virus spikes when viewed by negative stain EM, and their high-resolution X-ray diffraction and cryoEM structures have been determined.

Methodology: We immunized rabbits intramuscularly with native-like BG505 SOSIP.664 gp140 trimers (or, for comparison, gp120 monomers) in ISCOMATRIXTM adjuvant. The trimers were produced in 293T or 293S cells and with or without glycosidase digestion. We measured the autologous and heterologous NAb responses in the sera using the Tzm.bl cell assay, and assessed NAb epitope specificities using mutant viruses and specific competitors such as Env proteins and peptides.

Results: The trimers induced strong (titers of 50-3000) and consistent (16 of 16 animals) NAbs against the autologous, neutralization-resistant (Tier-2) BG505.T332N virus, much more so than the corresponding monomeric gp120. Heterologous Tier-1 NAbs were also induced efficiently, but other Tier-2 viruses were neutralized only weakly and inconsistently. The autologous NAb responses in the trimer-immunized rabbits were similar in magnitude to those found in the HIV-1 BG505 infected-infant, but over time the infant developed broader, heterologous responses not seen in the rabbits. The most

immunogenic linear peptide epitope was V3, but anti-V3 Abs neutralized only Tier-1 viruses (from multiple subtypes) and did not contribute to the autologous, Tier-2 response. Neutralization-inhibition experiments with peptides and proteins indicate that the autologous neutralization is directed to conformational epitopes on gp120, but not to linear variable loop peptides. The glycan-variant trimers did not differ markedly in immunogenicity, and mutant virus studies suggest that the autologous NAbs are not directed against the N332- or N160-dependent sites. Complex, variable-loop dependent epitopes as well as elements near the CD4bs are now being evaluated as the most likely target of autologous NAbs.

Conclusions: A native-like trimer based on a founder virus induces a NAb response that mimics what is often seen in primary infection; the NAbs are strong against the autologous virus but lack breadth against Tier-2 strains. The challenge now is to combine knowledge of the BG505 SOSIP.664 trimer structure with a better understanding of the immunology of bNAb development during infection, to guide improvements to Env trimer-based immunogens.

123 Identification of a New Neutralization Target at the N262/N448 Glycosylation Sites On HIV-1 gp120

Xueling Wu[1], **Tongqing Zhou**[2], Ivelin S. Georgiev[2], Sijy O'Dell[2], Mark Louder[2], Dennis R. Burton[3], Wayne C. Koff[3], Martin Markowitz[1], Peter D. Kwong[2], John R. Mascola[2]
[1]Aaron Diamond AIDS Research Center, New York, NY, United States, [2]Vaccine Research Center, Bethesda, MD, United States, [3]International AIDS Vaccine Initiative, New York, NY, United States

Background: Currently isolated broadly neutralizing antibodies (bnAbs) against HIV-1 demonstrate unusual genetic features such as restricted immunoglobulin (Ig)-gene usage, unusual CDR3 lengths and extremely high levels of somatic hypermutation, imposing potential elicitation barriers. Alternatively, it may be beneficial to induce anti-viral antibodies by balancing the feasibility for elicitation and the requirements for anti-viral function, as suggested by the recent findings from the RV144 trial that certain gp120-binding antibodies correlate with reduced infection risk.

Methodology: Using the resurfaced stabilized gp120 core protein, RSC3, to preserve and expose the site for CD4 attachment, we previously identified VRC01 and its class of anti-HIV-1 bnAbs targeting the CD4-binding site (CD4bs) of gp120. Taking the advantage of the fact that RSC3 also preserves the surface glycans on gp120, we used RSC3 to probe IgG+ memory B-cells to identify monoclonal antibodies (mAbs) that may target glycans on gp120.

Results: From a RSC3-probed B-cell sort, we identified the VRC01-class mAbs VRC-PG04 and VRC-PG04b from the IAVI protocol G participant #74. Additionally, we identified a new mAb VRC-PG05 from the same donor and the same B-cell sort. VRC-PG05 by itself neutralized 29% of 178 tested Env-pseudoviruses; when combined with VRC-PG04, it complemented VRC-PG04 to enhance neutralization coverage and potency. The atomic-level structure of VRC-PG05 in complex with gp120 revealed a novel glycopeptide epitope relying on two highly conserved glycans at N262 and N448 (based on HXB2 numbering) on gp120, located posterior to the CD4bs. Removal of either glycosylation site resulted in complete loss of VRC-PG05 activity. The sequence characteristics of VRC-PG05 do not appear to be unusual in the human antibody repertoire, and its levels of somatic hypermutation are moderate, only 1/3 of those of VRC01 and VRC-PG04. We used a VRC-PG05 highly-sensitive strain, AC10.29, to derive monomeric gp120 recombinant proteins with point mutations to screen plasmas from 85 HIV-1 seroconverters. Using gp120 mutants lacking a glycan at either N262 or N448, we identified 17 (20%) with antibodies directed to the N262/N448 glycan-specificity. In comparison, using the D368R gp120 mutant, we identified only 2 (2%) with antibodies directed to the CD4bs.

Conclusions: Our results suggest that in HIV-1-infected individuals, antibodies targeting the N262/N448 glycan-specificity are more prevalent than those to the CD4bs. This property, along with the ability for co-elicitation with the CD4bs-directed VRC01-class and the moderate somatic hypermutation of VRC-PG05, renders this antibody specificity a new and attractive target for HIV-1 envelope-based immunogen design.

124 CD169 Mediates HIV-1 Evasion From Detection by α-gp120 Neutralizing Antibodies in Dendritic Cells

Hisashi Akiyama[1], Nora G. P. Ramirez[1], Manasa Gudheti[2], Suryaram Gummuluru[1]
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Background: A hallmark of chronic HIV-1 infection is constitutive immune activation associated with elevated serum levels of proinflammatory cytokines, mainly induced by microbial translocation across the gut mucosa. We have previously demonstrated that dendritic cells (DCs) matured in the presence of IFNα or LPS, up-regulate a myeloid cell-specific receptor CD169 or Siglec1, the predominant DC receptor responsible for HIV-1 capture and transfer to CD4+ T cells. Our previous results have also demonstrated the relative inability of α-gp120 broadly neutralizing antibodies (bNAbs) to inhibit mature DC-mediated HIV-1 transmission to CD4+ T cells. In this study we tested the hypothesis that CD169-mediated HIV-1 capture and retention in unique non-lysosomal compartments not only preserves virus infectivity but also provides evasion from detection and neutralization by α-gp120 bNAbs.

Methodology: To characterize HIV-1+ compartments in mature DCs, CD14+ monocyte-derived DCs, stimulated with IFNα or LPS were pulsed with HIV-1, stained for p24gag and CD169 and visualized via deconvolution or super-resolution microscopic analysis. To examine the ability of α-gp120 neutralizing agents to detect CD169-associated HIV-1 in DCs and inhibit transmission to CD4+ T cells, DC-laden HIV-1 were incubated with VRC01 (α-gp120 bNAb) or sCD4-183 (two-domain soluble CD4), washed and analyzed by immunofluorescence or co-cultured with CD4+ T cells to determine HIV-1 transmission.

Results: IFNα and LPS stimulation of DCs greatly enhanced CD169 expression and HIV-1 trans-infection of CD4+ T cells. Super-resolution microscopy revealed intimate association of CD169 with HIV-1 in DCs, forming densely packed HIV-1+ clusters within surface-exposed plasma membrane invaginations, some of which were at a depth of up to 1μm from the cell surface, especially in LPS-matured DCs. Interestingly, virus particles in these compartments were inaccessible to surface-applied α-gp120 bNAbs in the absence of membrane permeabilization. Moreover, CD169+ DC-mediated HIV-1 trans-infection to CD4+ T cells was significantly more resistant to neutralization by VRC01, but not to a small molecular weight inhibitor, sCD4-183, compared to that observed with cell-free infection, suggesting that virus particles retained in surface-exposed CD169+ compartments in DCs are protected from detection by α-gp120 bNAbs.

Conclusions: These results suggest that capture of HIV-1 by CD169 in DCs not only results in trafficking and retention of virus particles in non-degradative compartments but can also provide HIV evasion from humoral responses. Since serum IFNα and LPS levels are elevated in patients chronically infected with HIV-1, this CD169-dependent evasion mechanism may contribute to HIV-1 persistence in vivo.

125 Tetherin Antagonism by Vpu Protects HIV-Infected Cells From ADCC

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Background: HIV-1 Vpu facilitates virus replication by downmodulating at least three different cellular proteins: Tetherin (BST-2 or CD317), a restriction factor that interferes with the detachment of nascent virions from infected cells, CD4, the primary receptor for virus entry, and NTB-A, a co-stimulatory molecule required for natural killer (NK) cell activation. While the mechanisms of these Vpu activities have been studied in detail, their role in immune evasion is not well understood.

Methodology: Using an assay recently developed in our laboratory to measure the ability of antibodies to direct the killing of HIV-infected cells by antibody-dependent cell-mediated cytotoxicity (ADCC), we compared the effects of IFNα-treatment, mutations that differentially affect functional activities of Vpu, and RNAi-knockdown of tetherin, CD4 and NTB-A, on the susceptibility of HIV-infected cells to Env-specific antibodies.

Results: Treatment with increasing concentrations of IFNα resulted in a dose-dependent increase in the susceptibility of HIV-infected cells to ADCC, which corresponded to a dose-dependent increase in cell-surface expression of tetherin, but not NTB-A or CD4. Mutations in Vpu that specifically impair tetherin antagonism, without affecting CD4- or NTB-A-downmodulation, increased the susceptibility of HIV-infected cells to ADCC. Conversely, RNAi-knockdown of tetherin, but not NTB-A or CD4, decreased the susceptibility of virus-infected cells to ADCC.

Conclusions: Our results reveal that Vpu protects HIV-infected cells from ADCC as a function of its ability to counteract restriction by tetherin. These observations suggest that by preventing the accumulation of nascent virions on the cell surface, the anti-tetherin activity of Vpu reduces the exposure of HIV-infected cells to antibodies that might otherwise result in their elimination by antibody-dependent immune responses. By serving as link between innate and adaptive immunity, the antiviral activity of tetherin may be augmented by virus-specific antibodies, and hence much greater than previously appreciated based solely on its ability to inhibit virus replication in cell culture assays.

126 HIV Nef and Vpu Protect HIV-infected CD4+ T Cells From ADCC Through Downmodulation of CD4 and BST2

Tram N. Q. Pham[1], Sabelo Lukhele[1], Fadi Hajjar[1], Jonathan Richard[1], Rajesh M. Valanparambil[2], Halima Medjahed[3], Mathieu Coutu[3], Andres Finzi[3, 4], Eric A. Cohen[1, 4]

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Background: HIV accessory proteins like Nef and Vpu are capable of modulating host proteins such as CD4 and BST2 to evade ultimately host's immune defenses. Indeed, the CD4 receptor is down-regulated by Nef, and to a lesser extent, by Vpu and envelope (Env). BST2 retains new virions at the cell surface restricting their release; and this action is antagonized by Vpu via BST2 downregulation. In recent years, Fc-mediated effector functions including antibody-dependent cell-mediated cytotoxicity (ADCC) have been increasingly recognized as a potentially powerful host response against HIV. Latest evidence has suggested that the epitopes that are recognized by ADCC-potent anti-HIV antibodies (Abs) (e.g., A32) are transitionally exposed upon CD4-Env interaction, the first step of the HIV entry. Thus, we hypothesized that by down-modulating CD4 and BST2 expression at the cell surface, Nef and Vpu could protect HIV-infected CD4+ T cells from ADCC by alleviating exposure of Env epitopes targeted by ADCC-competent Abs.

Methodology: Primary and CEM.NKR CD4+ T cells were infected with CCR5-tropic GFP-marked HIV-1 NL4.3 ADA virus or derivatives lacking Nef (N-), Vpu (U-) or both (N-U-), and examined by FACS for Env expression using anti-Env Abs including A32 and broadly-neutralizing 2G12. Infected cells were evaluated for their susceptibility to ADCC (FACS-based assay) by peripheral blood mononuclear cells (PBMC) using A32 and 2G12 as model Abs.

Results: A32 staining was consistently, markedly highest on CD4+ T cells infected with N-U- virus compared to those infected with the other viruses. The enhanced recognition of the A32, but not of the 2G12, epitope was intimately dependent on cell-surface CD4 expression, and correlated with heightened ADCC activity. CD4-Env interaction was required for this process since the use of the N-U- Env D368A mutant, which blocks CD4-Env engagement, significantly reduced the magnitude of A32 staining and ADCC. Depletion of BST2 from target cells abolished the residual ADCC activity observed with the N-U- Env D368A mutant. Both natural killer cells and monocytes/macrophages within the PBMC population were found to contribute to cell lysis by ADCC.

Conclusions: Our findings strongly suggest that CD4 and Env interaction during virus genesis induces conformational changes on the Env such that ADCC-competent anti-HIV Abs can bind to their epitopes on infected CD4+ T cells and mark them for lysis by immune cells. By cross-linking nascent virions at the plasma membrane, and hence, increasing the Env density at the cell surface, BST2 further enhances the efficiency of this process. Collectively, our data unveil a potential molecular mechanism by which HIV Nef and Vpu function synergistically to spare infected T cells from ADCC and promote viral persistence.

127 Identification of HIV-infected CD4+ T Cells Using HIV RNA and Broadly Neutralizing Antibodies

Joseph P. Casazza[1], Alexander C. Vostal[1], Irene R. Primmer[1], David R. Ambrozak[1], Amarenda Pegu[2], Eli Boritz[3], Mark K. Louder[3], Daniel C. Douek[3], John R. Mascola[3], Richard A. Koup[1]

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Background: HIV envelope proteins are expressed on the surface of HIV-infected CD4 T cells prior to and during viral budding. The manufacture of multiple broadly neutralizing antibodies has raised the possibility of using these biologics as immunotherapeutic agents in chronic HIV infection. We have used these agents and real time PCR of HIV RNAs to identify individual HIV-infected cells.

Methodology: *In vitro* BAL infected CD4 T cells were used to screen MPER, V1V2, V3 glycan and CD4bs antibodies for their ability to identify HIV-infected cells. HIV-infection was confirmed by either p24 staining, or quantitation of spliced Tat- and Rev-associated RNA and Gag RNA. Anti-envelope antibodies capable of identifying *in vitro* infected CD4 T cells were identified for V1V2, V3 glycan and CD4bs antibodies. To detect HIV-expressing cells *ex vivo*, live $CD8^-$ T cells from individuals not on antiretroviral therapy were sorted into CD4 bright, dim and null populations and the frequency of cells actively transcribing HIV RNA determined using limiting dilution analysis. Individual cells from the CD4 dim population that did or did not stain with anti-env antibodies were index sorted and characterized with respect to maturational and activation phenotype.

Results: Surface staining with PG9, PGT121 and VRC07 easily identified live, *in vitro* HIV-infected CD4 T cells. CD4 T cells positively stained for env proteins actively transcribed HIV RNA and produced p24. *Ex vivo*, the greatest number of T cells actively transcribing HIV RNA was found in the CD4 bright population, but the highest frequency of cells transcribing HIV RNA was found in the dim population. Median intracellular copy number of HIV RNAs was significantly higher in the CD4 dim population than in the CD4 bright population; in some individuals the frequency of cells actively transcribing viral RNA approached 2%. The frequency of CD4 null cells was so low that we could not accurately measure this value in most subjects. Down-regulation of surface expression of CD4 in individual cells actively transcribing HIV RNA *ex vivo* was rarely more than one log, whereas down regulation of CD4 surface expression *in vitro* was often greater than 2 logs. *Ex vivo* surface staining of env proteins by PG9, PGT121 and VRC 07 was marginal with no clear population of env staining cells identified in the dim population.

Conclusions: Env staining is less bright *ex vivo* than in *in vitro* infected CD4 T cells and should make the targeting of HIV-infected CD4 T cells by monoclonal antibodies more difficult *ex vivo* than *in vitro*. Nonetheless the identification of individual HIV-infected cells *ex vivo* is important for targeted elimination strategies.

128 Type I Interferon Signaling Is Critical for Early Control of Immune System Damage

Netanya G. Sandler[1], Steven E. Bosinger[2], Jacob D. Estes[3], Eli Boritz[4], Brandon F. Keele[3], Jerome A. Langer[5], Jeffrey D. Lifson[3], Srini S. Rao[4], Gideon Schreiber[6], Daniel C. Douek[4]

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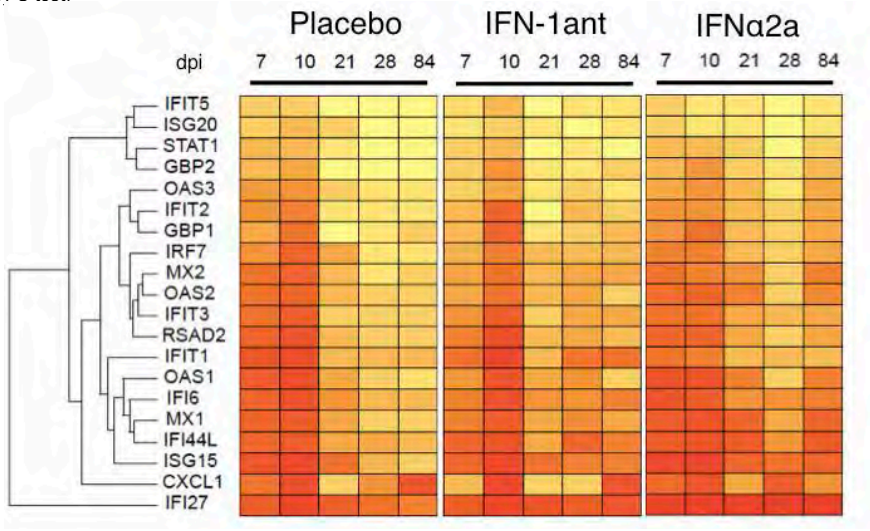
Background: Whether type I IFN (IFN-I) is beneficial in HIV infection by inducing antiviral genes or detrimental by driving immune activation is controversial. IFN receptor antagonist (IFN-1ant) treatment during acute SIV infection accelerated progression to AIDS and death. Its mechanism and the consequences of exogenous IFN-I treatment during acute infection are unknown.

Methodology: 6 rhesus macaques (RMs) received IFN-1ant and 9 RMs placebo starting at challenge through 4 weeks post-infection (wpi). 6 RMs received pegylated IFNα2a weekly from 1 week before challenge through 4 wpi and 3 RMs IFNα2a but no challenge. All challenges were done with high dose rectal SIVmac251. We evaluated SIV+ cells by in situ hybridization, APOBEC3G and TRIM5α by immunohistochemistry (IHC), lymphocyte activation and responses by flow cytometry and transcriptional profiles by mRNA deep sequencing (mRNAseq). P-values were calculated by Kaplan-Meier survival curves and differences between groups by the Mann-Whitney U test.

Results: IFN-1ant RMs had delayed and reduced upregulation of IFN-stimulated genes (ISGs, see figure) and lower lymph node (LN) levels of the IFN-inducible restriction factors APOBEC3G and TRIM5α compared to placebo. They had more SIV+ cells in their LN at 12 wpi and greater LN CCR5+ CD4 T cell depletion at 4 (P=0.02) and 12 wpi (P=0.03). IFN-1ant RMs had decreased frequencies of LN HLA-DR+ CD4 (P=0.009) and CD8 (P=0.02) T cells and peripheral blood (PB) CD16+ NK cells (P=0.01) but not SIV-specific CD4 or CD8 T cells at >12 wpi. IFNα2a RMs required more challenges to be infected than placebo (P=0.0002) and had fewer transmitted/founder variants (P=0.04). After infection, IFNα2a RMs had lower peak ISG



levels, more PBMC-associated SIV gag DNA at 10, 14 and 28 dpi (P=0.04, 0.04, 0.002) and greater LN CCR5+ CD4 T cell depletion at 4 (P=0.02) and 12 wpi (P=0.03). PB CD16+ NK cells (P=0.03) but not SIV-specific T cells were decreased in IFNα2a RMs at >12 wpi. SAMHD1, TRIM22 and TRIM5 expression were transiently increased in PBMCs and rectal biopsies from unchallenged RMs treated with IFNα2a.

Conclusions: Delayed and decreased ISG expression during acute SIV infection in IFN-1ant RMs resulted in increased LN virus burden and CD4 T cell depletion, suggesting that IFN-Is are critical for early control of immune system damage. While increased IFN signaling can stimulate antiviral genes and protect against infection, it may result in less ISG upregulation after infection and accelerated disease progression.

129 miR-422a: A Solitary MicroRNA Biomarker of Interferon-α Anti-HIV-1 Activity In Vivo

Mohamed Abdel-Mohsen[1,2], Xutao Deng[2], Teri Liegler[1], Andri Rauch[3], Bruno Ledergerber[4], Huldrych F. Günthard[5], Joseph K. Wong[1,6], Satish K. Pillai[1,2]

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Background: The cytokine interferon-α (IFN-α) potently suppresses HIV-1 in vitro and in vivo. IFN-α therapy was also recently associated with significant reduction in the size of the HIV-1 latent reservoir. We hypothesized that microRNAs (miRNAs) contribute to the IFN-α-mediated suppression of HIV-1. To inform the development of novel miRNA-based antiretroviral strategies, we investigated the effects of exogenous IFN-α treatment on global miRNA expression profile, HIV-1 viremia, and potential regulatory networks between miRNAs and cell-intrinsic anti-HIV-1 host factors in vivo.

Methodology: Longitudinal PBMC samples were obtained from seven HIV/HCV-coinfected, ART-naïve individuals enrolled in the Swiss HIV Cohort Study before, during, and after pegylated interferon-α/ribavirin therapy (IFN-α/riba). The expression of 754 cellular miRNAs, the Drosha, Dicer1 and DGCR8 miRNA machinery genes, and 34 anti-HIV-1 restriction factors was measured in PBMC using real-time PCR. False discovery rates (FDR) were calculated to account for multiple comparisons in statistical analyses. We identified potential regulatory networks between miRNAs and restriction factors by analyzing inverse expression relationships and sequence homology between miRNA seed sequences and restriction factor mRNA 3'-UTRs

Results: IFN-α/riba decreased HIV-1 viral load by 0.80 (±0.33) log10 copies/ml. Of all 754 miRNAs measured, only one miRNA, miR-422a, was significantly modulated by IFN-α/riba in vivo ($p<0.0001$, paired t test; FDR<0.037). miR-422a log fold-reduction was significantly correlated with HIV-1 log viral load reduction during IFN-α/riba ($r2 = 0.72$; $p<0.015$). IFN-α/riba did not significantly affect expression levels of miRNA machinery genes. Out of 62 inverse-correlated miRNA-mRNA pairs, 38 exhibited significant sequence homology between miRNA and restriction factor mRNA. This frequency (38/62) was significantly higher than the background (8455/25636), estimated by examining random miRNA-mRNA pairs ($p = 8.0*10e-6$, odds ratio = 3.2 [C.I. = 1.9 to 5.6], Fisher's exact test). In particular, miR-422a exhibited potential regulatory relationships with TRIM19, TRIM22, HERC5, and IFITM3.

Conclusions: Our data suggest that the specific suppression of miR-422a contributes to the anti-HIV-1 capacity of IFN-α in vivo, possibly via regulation of multiple retroviral restriction factors. Taken within the context of recent clinical trials demonstrating the effectiveness of miRNA targeting to treat HCV infection, miR-422a may represent a promising pharmacological target to treat or eradicate HIV-1 infection. Moreover, our regulatory network analysis presents additional candidate miRNAs that may be targeted to enhance anti-HIV-1 restriction factor expression in vivo.

Session O-10 Oral Abstracts

10:00 AM – 12:00 PM **Ballroom B/C**

CV and Other Complications

130 Increased Arterial Inflammation Relates to High-Risk Coronary Plaque Morphology in HIV+ Patients

Ahmed Tawakol[1], **Markella V. Zanni**[2], Janet Lo[2], Ezinne J. Ihenachor[2], Allison Han[2], Megan MacNabb[1], Bryan Wai[3], Udo Hoffmann[3], Suhny Abbara[3], Steven Grinspoon[2]

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Background: CVD is increased in HIV, but specific mechanisms remain unknown. Among HIV+ patients, independent studies demonstrate increased arterial inflammation (by ^{18}F-FDG-PET) and increased high risk morphology (HRM) coronary atherosclerotic plaque (by coronary CT angiography, CTA). However, the critical interrelationship between these features in HIV+ patients has not been assessed. We hypothesized that arterial inflammation and HRM coronary plaque would be closely related when simultaneously assessed among HIV+ patients.

Methodology: 41 HIV+ patients on stable ART without a history of CVD but found to have coronary plaque on coronary CTA were evaluated with ^{18}F-FDG-PET. HIV+ patients were stratified into two groups based on relative degree of arterial inflammation (aortic TBR) on PET. High risk coronary atherosclerotic plaque morphology features (low attenuation plaque and positive remodeling) - along with demographic/CVD risk/HIV-specific parameters - were compared between the groups with relatively higher and lower arterial inflammation.

Results: The HIV+ patients with higher and lower TBR's were similar with respect to traditional CVD risk factors and HIV-specific parameters such as duration of HIV, ART use, and viral load. Among HIV+ patients with higher TBR, there was an increased percentage of patients with at least one low attenuation coronary atherosclerotic plaque (40% vs. 10%, $p=0.02$) and one coronary atherosclerotic plaque characterized by both low attenuation and positive remodeling (35% vs. 10%, $p=0.04$). Moreover, in the higher TBR group, both the number of low attenuation plaques/subject ($p=0.02$) and the number of high risk features in the most high risk plaque ($p=0.02$) were increased. In multivariate modeling among the entire HIV+ group,

arterial inflammation category (TBR grouping) remained significantly related to the number of low attenuation plaques/subject (β=0.35, p=0.004), controlling for age, gender, LDL, duration of HIV, and CD4.

Conclusions: These data are the first to demonstrate a relationship between arterial inflammation and high risk morphology coronary plaque in HIV+ patients. Further studies are needed to determine whether arterial inflammation in HIV renders coronary atherosclerotic plaque more likely to rupture, resulting in MI. If so, clinical strategies aimed at reducing the magnitude and chronicity of arterial inflammation may be tested for their potential to stabilize coronary atherosclerotic plaques in HIV+ patients.

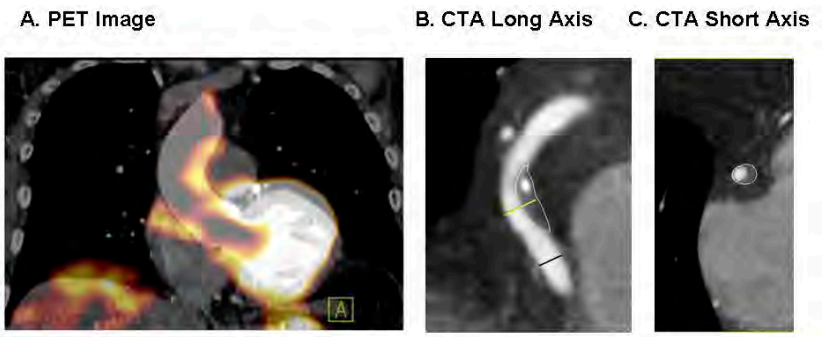

Figure 1. **Panel A.** Representative 18F-FDG-PET image from a subject with increased (2.36) aortic target to background ratio (TBR) demonstrated on coronal imaging. **Panels B and C.** Representative coronary computed tomography (CTA) long-axis (**B**) and short-axis (**C**) images in the same subject as Panel A, demonstrating a low attenuation, positively remodelled plaque with spotty calcification in the mid right coronary.

131 Arterial Inflammation in HIV as Measured by FDG-PET/CT Is Associated With Splenic Activity

Priscilla Y. Hsue[1], Megan MacNabb[2], Rebecca Kaplan[2], Elaine Nitta[1], Steven Deeks[3], Jeffrey Martin[3], Miguel Pampaloni[3], Peter Ganz[1], Ahmed Tawakol[2]
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Background: HIV-infected individuals have increased arterial inflammation and higher risk of cardiovascular disease (CVD), likely related to chronic monocyte/macrophage (MΦ) activation. Arterial inflammation as assessed by 18fluorodeoxyglucose (FDG) PET/CT correlates with MΦ activity and is predictive of CVD risk. Since MΦ that participate in atherosclerosis originate in the bone marrow and transiently reside in the spleen, we sought to evaluate the relationship between arterial inflammation and bone marrow and spleen activity in HIV using FDG-PET/CT.

Methodology: 20 HIV-infected men and 20 non-infected controls (matched for age, gender and Framingham Risk Score) were studied. For the HIV group, 11 (55%) were treated and had an undetectable HIV viral load, and 9 were untreated (45%). Individuals underwent PET-CT imaging and FDG uptake was quantified as standardized uptake values, (SUV) in the bone marrow, spleen, wall of the ascending aorta, and control tissues (muscle and subcutaneous fat) . For between-subject comparisons, SUV was corrected for blood background (SUVc).

Results: The mean age (±SEM) of the participants was 54±2. Arterial inflammation was higher among HIV infected individuals vs. controls (SUVc:3.07±0.17 vs. 2.05±0.06, p<0.001). Similarly SUVc in both the bone marrow and spleen were higher among in HIV (2.87±0.28 vs 1.73±0.07 p=0.002 and 2.10±0.20 vs 1.56±0.05 p=0.006, respectively). Aortic SUV was strongly related to splenic SUV (r= 0.69, p<0.001, Figure 1) and bone marrow SUV (r=0.62, p<0.001) but was not associated with SUV of muscle (r=0.26, p=0.11) or fat (r=0.24, p=0.20).

Conclusions: We demonstrate that arterial inflammation is increased in HIV-infected individuals and is significantly associated with bone marrow and splenic activity. In contrast, FDG-uptake in control tissues does not correlate with arterial inflammation. Thus, upregulation of immune cell activity in the bone marrow and splenic reservoir may contribute to arterial inflammation in the setting of HIV infection.

132 Replicative Senescence of Circulating Osteogenic Cells and Low BMD in Perinatally Infected Men

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Background: We have previously demonstrated that men infected with HIV early in life have 6-19% lower volumetric bone mineral density (vBMD), markedly abnormal trabecular plate and cortical microarchitecture, and decreased whole bone stiffness by High Resolution peripheral Quantitative CT (HRpQCT) of the radius and tibia. We hypothesize that early HIV infection is associated with accelerated replicative senescence and exhaustion of the cellular proliferative capacity of bone cell precursors, which negatively impacts bone formation.

Methodology: A cross-sectional study was performed in 30 HIV-infected men on stable ART and 15 HIV-uninfected men aged 20-25 years utilizing HRpQCT and flow cytometry to identify circulating ostegeogenic cells in peripheral blood mononuclear cells (PBMCs). Among HIV-infected men, 15 were perinatally-infected (PNI) and 15 were infected during adolescence (ADI). Runx2, osteocalcin (OCN) and CD34 antibodies, were used to identify specific osteogenic cell populations in lineage (LIN) negative PBMCs enriched for stem and progenitor cells. Our previous studies suggest that OCN+CD34- cells are more mature osteogenic cells than OCN+CD34+ cells, since they have lost the hematopoietic CD34 marker and express higher mRNA levels of Runx2, and alkaline phosphatase. Relative average telomere length was measured in sorted osteogenic cells (LIN-/OCN+/Runx2+) using qPCR, and expressed as the relative ratio of telomere (T) to nuclear DNA (S) copies.

Results: Percentage of circulating osteogenic cells (LIN-/OCN+/Runx2+) in PBMCs was lower in both the PNI group (0.15+/-0.10%) and the ADI group (0.22+/-0.12%) than in uninfected controls (0.39+/-0.26%; p<0.05); but did not differ between HIV-infected groups. In contrast, the PNI group had a significantly lower percentage of mature osteogenic cells (LIN-/OCN+/Runx2+/CD34-; 55.6+/-27.3%) than both the ADI group (73.2+/-11.4%; p<0.05) and uninfected controls (67.2+/-6.8%; p<0.05). Similarly, the PNI group had shorter telomere lengths (T/S ratio: 2.3+/-0.2) in LIN-/OCN+ cells than both

the ADI group (T/S ratio: 2.5+/-0.2; p<0.05) and uninfected controls (T/S ratio: 2.6+/-0.4; p<0.05). Percentage of OCN+RUNX2+ cells correlated with total vBMD at the radius (r=0.442, p=0.005), as well as cortical and trabecular vBMD, and cortical and trabecular thickness; but not with tibial HRpQCT parameters.

Conclusions: These data suggest that HIV infection early in life, especially perinatal infection, is associated with replicative senescence and decreased numbers and maturation of circulating osteogenic cells, which may result in decreased number and function of osteoblasts and contribute to reductions in BMD and microarchitectural deficiencies.

133 High-Dose Vitamin D and Calcium Attenuates Bone Loss With ART Initiation: Results From ACTG A5280

Edgar T. Overton[1], Ellen S. Chan[2], Todd T. Brown[3], Pablo Tebas[4], Grace A. McComsey[5], Kathleen M. Melbourne[6], Andrew Napoli[7], Royce Hardin[8], Heather J. Ribaudo[2], Michael T. Yin[9], ACTG A5280 Study Team

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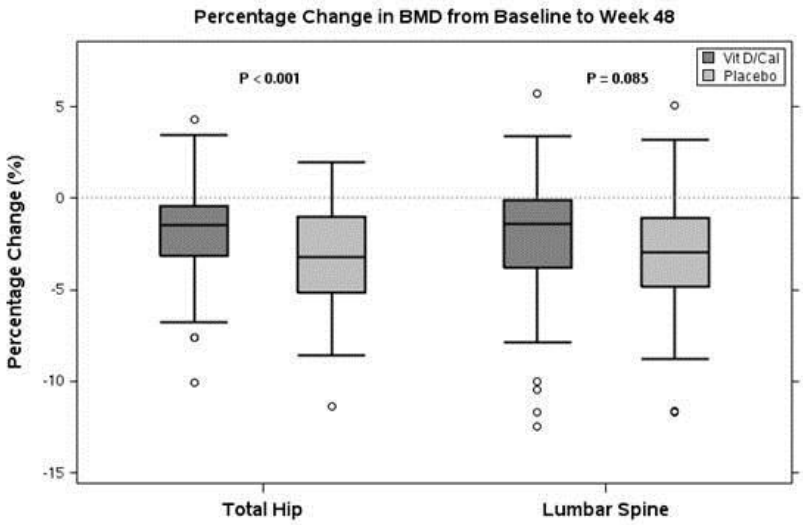
Background: Low bone mineral density (BMD) is common among HIV-infected persons, and the initiation of ART (particularly tenofovir-containing regimens) is associated with 2-5% loss in BMD. Vitamin D deficiency is common among HIV-infected and uninfected individuals; further, efavirenz decreases vitamin D levels. Vitamin D and calcium supplementation have well-described beneficial effects on bone health.

Methodology: 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) on BMD in HIV-infected subjects initiating ART with efavirenz/emtricitabine/tenofovir. The primary endpoint was percentage change in total hip BMD over 48 weeks. Group comparisons by intent-to-treat analysis (ITT) used exact Wilcoxon rank sum tests stratified by screening 25(OH) vitamin D level.

Results: Of 165 eligible subjects enrolled (79 Vitamin D/calcium (Vit D/Cal); 86 placebo), 142 subjects had evaluable DXA data at baseline and week 48 and were included in ITT analysis. The study arms were well-balanced, including reported dietary calcium and vitamin D intake (813 mg and 131 IU daily, respectively). The population was 90% male; 37% non-Hispanic white, 33% non-Hispanic black, 25% Hispanic. Median age was 33 years, BMI 24.4 kg/m^2, CD4 count 341 cells/mm^3, HIV-1 RNA level 4.5 $\log_{10}$ copies/mL, and 25(OH) vitamin D 23 ng/mL. Vitamin D/calcium supplementation was well tolerated; only 3 subjects discontinued due to toxicities (1 vit D/cal, 2 placebo); grade 3 or 4 events were reported in 22% in Vit D/cal arm and 23% in placebo arm. At week 48, 90% of subjects had HIV-1 RNA < 50 copies/mL. Subjects receiving vitamin D/calcium supplementation had less decline in total hip BMD (median: -1.46%; 1st-3rd quartile (Q1, Q3): -3.16%,-0.40%) than placebo (-3.19%; -5.12%, -1.02%) (p=0.001). BMD loss at lumbar spine was similarly reduced with vitamin D/calcium supplementation (-1.41%; -3.78%, 0.00% vs. -2.91; -4.84%, -1.06%) but failed to achieve statistical significance (p=0.085).



The lower and upper edges of the box indicate the first and third quartiles (the 25th and 75th percentiles); The line inside the box indicates the median value.

Conclusions: Vitamin D/calcium supplementation mitigated the loss of BMD seen with initiation of efavirenz/emtricitabine/tenofovir, particularly at the total hip, which is the site of greatest concern for fragility fracture. Future research will evaluate the potential of this safe, low-cost preventive measure to attenuate bone loss associated with other ART regimens.

134 Rosuvastatin Improves Hip Bone Mineral Density But Worsens Insulin Resistance

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Background: The effect of statin therapy on bone mineral density (BMD) in HIV-infected subjects on antiretroviral therapy (ART) is unknown. Also, there are conflicting reports on statin increasing the risk of diabetes in HIV-infected subjects.

Methodology: The 96-week 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 statins on markers of cardiovascular risk and skeletal health in HIV. Subjects were ≥ 18 years, on stable ART, with HIV-1 RNA <1000 copies/mL, LDL-cholesterol <130 mg/dL and evidence of immune activation (defined as having 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 (t score at lumbar spine or total hip < -1). The primary bone endpoint was DEXA-measured changes in total hip BMD. Primary analyses were intent-to-treat. Statistical tests included multivariable linear regression.

Results: 147 subjects enrolled; 78% male, 70% blacks. Median age was 47 years and CD4 count 613 cells/μL; 49% were on PI therapy with median ART and PI duration of 64 and 42 months, respectively; 89% were on TDF; 23% were osteopenic at the hip and 22% at the spine; 78% had HIV-1 RNA <50 copies/mL. Study arms were well balanced. At week 48, statin therapy was associated with a significant increase in total hip BMD (mean ± SD 0.6% ± 2.3%) vs. a decrease in placebo (-0.6% ± 2.9%); p=0.017. Changes in trochanter BMD was also significantly better with statin (0.9% increase vs. 0.7% decrease in placebo; p=0.042). Changes in spine BMD were similar between treatment groups (p=0.66). In addition to the significant statin effect, larger increases in hip BMD were independently and significantly associated with lower baseline soluble tumor necrosis factor-receptor I (sTNF-RI; but not other inflammation markers), and greater 96-week increases in BMI and sTNFR-I (but not other inflammation markers). Within the statin group, the mean (SD) percent increases from baseline in insulin and HOMA-IR were 52% (116%) and 72% (173%), respectively (differences between groups p<0.01 for both). One subject (in placebo group) with entry fasting glucose of 87 mg/dL developed overt diabetes at week 48.

Conclusions: Rosuvastatin therapy increased total hip and trochanter BMD in HIV-infected subjects on ART, regardless of baseline bone density and concomitant PI therapy. Markers of insulin resistance worsened significantly after statin therapy. Follow up to 96 weeks is continuing and will assess the longer term changes in these endpoints.

135 Effects of Tesamorelin On Hepatic Fat in HIV Patients: A Randomized, Placebo-Controlled Trial

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Background: Hepatic fat is often increased in HIV-infected patients with abdominal fat accumulation and may contribute to metabolic abnormalities. Currently, no strategies exist to reduce fat in this critical depot among HIV-infected patients. Tesamorelin, a growth hormone releasing hormone analogue, is FDA-approved for reduction of visceral fat in HIV, but its effects on hepatic fat are unknown. The purpose of this study was to investigate the effects of tesamorelin on hepatic fat. In addition, we investigated novel effects on other fat depots, detailed measures of insulin sensitivity, and cardiovascular risk markers, including carotid intima- media thickness (cIMT).

Methodology: Fifty antiretroviral-treated HIV-infected men and women with abdominal fat accumulation (waist ≥ 95 cm and waist:hip ≥ 0.94 for men; waist ≥ 94 cm and waist:hip ≥ 0.88 for women) were randomized to receive tesamorelin 2mg vs. placebo SC daily for 6 months. Primary endpoints were change in liver fat as measured by magnetic resonance spectroscopy and change in visceral adipose tissue (VAT) as measured by computed tomography. Secondary endpoints included intramyocellular lipid (IMCL), measures of glucose and insulin sensitivity, and cIMT.

Results: Tesamorelin significantly reduced VAT over 6 months (Δ -34±9 vs. 8±11 cm^2, P = 0.005) and hepatic lipid (Δ -2.0 [-6.4, 0.1] vs. 0.9 [-0.6, 3.7] lipid-to-water %, median [IQR], P = 0.004, tesamorelin vs. placebo) over 6 months, yielding a median 40% decrease in baseline liver fat in the treated group. Reduction in VAT was significantly associated with decrease in liver fat (ρ = 0.31, P = 0.047). Trunk fat also decreased (-0.4 [-1.4, 0.7] vs. 0.6 [0.1, 1.7] kg, tesamorelin vs. placebo, P = 0.01), whereas subcutaneous adipose tissue (SAT) and IMCL did not significantly change between groups. Fasting glucose increased in the tesamorelin group at 2 weeks (change from baseline 9 ± 10 vs. 2 ± 12 mg/dL, tesamorelin vs. placebo, P = 0.03), but changes in fasting and 2 hour glucose and fasting insulin at 3 and 6 months were not significantly different between tesamorelin and placebo. By euglycemic hyperinsulinemic clamp, insulin-stimulated glucose disposal, a measure of insulin sensitivity, worsened after 3 months but returned to baseline after 6 months. cIMT decreased by 4% over 6 months within the tesamorelin group (-0.03 ± 0.02, P = 0.04) but did not change in the placebo group (0.00 ± 0.02, P = 0.89) (between group P-value = 0.15). IGF-I increased as expected in the tesamorelin group vs. placebo (P≤0.001).

Conclusions: Tesamorelin significantly reduces hepatic fat in association with VAT reduction among HIV-infected patients with abdominal fat accumulation with no significant changes in glucose homeostasis after 6 months of treatment.

Session O-12 Oral Abstracts
10:00 AM – 12:15 PM **Ballroom A**
Persistence

136LB Early Treatment in Acute SIV Infection Limits the Size and Distribution of the Viral Reservoir

Afam A. Okoye[1], Mukta Rohankhedkar[1], Matthew Reyes[1], Joseph Clock[1], Derick Duell[1], Yoshinori Fukazawa[1], Richard Lum[1], Haesun Park[1], Jeffrey D. Lifson[2], Louis J. Picker[1]
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Background: Recent reports suggest that early treatment intervention during primary HIV infection has a profound impact on the viral reservoir. Indeed, the case of the Mississippi baby and the VISCONTI cohort suggests that reservoirs established early during acute HIV replication may be quantitatively and qualitatively different from reservoirs established later in chronic infection and perhaps be more amenable to cure. Here we sought to investigate the effect of early treatment on the viral reservoir in SIV-infected rhesus macaques (RM) when antiretroviral therapy (ART) is initiated either prior to peak viral replication, at or near peak viral replication, or in early chronic infection.

Methodology: To test the effect of timing of treatment on viral reservoirs, RM infected intravenously with SIVmac239 were subjected to multi-drug ART consisting of tenofovir, emtricitabine, dolutegravir and darunavir boosted with ritonavir starting day 7 (group A), day 10 (group B) or day 42 (group C) post-challenge. Plasma viral loads (pvl) and cell-associated viral loads of peripheral blood mononucleocytes (PBMC), bone marrow (BM), small intestinal mucosa (GUT) and lymph node (LN) biopsy samples were assessed by real-time quantitative PCR/RT-PCR at various time points.

Results: In group A (n=2), pvl continued to rise after therapy was initiated, peaking by day 12 to an average of 71000 SIV RNA copies/ml then declined below the limit of detection (<30 copies/ml) after just 6 weeks of ART. In group B (n=2), pvl peaked on day 12 to an average of 1.8x10e6 copies/ml and

required 18 weeks of ART to decline below the limit of detection. In group C (n=18), peak pvl was reached between days 12-14 to an average of 1.4x10e7 copies/ml but complete virus suppression was not achieved in all RM even after 20 weeks of ART. SIV DNA per 10e8 PBMC were on average 1020, 8606, 43914 copies in groups A, B and C, respectively, at 17 weeks post-challenge and a combined analysis showed there was a significant correlation between peak plasma SIV RNA and the levels of total SIV DNA in PBMC (p=0.03). In addition, SIV DNA in LN, BM and GUT were lower, on average 497, 1929 and 324 copies/10e8 cells, respectively, in group A, compared with an average of 9647, 4069 and 35090 copies/10e8 cells, respectively, in group B 17 weeks post-challenge.

Conclusions: These results demonstrate that early ART, when initiated prior to peak virus replication, limits systemic virus dissemination and seeding of the reservoir in peripheral and extra lymphoid mucosal compartments. A delay as short as three days during the "hyperacute" phase can result in over a log higher tissue-based reservoir size, once therapy is started and maintained. Aggressive monitoring for acute infection with immediate introduction of ART could profoundly influence treatment outcomes.

137 CD4 T-Cell Subset Composition of HIV Reservoirs in Gut, Lymph Node, and Blood During HAART

Steven A. Yukl[1,2], Teri Liegler[1], Mohamed Abdel-Mohsen[1], Elizabeth Sinclair[1], Hiroyu Hatano[1], Frederick Hecht[1], Ma Somsouk[1], Sarah Palmer[3,4], Steven G. Deeks[1], **Joseph K. Wong**[1,2]

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Background: Central and transitional memory CD4 Tcell maturation subsets comprise the largest fraction of the HIV reservoir in peripheral blood but less is known about the cellular composition of HIV reservoirs in those lymphoid tissues that disproportionately harbor HIV during suppressive ART.

Methodology: 8 subjects on ART (5 started treatment during chronic infection, 3 during early infection, ART duration >3years, VL<50c/ml, CD4>350) underwent leukapheresis, lymph node biopsy and rectal biopsy. Following cell isolation, flow-based sorting was used to isolate naïve (Nv), central- (CM), transitional- (TM) and effector- (EM) memory populations. Cellular HIV DNA and RNA were measured using previously published real time PCR assays and were normalized by simultaneous measurement of TERT and GAPDH, respectively. Infection frequencies and HIV expression was compared among sites and Tcell subsets.

Results: HIV DNA was measurable from a majority of CD4 T cell maturation subsets from all three sites. The highest HIV DNA concentrations were in EM cells in rectum (median 2289 [IQR 1269-6424] c/10^6, p=0.008 for comparison with concentrations in EM, TM and CM from blood). HIV DNA levels in TM/CM cells in rectum were also higher than in CM or TM (p=0.016) and EM (p=0.16) in blood. HIV+ cell concentrations were intermediate for T cell subsets in lymph node. As expected, Nv cells had low infection frequencies. Paradoxically, HIV expression per infected cell (expressed as ratio of HIV RNA to DNA) was lower in all subsets in rectum compared to blood; expression levels were intermediate in lymph node cells. The contribution of each T cell subset to the total HIV reservoir differed strikingly by site. Infected EM cells comprised 80% of the total T cell reservoir in rectum, 40% of the reservoir in lymph node but <20% in blood. With the caveat of a small study size, infection frequencies tended to be lower in early treatment subjects compared to chronic treatment subjects while the distribution of infection among T cell subsets were not appreciably different between subject groups.

Conclusions: The distribution of the reservoir is tissue dependent, with rectal tissues notable for a high frequency of HIV DNA in EM cells, but low levels of HIV RNA expression in these and other memory cells. The majority of the infected cells in rectum and ai sizable minority of infected cells in lymph node are found in EM cells, while most of the infected cells in blood are in CM/TM cells. These data suggest that the local host environment affects HIV expression and how latently infected cells take up residence. The impact of potentially curative interventions on HIV persistence is expected to be different across anatomic sites.

138 Proliferation of Cells With HIV Integrated Into Regulatory Genes Is a Mechanism of Persistence

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Background: Understanding the mechanisms of HIV persistence during ART is important for developing curative strategies. Our previous work suggests that proliferation of HIV-infected cells helps sustain the HIV DNA reservoir during ART. To confirm that HIV-infected cells proliferate and investigate how specific HIV-infected cells persist during suppressive ART, viral integration sites and the associated envelope sequences were determined.

Methodology: PBMC DNA from participants on long-term suppressive ART was diluted to a single HIV template per PCR. The chromosomal integration site and the associated HIV env (C2-V5) was sequenced. Integration sites were identified with BLAST. For integration sites located within a gene, the biological function of the gene (gene ontology) and statistical enrichment of genes associated with defined biological processes was evaluated with Bioconductor.

Results: 538 integration sites were determined following single-templete PCR of DNA diluted from 9 specimens from 3 participants after ~2, ~6, and ~10 years of suppressive ART. Multiple identical HIV integration sites were detected within each individual; these replicates accounted for 39.6% (213/538) of integration sites. Linked HIV env sequences were amplified from 68 integration sites. All env sequences amplified from the same integration site (32 env sequences from 13 integration sites) were identical, whereas only one env sequence was shared between 37 different integration sites (Fischer's exact, 13/13 v 1/37, P<0.0001), a distribution consistent with infected cell proliferation. 372 different integration sites were identified, of which 63.7% (237/372) were located in genes. The integration site recovered most frequently (32 times) was in MDC1, which has a known role in cell cycle arrest and apoptosis. The only gene with HIV integrated into multiple sites and in multiple (2 of 3) participants was BACH2, recently identified as a tumor suppressor. HIV that persisted during suppressive ART was statistically enriched for integration into genes controlling various biologic processes, especially genes involved in the

cell cycle, such as cell activation, differentiation, and proliferation. These results strongly suggest that the specific gene disrupted by HIV integration may impact cellular proliferation and survival.

Conclusions: A disproportionate number of integrations at identical sites in the human chromosome spanning many years and linked to identical HIV env sequences indicates that proliferation of infected cell contributes to the persistence of HIV cellular reservoirs. Furthermore, HIV integration into specific sites in the human chromosome may modify gene function, allowing proliferation and prolonged persistence of specific infected cells.

139 Novel Ex Vivo Approaches Distinguish Effective and Ineffective Drugs for Reversing Latency In Vivo

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Background: HIV-1 persists in a latent reservoir (LR) despite antiretroviral therapy (ART). This reservoir is the major barrier to HIV-1 eradication. Current approaches to purge the LR involve pharmacologic induction of HIV-1 transcription and subsequent killing of infected cells by cytolytic T lymphocytes or viral cytopathic effects. Agents that reverse latency without activating T cells have been identified using in vitro models of latency, however their effects on latently infected cells from infected individuals remain largely unknown.

Methodology: We evaluated the effects of candidate latency reversing agents (LRAs) on resting CD4+ T cells (rCD4s) from HIV-1 infected patients on suppressive ART. Disulfiram, JQ1, bryostatin-1 and the HDAC inhibitors vorinostat, romidepsin, and panobinostat were tested at clinically relevant concentrations that effectively reversed latency in a primary cell in vitro model. Two novel independent assays were developed for ex vivo evaluation of the leading candidate LRAs. We first tested LRAs for their ability to induce viral outgrowth from latently infected patient cells. Next, we evaluated the ability of LRAs to induce increases in intracellular HIV-1 mRNA in patient rCD4s.

Results: We treated purified rCD4s from patients on ART with individual LRAs for 18 hours and then cultured them with MOLT-4/CCR5 cells for 14 days to allow viral outgrowth. Surprisingly, none of the LRAs induced viral outgrowth from cells from any patient tested. Vorinostat, romidepsin, panobinostat, disulfiram, and JQ1 all failed to increase intracellular HIV-1 mRNA in patient rCD4s after 18 hours treatment. Only the PKC agonist bryostatin-1 caused significant increases, though the effect was only seen in some patients. Similar results were observed after 6 hours of LRA treatment. While a previous study reported modest increases in transcripts containing HIV-1 gag sequence in patient rCD4s after ex vivo and in vivo vorinostat treatment (Archin et al., Nature 2012), we show that such small increases are likely a result of host promoter initiated read-through transcription of the integrated HIV-1 provirus.

Conclusions: The novel assays presented herein facilitated the first comparative ex vivo evaluation of candidate LRAs. None of the candidate non-T cell activating LRAs tested disrupted the LR ex vivo. The striking discordance between the effects of non-T cell activating LRAs in models of HIV-1 latency and the ex vivo effects we observed in rCD4s from patients on ART indicates that these in vitro models do not fully capture all mechanisms governing HIV-1 latency in vivo. We conclude that these compounds are unlikely to drive the elimination of the LR in vivo when administered individually, as has been proposed.

140 Effect of Vorinostat On Host Gene Expression in HIV Infected Patients On Antiretroviral Therapy

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Background: Histone deacetylase inhibitors (HDACi) activate HIV production in latently infected T-cells in vitro. Recently, the HDACi vorinostat was shown to significantly increase cell associated unspliced (CA-US) HIV RNA in HIV infected subjects on suppressive antiretroviral therapy (ART). However, the effects of vorinostat on host gene regulation and the relationship of these changes to efficacy in activation of HIV transcription is unknown. The main aim of this study was to determine the effects of multi-dose vorinostat on host gene expression in HIV infected patients on ART.

Methodology: We evaluated differential gene expression in blood from 20 HIV infected patients on ART who received vorinostat (400mg/day) for 14 days. Gene expression was analyzed at baseline and two time points on vorinostat (d1 and d14) and post-cessation of vorinostat (d84). Differential gene expression was assessed using a (moderated) t test. For data mining and functional analyses, the genes selected satisfied a false discovery rate (FDR) corrected p-value ≤ 0.05.

Results: There was clear difference in gene expression for all patients at d1, d14 and d84 compared to baseline. At d1, there was a distinct pattern of response in 7/20 patients with marked up-regulation of genes and enrichment of pathways involved in transcription, chromatin remodeling, translation elongation and cell survival. We could also observe the selective upregulation of genes involved in the regulation of HIV latency including CDK9, HEXIM2 and RELA. Transcriptional activity associated with chromatin remodeling disappeared by day 14 in all patients but there was persisting differential gene expression at day 14 and day 84 compared to baseline. At day 14, the major differentially expressed genes were associated with reduction of oxidative stress/inflammation and genes associated with DNA repair. At day 84, the major differentially expressed genes were alpha defensins. Regression analysis of gene expression and CA-US HIV RNA revealed distinct transcriptomic profiles correlating with high and low levels of CA-US HIV RNA at day 1.

Conclusions: These results suggest that the effects of vorinostat on chromatin largely occur within the 1st day after the first dose of drug and that after 14 days of continuous dosing, there are compensatory mechanisms associated with transcriptional repression and cell survival. These results will guide future interventions testing SAHA's capacity to purge the HIV reservoir.

141 Cyclophosphamide Enhances SB-728-T Engraftment To Levels Associated With HIV-RNA Control

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Background: SB-728-T is a zinc finger nuclease-mediated, CCR5-modified autologous CD4 T-cell product that can provide a reservoir of CD4 T-cells that are resistant to HIV entry. Studies in ART-treated CCR5 Δ32 heterozygote HIV subjects showed VL reductions from peak during treatment interruption that correlated with estimated circulating bi-allelic CCR5-modified CD4 T-cells (maximal at ~200 cells/ul), supporting the importance of achieving this level of transferred T cells. We have now evaluated cyclophosphamide (CTX) conditioning prior to infusion of SB-728-T in HIV subjects. CTX enhances the engraftment and activity of adoptively transferred anti-cancer T-cells by homeostatic proliferation of the transferred T cells, an increase in endogenous cytokines (e.g. IL-7 and 15) and promotion of homing to lymphoid organs.

Methodology: A dose escalation study of IV CTX, 200 mg (n=3); 500 mg/m^2 (n=6) and 1 g/m^2 (n=3) administered 1-3 days prior to SB-728-T infusion was performed in aviremic, ART treated HIV subjects with CD4 T cell counts > 500.

Results: CTX was well tolerated at all doses, except for low grade GI side-effects which were treated with anti-emetics. No clinically significant decreases in neutrophils, WBC, platelets or Hgb/Hct were seen. A dose-related increase in total CD4 count and engraftment of CCR5 modified cells was observed (median estimated bi-allelic modified CD4 cells and median increase in total CD4 at six weeks post infusion of 14/μL and 299/μL at 200 mg, 74/μL and 771/μL at 500 mg/m^2 and 148/μL and 2077/μL at 1 g/m^2, respectively). By comparison, total CD8 cell count at wk 6 was not affected by the CTX dose administered (median of 783/μL at 200mg, 536/μL at 500 mg/m^2 and 679/μL at 1 g/m^2). Engraftment of estimated bi-allelic CCR5 modified CD4 cells with the 1 g/m^2 CTX dose was near levels associated with anti-viral effects in CCR5Δ 32 heterozygote HIV subjects**. A** 1.1 to 1.5-log VL reduction from peak was seen in 2 subjects at the 500mg/m^2 dose level and in another subject at the 1 gram/m^2 dose level during a 16 week TI. The latter subject had an increase of CD4 T-cells of 3496 cells /μl at wk 1, and estimated bi-allelic modified CD4 T-cells of 148 cells/μL at six weeks post infusion with VL reduction from 235K to 7.9 K (VL set pt 35,500).

Conclusions: CTX pre-treatment is well tolerated up to 1 g/m^2 in ART treated HIV subjects with no adverse effects on hematologic parameters. A dose-related increase in engraftment of SB-728 T cells occurred to levels obtained in CCR5Δ 32 heterozygote HIV subjects who have achieved unmeasurable VL during TI. CTX conditioning may be a useful strategy to 1) maximize the engraftment and anti-viral effects of SB-728-T adoptive T cell therapy in HIV subjects and 2) may be an important immunomodulatory chemotherapeutic agent for immunotherapy in HIV.

142 Stimulation of Subdominant CTL Response Is Required for the Elimination of HIV-1 Latent Reservoir

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Background: HAART can control viral replication in HIV-1 infected individuals, but can't eliminate the virus due to viral persistence in latent reservoirs. Eradication strategies have focused on reactivation of latent HIV-1 in the reservoir without global T cell activation. Our recent study suggested reactivation of latent HIV-1 alone might not be enough, and stimulation of HIV-1-specific CTL response facilitated clearance of the latent reservoir. However, plasma HIV-1 develops CTL escape mutations to evade immune response. CTL escape of HIV-1 has been studied extensively through the analysis of plasma virus, but little is known regarding the potential presence of CTL escape variants in the latent reservoir. This raises a critical issue for CTL-based eradication strategies: if CTL escape variants are archived in the latent reservoir, the host CTL response may fail to recognize and clear infected cells after latency is reversed.

Methodology: Proviral DNA from HAART-treated patients was extracted, Gag was amplified by PCR and deep-sequenced in search for CTL escape mutations. Latent HIV-1 was recovered from patients' resting CD4+ T cells using a viral outgrowth assay. Gag from the outgrown viruses was sequenced and compared with the proviruses. Outgrown viruses were used to infect CD4+ T cells from the same patients. Autologous pre-stimulated or non-stimulated CD8+ T cells were cocultured with infected CD4+ T cells to access killing.

Results: CTL escape variants dominate in the latent reservoirs of chronic phrase-treated patients, but not in acute phrase-treated patients. After reactivation, outgrown viruses still carried the same CTL escape variations with provirus in the reservoir. CD4+ T cells infected by these escape variants were insensitive to the relevant epitope-specific CTL clones, but can be killed by broad spectrum CTL response. More importantly, we were able to identify and stimulate subdominant CTL clones in chronically infected patients which can recognize and kill autologous target cells infected with these escape variants.

Conclusions: Our study demonstrates that the dominant presence of CTL-resistant viruses in the latent reservoir poses great hurdles to the viral eradication. Boosting broad spectrum or more specifically, subdominant CTL responses is required for the elimination of viral latent reservoir.

143 Dendritic Cell-Based HIV Therapeutic Vaccine Increases Residual Viremia in Individuals On ART

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Background: We evaluated the impact of therapeutic vaccination with an autologous dendritic cell (DC) vaccine pulsed with autologous, inactivated HIV-1-infected apoptotic cells on the level of residual plasma viremia in individuals on suppressive antiretroviral therapy (ART) and following analytic treatment interruption (ATI).

Methodology: Autologous HIV-1 was obtained from 10 ART-naïve subjects prior to starting ART. The vaccine was composed of monocyte-derived DCs (matured with TNFα, IL-1β, IFNγ, Poly I:C) pulsed with apoptotic cells generated from autologous lymphocytes infected with autologous HIV-1. After at least 12 weeks of virologic suppression, subjects received 3 doses of vaccine (10^7 DC/dose, 2 weeks apart). Six weeks after the third vaccination, subjects underwent ATI with a 4th vaccine dose given 2 weeks into ATI. Plasma samples from Pre-ART, 3 time points pre-ATI, and 2 and 4 weeks post ATI were assayed for residual viremia by single copy assay targeting HIV-1 integrase (iSCA). PBMCs were obtained at baseline and right before ATI to evaluate levels of immune activation (HLA-DR+CD38+) and regulatory T cell (Treg) frequencies (CD4+CD25+FOXP3+).

Results: After at least 8 weeks of HIV RNA suppression <50 cps/ml (Roche Amplicor v1.5), 6/9 subjects had residual viremia detected by iSCA ranging from 2.0-49.5 cps/mL. In 4/10 subjects, levels of residual viremia increased 2.9- to 41.8-fold (mean=14-fold) after vaccination and before ATI despite continuous ART. CD4+ and CD8+ T cell activation increased after the 1st vaccine dose but returned to pre-vaccine levels before ATI, whereas residual viremia in the 4 subjects continued to increase. There was no correlation between residual plasma viremia and activation of $CD4^+$ (r=-0.44; p=0.23) or $CD8^+$ cells (r=-0.30; p=0.41). Treg frequencies did not change and did not correlate with levels of residual viremia. Two weeks after ATI, 8 subjects were undetectable by the Roche assay, but 6 of 8 had detectable viremia by iSCA (range=19.9 to 3322 cps/mL; median=145.9 cps/mL). Plasma viremia measured by both assays rebounded to pre-ART levels by week 6 of ATI in 7/10 subjects.

Conclusions: Vaccination with an autologous DC-HIV vaccine did not prevent viral rebound after ATI and increased residual viremia in 40% of subjects despite continuous ART. The increase in residual viremia was not associated with changes in T cell activation or Treg frequency. Therapeutic vaccination may increase HIV-1 replication or expression from latent reservoirs.

144LB HIV-1 Rebound Following Allogeneic Stem Cell Transplantation and Treatment Interruption

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Background: We reported the loss of detectable HIV-1 reservoirs in 2 individuals following reduced-intensity conditioning allogeneic hematopoietic stem cell transplantation (HSCT) from CCR5 wild-type donors. HIV-1 remained undetectable from blood and rectal tissue on ART despite the testing of large numbers of PBMCs or CD4+ T cells in the setting of full donor chimerism. As a result, analytical treatment interruption (ATI) was performed, and we now provide an in-depth analysis of HIV-1 viral/immune dynamics during ATI and after viral rebound.

Methodology: ATI was performed in consenting patients with weekly to biweekly monitoring of viral load (VL) and proviral DNA by clinical assays. Large-volume blood draws, leukapheresis, and cerebral spinal fluid sampling was performed before, during and/or after ATI to perform: 1) quantification of HIV-1 DNA in PBMCs and in sorted CD4+ T lymphocyte subsets (central memory, effector memory, stem cell memory, terminally differentiated, and naive cells), 2) plasma RNA quantification by single copy assay (SCA), 3) characterization of HIV-specific T cell immunity and viral rebound and decay following ART re-initiation, and 4) single-genome analysis of full-length HIV-1 env sequences from DNA prior to HSCT and post-rebound plasma RNA.

Results: During ATI, patient A had no detectable plasma RNA or cell-associated HIV-1 DNA for 3 months and patient B had no detectable virus for 8 months after ART cessation prior to eventual rebound. Patient B also had negative PBMC DNA (<0.07 copies/10^6 PBMCs) and viral RNA by SCA (<0.4 copies/mL) by ultrasensitive assays 5 and 18 weeks into ATI. Once detected, plasma RNA increased rapidly, reaching 2-4x10^6 copies/ml within 2-3 weeks; rebound plasma viremia was mono/oligophyletic. Both patients developed symptoms of acute retroviral syndrome, including aseptic meningitis and new NNRTI resistance in one patient that developed early after ART-initiation. Symptoms rapidly resolved with initiation of active ART and subsequent viral suppression in both patients. Patient A had detectable but low-level HIV-1 DNA in pre-ATI terminally differentiated lymphocytes isolated from 200x10^6 PBMCs from post-hoc testing after rebound, but from no other subsets; patient B had no detectable HIV-1 DNA.

Conclusions: Our results suggest that allogeneic HSCT may lead to loss of detectable HIV-1 from blood and gut tissue, but viral rebound can occur despite up to a 3-4 log10 reduction in reservoir size. Long-lived tissue reservoirs, including host macrophages that may be replaced more slowly than T-lymphocytes following HSCT may have contributed to viral rebound. More sensitive assays for detecting HIV persistence are needed; ATI remains the most reliable measure of viral persistence following therapeutic intervention.

Session O-13 Oral Abstracts

10:00 AM – 12:00 PM **Room 304**

Antiretroviral Scale-Up in Sub-Saharan Africa: Challenges and Opportunities

145 Age-Disparate Relationships and HIV Incidence Amongst Rural South Africa Women

Guy Harling[1], Marie-Louise Newell[2, 3], Frank Tanser[3], Ichiro Kawachi[4], SV Subramanian[4], Till Bärnighausen[1, 3]

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Background: Age-disparate relationships are considered risky for young women due to older men having higher levels of both incident and prevalent HIV, and more social and economic power to coerce women into riskier sex. Both these effects are likely to be weaker for older women. Several public health campaigns have been run to discourage young women from relationships with older men. However, longitudinal evidence relating sex-partner age-disparity on HIV acquisition is lacking.

Methodology: We analyzed a population-based cohort of women in rural KwaZulu-Natal, South Africa who were HIV seronegative at first interview between January 2003 and June 2012. We stratified our cohort by age into younger (15-29 years; n=2,444) and older (30-50 years; n=1,737). Using proportional hazards models, we measured whether the age-disparity of a woman's most recent sexual partner at each annual round of HIV testing was associated with subsequent HIV acquisition.

Results: Amongst younger women, 458 HIV seroconversions occurred over 5,913 person-years of follow-up (incidence rate [IR]: 7.75 per 100 person-years). The age-disparity of women's partners was not associated with HIV acquisition when measured either continuously (hazard ratio [HR] for a one-year increase in partner's age: 1.00, 95% confidence interval [CI]: 0.97-1.03) or categorically (man ≥5 years older: HR 0.98, 95%CI 0.81-1.20; man ≥10 years older: HR 0.98, 95%CI 0.67-1.43).

Amongst older women, 116 seroconversions occurred in 5,714 person-years of follow-up (IR: 2.03 per 100 person-years). As partner age rose, HIV incidence risk fell significantly: a five-year older partner was associated with a one-third reduction (HR: 0.63, 95%CI: 0.52-0.76) and a ten-year older partner with a one-half reduction (HR: 0.48, 95%CI: 0.35-0.67), compared to a same-aged partner.

Results for both age-groups were robust to adjustment for known socio-demographic and behavioural HIV risk factors, and did not vary significantly by women's age, marital status, education attainment, or household wealth. Associations did not vary significantly by woman's age within each age-group.

Conclusions: In this rural KwaZulu-Natal setting with very high HIV incidence, older partner age did not predict HIV acquisition amongst young women, and appeared protective for older women. Campaigns to reduce age-disparate sexual relationships may not be a cost-effective use of HIV-prevention resources for the young, and may be inappropriate or even harmful for older women.

146 Introduction of HIV into Stable Heterosexual Couples in Rakai, Uganda Before and After ART

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Background: HIV transmission within stable heterosexual couples is common and accounts for a substantial proportion of new HIV infections in sub-Saharan Africa. This is partly because once virus is introduced by one partner there is often rapid transmission to the second partner. While studies of prevalent HIV discordant couples are common, the dynamics of viral introduction into initially uninfected couples are poorly understood.

Methodology: We followed 4,570 initially concordant HIV negative couples for 21,535 couple-years in the Rakai Community Cohort Study, a prospective HIV and behavioral surveillance study in rural Rakai, Uganda. Couples were followed annually between 1997-2011. HIV testing and counseling were offered, and ART became available in 2004. Data on demographics, sexual behaviors, and extra-couple relationships were obtained from both partners. Multivariate Cox proportional hazards models were used to identify factors associated with a first incident infection (i.e. HIV introduction) into the relationship.

Results: We identified 135 HIV introductions into stable couples. In 29/135 (21.5%) of these couples, the second partner seroconverted during the same study interval that virus was introduced. Among the remaining 106 incident couples who were HIV-discordant, 66 (62.3%) infections were introduced by males, and 40 infections (37.7%) by females. Self-report of extra-couple relationships in the past year was strongly associated with viral introduction (male only: adjHR=2.3, 95%CI: 1.5-3.7; female only: adjHR=5.3, 95%CI: 1.9-15.1; both partners: adjHR=6.5, 95%CI: 2.5-17.5); however, only 29.0% of initially infected females and 69.6% of initially infected males admitted to having external sexual partners. Self-reported genital ulcer disease in both partners at the prior visit was also associated with increased risk for HIV introduction (HR: 3.2, 1.5-6.8). ART availability after 2004 was associated with a 46% reduction in risk for HIV introduction into couples (post vs. pre ART period adjHR=0.54; 95%CI: 0.35-0.83).

Conclusions: This is the first study of incident HIV introduction into stable initially uninfected couples in rural Africa before and after the availability of ART. Both males and females introduced infection into relationships, highlighting the need for prevention strategies targeting both genders to prevent discordancy. Couples with a history of extra-marital relationships and genital ulceration are at elevated risk; however, underreporting of external partnerships may hinder targeted prevention to stable couples. Availability of ART was associated with a substantial reduction of risk for HIV introduction, potentially due to lower HIV exposure to untreated extra-marital partners.

147 One Year Outcomes Following Community-Based HIV Self-Testing: A Prospective Study in Malawi

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Background: HIV testing and counselling (HTC) is key to care and prevention, but only ~25% of adults in sub-Saharan Africa report testing for HIV in the preceding 12 months. HIV self-testing (HIVST) is a novel approach that could promote increased coverage and frequency of HTC. We investigated HIVST including subsequent linkage into care.

Methodology: 16,660 adult (≥16 years) residents of 14 high-density neighbourhoods (HIV prevalence 18.5%) were included in a cluster randomised trial. Two residents were trained in each neighbourhood to provide HIVST from their homes (one test per resident per year). Clients received written and verbal information to promote linkage into HIV care coupled with home-initiation of HIV care if requested. Population-level uptake was estimated from enumeration denominators. Accuracy of HIVST was assessed through quality assurance (QA) re-testing (2 parallel rapid tests) with a 10% random sample of self-testing

clients asked to retest. A strong community-based reporting system was in place for monitoring adverse events. Data were analysed using summary statistics and logistic regression adjusted for clustering.

Results: Overall, 13,966 self-test kits were distributed with 89% returned as used kits with feedback forms. Uptake was 76% (12,658/16,660), including 5,840 (67%) of all men. The highest uptake was in the youngest age group (16-19 years: 2,360/2,539, 93%) falling to 41% (298/733) in men ≥50 years. Early HIVST adopters (2,658 in 1st month) were significantly more likely to be female, adjusted odds ratio (aOR) 1.20 (95% CI 1.06-1.36); younger Ptrend<0.001, and not in a couple aOR 2.22 (95% CI 1.54-3.16). In total, 851/16660 (9%) residents confided positive HIVST results with 25% already on ART and 500/638 (78%) accessing HIV care (pre-ART or ART). QA showed 99.1% agreement with self-reported HIVST results (sensitivity 93.8% [95% CI 85.0-98.3%], specificity 100% [95% CI 100-100%]). No suicides or assaults were reported, but coercion was reported by 147 (3.7%) male and 119 (2.2%) female respondents; p-value<0.001, mostly from partners.

Conclusions: Uptake of HIVST, subsequent linkage into care, and accuracy were high with this strategy. Uptake of HIVST, subsequent linkage into care, and accuracy were high with this strategy. Coercive testing and retesting on ART are concerning aspects of HIVST that need to be anticipated and discouraged. Community-based HIVST offers high potential to increase knowledge of HIV status, assisting with increasing access to HIV care and prevention when combined with proactive linkage strategies. Community-based HIVST offers high potential to increase knowledge of HIV status, assisting with increasing access to HIV care and prevention when combined with proactive linkage strategies.

148 Community HIV Testing and Linkage To Care Reduces Population Viral Load in South Africa and Uganda

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Background: High coverage of HIV counseling and testing (HCT) through community campaigns and linkage of HIV+ people to care has the potential to decrease HIV incidence if most eligible people initiate antiretroviral therapy (ART) and are virally suppressed.

Methodology: We conducted community-wide home-based HCT in KwaZulu-Natal, South Africa, and Mbarara, Uganda, from September 2011 to May 2013. Resident adults within a geographically defined community were offered HCT. HIV+ persons received point-of-care CD4 results (PIMA), counseling about HIV and ART, referral for HIV care, and follow-up visits at months 1, 3, 6, 9 and 12. HIV viral load was measured among all HIV+ persons at baseline, 6 and 12 months.

Results: 3,546 adults from 1,549 households were enrolled and 636 HIV+ persons were identified - 404 in South Africa (32% prevalence) and 232 (11% prevalence) in Uganda. Of the 636 HIV+ persons identified, 230 (36%) were newly-identified. The median CD4 count was high: 456 (IQR, 289-633). At baseline 254/636 (40%) of HIV+ persons were on ART, and 126/636 (20%) were not on ART but were ART eligible by national guidelines (CD4≤350 cells/μL). Mean viral load among all HIV+ persons who reported not being on ART at baseline was 3.86 log10 copies/mL.

By month 12, >97% of HIV+ persons visited an HIV clinic and 142 initiated ART, including 94/126 who were eligible for ART at baseline (CD4≤350 cells/μL). 570 (90%) of HIV+ persons had a month 12 viral load, including 114/126 (90%) of ART eligible participants at baseline. From baseline to month 12, mean HIV viral load decreased 0.55 log10 copies/mL (p<0.001) among all (N=570) HIV+ persons, 0.93 log10 copies/mL (p<0.001) among 331 HIV+ persons not on ART at baseline, and 1.96 log10 copies/mL (p<0.001) among 114 ART eligible persons who were not on ART at baseline. The proportion of HIV+ persons with a viral load of <1,000 increased from 50% to 65% (p<0.001). In multivariate analysis, higher baseline viral load was associated with lower clinic linkage (HR 0.81 per log10 increase; 95% CI 0.77-0.86) over 12 months. During 12 months of follow-up among ART eligible HIV+ persons, CD4 201-350 vs. CD4 ≤200 and baseline viral load were associated with a lower ART initiation (HR 0.34; 95% CI 0.22-0.52 and HR=0.80 per log10 increase; 95% CI, 0.65-0.99, respectively).

Conclusions: Community-based HCT can achieve high coverage of testing, linkage to care, uptake of ART and significant suppression of viral load at population level 12 months after HCT. Viral load suppression has the potential to decrease onward transmission of HIV. The association between higher viral load and lower uptake of ART may indicate the benefit of viral load criteria for ART initiation and the need for strategies to motivate persons with higher viral load to initiate ART.

149 Enhanced HIV Surveillance To Evaluate the National Response To HIV/AIDS in Kenya

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Background: Kenya has conducted two AIDS Indicator surveys (AIS) to monitor HIV prevalence and the impact of HIV care, treatment, and prevention services in the country. The first AIS was conducted in 2007 (KAIS 2007) and the second in 2012 (KAIS 2012).

Methodology: KAIS 2012 used a two-stage stratified cluster sampling design to achieve a nationally representative sample. Questionnaires were administered to persons aged 15-64 years, and blood was collected from persons aged 18 months-64 years for HIV, CD4, and viral load testing. All analyses were weighted to account for the sampling design and non-response. Estimates from KAIS 2012 were compared with estimates from KAIS 2007 to measure programmatic progress from 2007 to 2012. A z-test was used to test for differences in proportions between the two surveys.

Results: Overall, 16,383 persons aged 15-64 years and 6,302 children aged 18 months-14 years were eligible in KAIS 2012. HIV prevalence was 5.6% (95% confidence interval [CI] 4.9-6.3) among persons aged 15-64 years and 0.9% (CI 0.5-1.3) among children. In 2007, HIV prevalence was 7.2% (CI 6.6-7.9) among persons aged 15-64 years. In 2012, 72% had ever been tested for HIV compared to 34% in 2007 ($p<0.001$). Among HIV+ persons, 47% correctly reported their HIV+ status compared to 16% in 2007 ($p<0.001$). The percentage of circumcised men increased from 85% in 2007 to 91% in 2012 ($p<0.001$), with the largest increase observed in Nyanza, from 48% in 2007 to 66% in 2012 ($p<0.001$). Among women who gave birth in the past five years and were diagnosed with HIV during their last pregnancy, 90% received prevention of mother-to-child transmission interventions. Among HIV+ persons aware of their infection, 89% were taking cotrimoxazole compared to 76% in 2007 ($p<0.001$). Overall, 59% of HIV+ persons were eligible for antiretroviral therapy (ART) based on the national ART guidelines (CD4≤350 cells/μL, tuberculosis disease, or current ART use). Among those eligible, 61% were receiving treatment, and of those, 75% were virally suppressed. Based on the 2013 World Health Organization (WHO) treatment guidelines (CD4≤500 cells/μL, tuberculosis disease, pregnant or breastfeeding women, discordant couples, or current ART use), 77% were eligible for ART, and of those, 46% were receiving ART.

Conclusions: KAIS 2012 provides evidence that significant progress has been made in Kenya in the areas of HIV prevention, care, and treatment. Should Kenya adopt the new the WHO treatment guidelines, need for ART increases by nineteen percentage points and coverage decreases by fifteen percentage points, representing an additional 214,000 persons who will need to be reached. These data will be instrumental to inform implementation of strategies and new national policies for HIV control in Kenya.

150 Unequal Benefits From ART: A Growing Male Disadvantage in Life Expectancy in Rural South Africa

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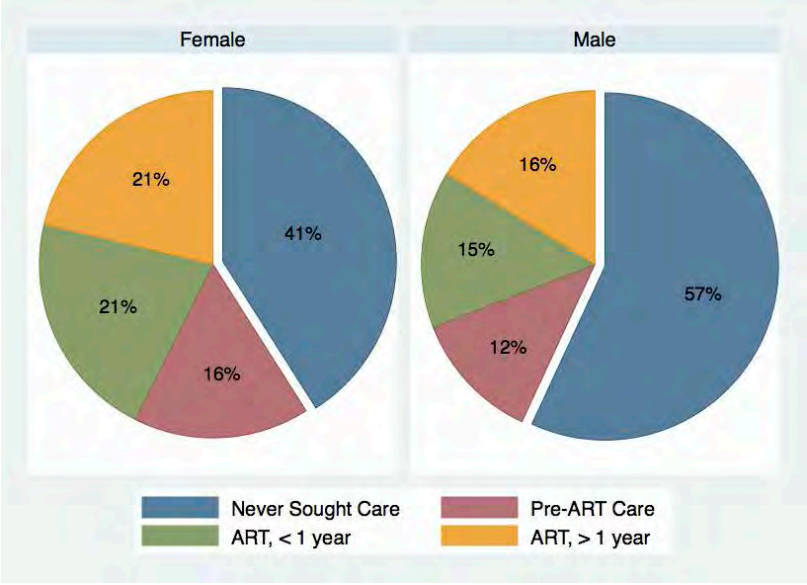
Background: Women have suffered the disproportionate burden of HIV infection in South Africa. However, with the scale-up of antiretroviral therapy (ART), women have been found to perform better throughout the "cascade of care", including: higher rates of HIV testing, earlier ART initiation, better adherence and retention, and better clinical prognosis. To date, no study has assessed the implication of ART scale-up on sex-disparities in all-cause and HIV-specific mortality at the population level.

Methodology: Demographic data on 54,477 women (6508 deaths from all causes and 3925 HIV-related deaths) and 46,809 men (6552 deaths from all causes and 3722 HIV-related deaths) were collected by health and demographic surveillance at the Africa Centre for Health and Population Studies for the period 2000-2011 for all members of all households in a 438 km2 surveillance area in rural KwaZulu-Natal. Cause of death was ascertained by verbal autopsy. Data were linked at the individual level to clinical records from the public-sector HIV treatment and care program. Annual rates of HIV-related and all-cause adult mortality were assessed separately for men and women. Annual female-to-male rate ratios were estimated in Poisson regression, with detailed controls for age. Trends in adult life expectancy and HIV-cause-deleted adult life expectancy were calculated. Finally, to illuminate opportunities for intervention, we assessed the proportion of HIV deaths in 2011 that accrued to men and women who had initiated ART, were in pre-ART care, or who never sought care for HIV in the public sector.

Results: Following the beginning of ART scale-up in 2004, HIV mortality declined among both men and women. The female-to-male rate ratio for HIV mortality declined from 1.05 (95%CI 0.91-1.21) in 2004 to 0.75 (0.58-0.96) in 2011. Adult life expectancy improved for both men and women during the period of study (by 9.0 and 13.2 years respectively); however, the gap between female and male adult life expectancy nearly doubled (from about 4.5 years in 2004 to nearly 9 years in 2011). For men (women), 57% (41%) of HIV-related deaths occurred among persons who never sought care for HIV.



Conclusions: ART scale-up has led to a much larger reduction in HIV mortality among women than among men, at the population level. A critical source of this disparity is the high number of deaths occurring among men who never seek clinical care for HIV. Further efforts to recruit men into HIV care and treatment are needed.

151 A New Paradigm for Evaluating the HIV Care Cascade

Margaret L. McNairy, Matthew Lamb, Batya Elul, Elaine Abrams, Wafaa El-Sadr, The Identifying Optimal Models of HIV Care in Africa Study
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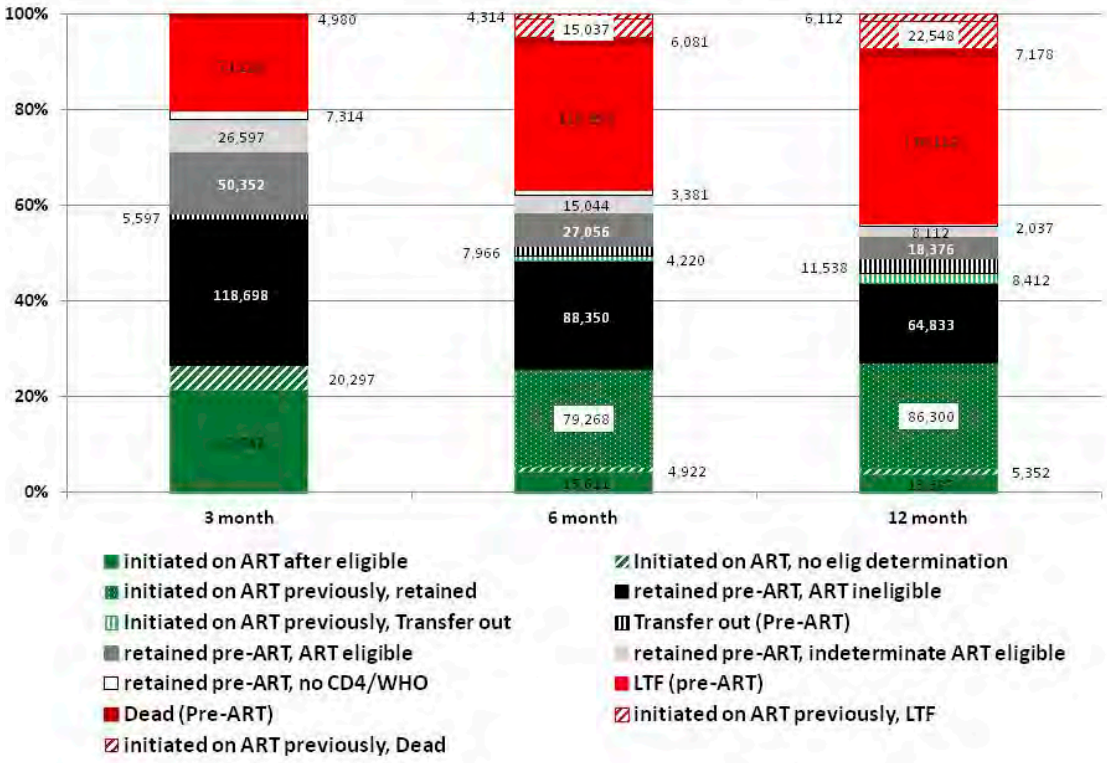
Background: The traditional HIV care cascade may underestimate program performance by focusing on ART retention as the primary outcome, with the exclusion of pre-ART outcomes and the timeliness of achievement of each step. We evaluated outcomes in 4 African countries using an alternate cascade that examines outcomes of all patients since enrollment in HIV care.

Methodology: Data from patients ≥15 years enrolled at clinics in Kenya, Mozambique, Rwanda and Tanzania from 1/2005-6/2011 were used. Retention was defined as percent known to be alive and attending clinic; lost to follow-up (LTF) as no clinic visit for >6 months (M) for ART and >12M for pre-ART patients. Cumulative incidence of retention 12M post ART start was done using Kaplan-Meier methods. Traditional cascade steps were: 1) assess for ART eligibility, 2) initiate ART for eligible patients, and 3) 12M retention post ART start. The alternate cascade reports the same steps at 3M and 12M post enrollment in care, including pre-ART outcomes.

Results: 390,603 patients completed ≥1 one follow-up visit at 217 ICAP-supported clinics. With the traditional cascade, 89% had ART eligibility assessed; of those, 48% were ART-eligible and 67% of eligible patients started ART. 91,211 (23% of all enrolled in care and 77% of all who initiated ART) were retained at 12M on ART. Using the alternate cascade, a similar percent had ART eligibility assessed within 3M and 12M of enrollment (87% vs 89%). For ART-eligible patients, 56% started ART within 3M with an additional 11% in 12M. 248,192 pre-ART patients had no outcomes reported as per the traditional cascade, but in the alternate cascade, pre-ART outcomes at 12M were 38.5% retained in care, 54% LTF, 2.9% dead, and 4.6% transferred. Among the pre-ART patients retained in care, 20% were ART-eligible but did not start ART. Compared to 23% retention 12M after ART start in the traditional cascade, the alternative cascade estimated that 56% of all patients enrolled in care were retained at 12M (fig 1).

Conclusions: The alternate cascade offers a more comprehensive assessment of program performance by including pre-ART patient outcomes and timeframes for each step. Use of both cascades provides complementary information to target interventions that enhance patient and program outcomes.

Figure 1: Alternate Cascade by months after enrollment into HIV care (N = 390,603)



152LB Moderate HIV Incidence and High ART Coverage in Rural Kwazulu-Natal: First Population-Based Survey

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Background: Kwazulu-Natal has one of the highest HIV prevalence in the world. Accurate data on HIV prevalence, HIV incidence and antiretroviral therapy (ART) services coverage are essential to define appropriate strategies of intervention in population. We assessed HIV prevalence, HIV incidence and ART coverage in Mbongolwane and Eshowe in Kwazulu-Natal, South Africa. Other HIV care services indicators were also evaluated.

Methodology: Cross-sectional population-based survey. A cluster sampling and geospatial random selection was used to identify the households visited. Persons 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 CD4 count, ART levels and viral load in HIV positive cases. ART coverage was defined as the proportion of HIV positive on ART (detectable blood levels) among those eligible according to current National Guidelines. Incidence was estimated using HIV LAg-Avidity assay corrected by viral load and ART status.

Results: In total 2377 houses were visited, 6688 individuals were eligible and 5649 (84.5%) were included: 62.3% women and 37.7% men. Overall HIV prevalence was 25.2% (95%CI: 23.6-26.9). Prevalence in women was twice that of men: 30.9% (95%CI: 29.0-32.9) vs 15.9% (95%CI: 14.0-18.0). Prevalence reached 56.0% (95%CI: 51.7-60.3) in women aged 30-39 years. Overall HIV incidence was 1.2/100 person-years (PY) (95%CI: 0.2-2.1), 2.5 times higher in women than in men: 1.6/100 PY (95%CI: 0.2-0.9) vs 0.6/100 PY (95%CI: 0.0-1.5). Women aged 20-29 years had the highest incidence: 4.0/100 PY (95%CI: 1.1-6.9) vs 1.0/100 PY (95%CI: 0.0-2.5) in men. ART coverage was 75.0% (741 on ART/988 eligible) and was better for women than men: 78.5% vs 63.9% ($p<0.001$). Coverage increased with age: 60.5% in younger than 30 years vs 81.3% in older ($p<0.001$). Among all individuals, 81.4% declared to have had an HIV test previously (88.4% of women vs 69.8% of men, $p<0.001$). Of the HIV positive, 75.8% were aware of their status prior to the survey. Viral load suppression (<1000 copies/ml) was achieved in 89.6% of individuals on ART for more than 6 months. Among the others, resistance to ART was found in 58.1% (95%CI: 44.7-70.3).

Conclusions: Overall HIV incidence was moderate in this high prevalence area. However, incidence was very high in young women, four times higher than in men. ART coverage and viral load suppression were relatively good and may be linked to incidence rates. HIV programs should maintain quality of care while carefully identifying HIV prevention and treatment strategies addressed to specific groups such young women for prevention and men for HIV testing and ART initiation. Surveys such as this are critical to evaluate ART programs and identify which groups to target.

Session S7 Symposium

4:00 PM – 6:00 PM **Room 304**

Interferon: Whatever Turns You On

154 HIV-1 Evades Innate Immune Recognition Through Specific Co-Factor Recruitment

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Background: HIV-1 is able to replicate in primary human macrophages without stimulating innate immune sensors despite reverse transcription of genomic RNA into double stranded DNA in the infected cell cytoplasm, an activity that might be expected to trigger innate pattern recognition receptors (PRRs). We hypothesized that if correctly orchestrated HIV-1 uncoating and nuclear entry is important for evasion of innate sensors, then manipulation of interactions with host factors that regulate these processes should trigger PRRs and stimulate type 1 interferon (IFN) secretion. For example, cofactors such as Cleavage and Polyadenylation Specificity Factor subunit 6 (CPSF6), Nup358, and Cyclophilin A have all been suggested to have a role in uncoating and/or nuclear entry. To test our hypothesis we used HIV-1 CA mutants N74D and P90A that are impaired in their interaction with CPSF6 or cyclophilins (Nup358 and CypA) respectively, leading to altered cofactor use at nuclear entry and retargeted integration preferences. To test the ability of these HIV-1 mutants to trigger innate sensors we infected human monocyte derived macrophages (MDM) with HIV-1 CA N74D or P90A and measured replication and production of soluble type-1 IFN. We found that HIV-1 encoding these CA mutations cannot replicate in MDM because it triggers cytoplasmic DNA sensors including cGAS, leading to nuclear translocation of NFκB and IRF3, the production of soluble type-1 IFN and induction of an antiviral state. Depletion of CPSF6 by shRNA expression in MDM allows wild type virus to trigger innate sensors and IFN production. In each case, suppressed replication is rescued by type 1 IFN-receptor (IFNAR2) blockade demonstrating a role for type 1 IFN in restriction. IFN production is dependent on viral reverse transcription consistent with viral DNA being the pathogen associated molecular pattern (PAMP). Finally, we show that we can pharmacologically induce wild type HIV-1 infection to stimulate IFN secretion and an antiviral state using a non-immunosuppressive cyclosporine analogue.

Conclusions: We conclude that HIV-1 has evolved to utilize CPSF6 and cyclophilins to cloak its replication allowing evasion of innate immune sensors and induction of a cell autonomous innate immune response in primary human macrophages. We hypothesise that successful infection of MDM depends on correctly orchestrated reverse transcription at the nuclear pore with a largely intact CA structure in complex with nuclear pore components including Nup358. We propose that uncloaking HIV-1 with non-immunosuppressive cyclosporines will cause HIV-1 to trigger IFN production during transmission and act as a powerful prophylactic for HIV/AIDS and possibly an important antiviral therapy.

155 Interferon Treatments for Chronic Hepatitis C

Markus H. Heim

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Background: Chronic hepatitis caused by infection with hepatitis C virus C (chronic hepatitis C (CHC)) is a leading cause of liver disease worldwide. For the past 25 years, recombinant interferon-α (IFNα) has been the main component of treatments for HCV infection. IFNα binds to its cognate cell surface receptor (IFNAR) and activates the Jak-STAT pathway, thereby regulating the expression of hundreds of genes. Collectively, IFNα induced effector proteins establish an antiviral state in the cell. IFNα signaling is regulated by inducible inhibitors of the Jak-STAT pathway such as SOCS1, SOCS3 and USP18. These negative regulators of IFNα signaling limit the therapeutic efficacy recombinant IFNα. Monotherapy with IFNα was the standard of care until 1998 and achieved a sustained virological response in 20-25% of patients. Treatment efficacy has shown a stepwise improvement following the pegylation of IFNα and its use in combination with other antiviral drugs, most notable ribavirin. However, viral escape mechanisms, refractory IFNα signalling in the liver and substantial drug toxicity still limit the efficacy of this treatment.

Conclusions: A new generation of HCV-specific antiviral drugs will probably further improve response rates and might replace IFNs in CHC treatment in the next few years. Without CHC, recombinant pegIFNα will lose its most important clinical application. However, recombinant pegIFNα might still be used in the treatment of chronic hepatitis B and chronic hepatitis D. Recombinant IFNs will hopefully be maintained in the 'therapeutic armamentarium', because their broad antiviral effects might become invaluable for the treatment of emerging viral infections in the future.

156 Perturbing Interferon Signaling in SIV Infection

Daniel C. Douek
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Background: Two studies will be presented which describe the consequences of type I interferon receptor blockade and interferon alpha administration in rhesus macaques during SIV challenge and acute infection.

Conclusions: Emphasis will be on analysis of interferon stimulated gene expression, innate immunity, virus replication, CD4 T cell depletion and clinical outcome

157 Type 1 Interferon-Mediated Selective Pressure On HIV-1 Transmission

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Background: Understanding host mechanisms of immune control of HIV-1 replication during the earliest stages of infection prior to systemic virus dissemination constitutes a key first step in the rational development of novel strategies to limit virus transmission. Production of type 1 interferons (IFNs), pleiotropic innate cytokines that mediate direct antiviral activity and exert a multitude of immunoregulatory effects, is one of the earliest innate responses triggered during many virus infections. Although type 1 IFNs are known to be produced at initial sites of HIV-1 replication in the mucosa and draining lymph nodes, their role in restricting early HIV-1 replication and the mechanisms by which they mediate their antiviral activity are poorly understood. We recently demonstrated that transmitted-founder (TF) viruses are more resistant to control by IFN-alpha than viruses present in the same subjects during early chronic infection, when type 1 IFNs are produced at much lower levels. This suggests that type 1 IFNs exert selective pressure on HIV-1 replication at initial infection sites, resulting in establishment of systemic infection by relatively IFN-resistant viruses. Here, this hypothesis was explored further by studying the relative IFN resistance of viruses from a virologically-linked transmission pair. Matched pairs of TF and 6-month consensus infectious molecular clones were also used to explore the genetic basis of the IFN-alpha resistance of TF viruses and the interferon-stimulated genes (ISGs) exerting selective pressure on HIV-1 transmission.

Conclusions: Together, our results support an important role for type 1 IFN-mediated antiviral activity in restricting HIV-1 replication at initial infection sites, resulting in preferential establishment of systemic infection by relatively IFN-resistant viral variants. The IFN resistance of TF viruses typically declines within the first 6 months of infection. Viruses from different subjects lose resistance to different interferon-stimulated genes during early infection, suggesting that multiple antiviral ISGs contribute to restriction of HIV-1 transmission.

Session S8 Symposium

4:00 PM – 6:00 PM **Room 311**

The Road To Elimination: Preventing and Treating HIV Infection in Infants

158 Treatment of Pregnant and Breast-Feeding Women: Evidence and Rationale for Option B+

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Background: Option B+, initiation of lifelong antiretroviral therapy (ART) for all pregnant and breastfeeding women, has generated great excitement and conjecture that it is the most promising approach to achieving global Elimination of Mother-to-Child-Transmission. As of January 2014, at least 20 countries had endorsed B+ for their national PMTCT programs and were actively implementing or developing operational plans to switch over. What is the evidence for this rapidly developing consensus? This presentation will review the current evidence informing the proposed benefits and potential risks of the B+ approach, distinguishing individual health concerns for mother and child from program delivery and public health issues. Current experience from Malawi, that highlights both the potential and the challenges of this approach, will be discussed.

Conclusions: For mothers and infants, B+ may offer significant benefits for transmission prevention and maternal health. However, several studies raise concerns about the safety of ART exposure to fetuses and infants, resistance in exposed infants, as well as adherence to treatment of pregnant and breastfeeding mothers. For program delivery and public health, B+ simplifies the delivery of PMTCT services, and thereby presents distinct advantages in terms of improved feasibility, access, uptake, and potentially retention in care. Despite being more costly in the short-term, B+ will likely be cost-effective over time. Within Malawi, B+ implementation has resulted in a substantial improvement in access to PMTCT services, although challenges with uptake, retention, and delivery of early infant diagnosis services remain.

As national programs adopt this approach it will be critical to carefully assess both short and long-term maternal and infant outcomes.

159 Achievements and Challenges With Option B+ Implementation in the Field To Date

Edward Bitarakwate
Elizabeth Glaser Pediatric AIDS Foundation, Kampala, Uganda

Background: Following launch of the Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive in June 2011, and the April 2012 WHO programmatic update that offered Option B+ for PMTCT, several countries including Uganda adopted the provision of triple ARVs to HIV positive pregnant and lactating women for life regardless of CD4 count. Option B+ covers the estimated 40-60% of HIV positive pregnant women accessing PMTCT who need treatment for their own health and account for nearly 90% of all vertical HIV infections but also contribute to sexual transmission. However the adoption of option B+ requires changes in national policies and guidelines, more effective integration of ART into MNCH while at the same time eliminating critical losses along the PMTCT cascade in order to ensure universal coverage and retention of mother-baby pairs. While option B+ is likely to have more impact on elimination of HIV in the high HIV burden countries the implementation of this strategy also presents health system challenges. Continuous review of these large scale HIV test and treat interventions will provide valuable lessons to improve the effectiveness of Option B+ programs.

Conclusions: For optimal reduction of MTCT population coverage for maternal and infant ARV uptake needs to be improved. Monitoring tools need to be revised to ease completion and improve quality of data. Evaluation and adoption of service delivery models that foster optimal retention and adherence for mother-baby pairs initiating ART through PMTCT will maximize the impact of Option B+ towards EMTCT.

160 No Free Rides: Consequences of Fetal & Infant ARV Exposure Among Children Remaining HIV Uninfected

Kathleen M. Powis
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Background: Implementation of World Health Organization guidelines for prevention of mother-to-child HIV transmission(MTCT)will result in increased in utero and breastfeeding antiretroviral (ARV)exposure among HIV-exposed uninfected (HEU) infants. In some regions of Africa, more than 25% of all children will experience prolonged ARV exposure. Many studies have evaluated associations between in utero or direct infant exposure to ARVs and health outcomes, with conflicting findings. Most studies in this field have been observational, and multiple biases related to the complexities of defining ARV exposure groups, controlling for maternal HIV disease severity, and assessing infant outcomes contribute to limitations in interpreting reported results. Among the most consistently reported short-term concerns regarding ARV use in pregnancy, regardless of regimen, have been associations with infants born small-for-gestational-age, preterm deliveries (PTDs), and stillbirths; specific associations between use of protease inhibitor-based regimens and PTD have also been reported. Longer-term effects of in utero ARV exposures include lower weight-for-age and length-for-age (LAZ) z-scores among HEU children, and a potential association between tenofovir-containing regimens and lower mean LAZ in at least one recent study. Few studies have evaluated neurodevelopmental outcomes beyond early childhood, but limited data do not suggest adverse neurodevelopmental consequences from in utero ARV exposure. While nucleoside reverse transcriptase inhibitors have been implicated in mitochondrial toxicity, the long-term clinical significance of this finding for HEU children remains uncertain. Among children who have received direct prophylaxis with ARV agents in early infancy, zidovudine (ZDV) exposure has been associated with anemia and neutropenia up to 3 months following discontinuation, as has the combination of ZDV and nevirapine. Long-term follow-up data for HEU children with extended periods of direct ARV prophylactic exposures are lacking.

Conclusions: Available observational data raise concerns that in utero ARV exposure may lead to short- and long-term health consequences for some children, but little research has been performed to understand the biological pathways underlying these associations. Universal ARV treatment for HIV-infected women during pregnancy and breastfeeding, and direct infant ARV prophylaxis to prevent MTCT, are proven public health interventions capable of virtually eliminating MTCT if broadly applied. As MTCT prevention programs expand globally and universal ARV treatment is more widely adopted, optimizing the duration and type of ARVs used for MTCT programs will be of paramount importance for the health of HEU children.

161 Treatment of HIV-Infected Newborns: Why, When, and What To Start?

Ellen G. Chadwick
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Background: Data have shown that early initiation of combination antiretroviral treatment (cART) in infants contributes to improved survival and neurodevelopmental, immunologic and growth outcomes. While cART cannot eradicate HIV infection in the majority of perinatally infected infants because of the long half-life of latently infected CD4 cells, time to achievement of viral suppression has been shown to correlate with the size of this resting CD4+ T cell reservoir in early-treated infants. The "Mississippi baby" has raised the possibility that neonatal cART may augment HIV-specific immune responses and block HIV persistence in acute infection, eventually leading to long-term control of HIV in the absence of therapy. This approach would require widespread availability of accurate neonatal diagnostic testing with rapid turnaround time and parental acceptance of aggressive antiretroviral therapy for high-risk infants. The choices for cART in the neonatal age group are limited by the lack of infant formulations and neonatal pharmacokinetic data for many antiretrovirals, as well as concerns about toxicity and efficacy.

Conclusions: The promise and challenges of early initiation of cART for high-risk infants will be discussed, but more data on pharmacokinetics, toxicity and efficacy of this approach are needed; if instituted, should be performed in a closely monitored setting, optimally within the context of a research study. At this time, empiric treatment interruption cannot be recommended until the durability of the approach in the Mississippi baby can be confirmed and the findings replicated in other children.

Session S9 Symposium

4:00 PM – 6:00 PM Room 312

Intimate Infections: What's Love Got To Do With It?

162 Oral Human Papillomavirus (HPV): Epidemiology and Role in Oropharyngeal Cancer

Gypsyamber D'Souza

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Background: Oral human papillomavirus (HPV) infection is now the major of cause oropharyngeal cancer and the incidence of this cancer is increasing in the U.S. People with HPV are at increased risk of HPV infection and HPV-related oropharyngeal cancer, due to increased sexual exposure to HPV and the effects of immunosuppression.

Conclusions: Oral HPV infection is more common in men than in women and is more common in people with HIV. Most people clear oral HPV infections within one year on their own but incidence and persistence are increased among immunosuppressed individuals. Common questions about oral HPV transmission, protection from the HPV vaccine, and risk among people with HIV will be discussed.

163 Bacterial Vaginosis

Landon Myer

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Background: This session focuses on current evidence for the role of bacterial vaginosis (BV) in HIV acquisition and transmission, and based on this, how future research on the vaginal microbiome may help to inform HIV prevention interventions. Our understanding of normal and abnormal vaginal flora, including BV, has undergone radical shifts during the past decade. While our thinking about BV continues to evolve, it is best understood as a polymicrobial condition in which the lactobacilli species which dominate vaginal flora under normal conditions are replaced by diverse populations of anaerobic and facultative anaerobic organisms. Evidence points to the role of predisposing host factors, including hormonal and immunological parameters, in facilitating BV occurrence and persistence. BV is consistently associated with high risk sexual behaviours such as multiple partners and lack of condom use. However a specific sexual aetiology of BV remains elusive. Several prospective studies have found that the presence of BV or abnormal vaginal flora in HIV-negative women appears associated with increased risk of HIV acquisition. This evidence is summarized in recent meta-analyses finding an increased risk of HIV infection in women with BV compared to women with normal vaginal flora, independent of measured sexual risk behaviours (hazard ratio, 1.69; 95% confidence intervals, 1.36-2.10). A range of mechanisms have been posited to explain this association. However the absence of a clear mechanistic model for vaginal HIV acquisition, coupled with well-documented challenges in adjustment for covariation in sexual risk behaviours, limit insights from existing epidemiological data. Also, BV occurs more commonly in women infected with HIV, and recently a groundbreaking study of serodiscordant partnerships demonstrated that BV was associated with increased risk of female-to-male HIV transmission; this finding is supported by studies showing increased shedding of HIV in the vagina under conditions of BV.

Conclusions: Given the available evidence, strategies to treat BV for HIV prevention are of clear interest. Yet the effective treatment of BV is notoriously challenging, with recurrence commonly observed following existing therapies in many women. Altogether it seems unlikely that additional epidemiologic studies investigating the association between BV and HIV acquisition, or intervention trials using existing treatment modalities, will yield significant new advances in HIV prevention. More productive new directions are likely to result from either more specific microbiologic definitions of BV that can be applied in studies of BV prevention, and/or more clearly defined mechanisms of female HIV acquisition that may be related to the vaginal microbiome.

164 Outbreak of Invasive Meningococcal Disease Among Men Who Have Sex With Men — New York City, 2010-2013

Alison D. Ridpath

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Background: During August 2010-February 2013, the New York City (NYC) Department of Health and Mental Hygiene (DOHMH) received 22 reports of serogroup C meningococcal (Neisseria meningitidis) disease (MenC) among men who have sex with men (MSM). Previous recognized outbreaks of MenC among MSM have occurred in Toronto in 2001 and Chicago in 2003. In the United States overall, MenC has a case-fatality rate of 15%. Cases in the NYC outbreak were identified through mandatory reporting by laboratories and health care providers; patients and providers were interviewed. DOHMH investigated to identify risk factors for infection, determine how the disease was spreading among this population, and implement control measures.

Conclusions: An outbreak of MenC occurred among NYC MSM with a case-fatality rate of 32%, twice the national rate. Common characteristics among cases included being HIV-infected (12 [55%]), black (11 [50%]), and a Brooklyn resident (10 [45%]). At least 5 (23%) patients met their sexual partners online during the month before illness. DOHMH responded to the outbreak by routine administration of antibiotic prophylaxis to close contacts of all patients and by developing targeted vaccine recommendations, initially for HIV-infected MSM residing anywhere in NYC, and ultimately expanding to MSM, regardless of HIV status, residing anywhere in NYC and who have close or intimate contact with men met online, with a digital application, or at a bar or party. DOHMH disseminated information about the outbreak and the need for vaccination to the MSM community, community-based organizations, and providers. Outreach included direct communication through conventional and social media, lectures, group meetings, and vaccination events at MSM-friendly bars, clubs, and Gay Pride events. Approximately 2,000 informational posters and 70,000 informational postcards were distributed. Social media dissemination included advertisements on sites where MSM meet sexual partners, Facebook messages, outreach to prominent bloggers, and e-mails to reach the population at risk. By December 1, 2013, ~23,448 doses of meningococcal vaccine had been administered by providers in NYC. The last

case of MenC in a NYC MSM was reported in February 2013. A multifaceted approach, involving prophylaxis of close contacts, DOHMH vaccination recommendations to targeted groups of MSM, and community outreach, appears to have been successful in decreasing transmission

165 *Lymphogranuloma venereum*

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Background: Lymphogranuloma venereum (LGV), caused by lymphotropic invasive strains of *Chlamydia trachomatis* (L1-L3 serovars), is a sexually transmitted infection characterised by severe inflammation, often with systemic symptoms. The clinical course of LGV can be divided into three stages. The primary stage, often unnoticed by the patient, consists of a small painless papule which may ulcerate. The secondary stage occurs a few weeks later and may manifest as either regional bubo formation or as the anorectal syndrome with haemorrhagic proctocolitis. The latter typically occurs in men-who-have-sex-with-men (MSM) or women practicing receptive anal intercourse. If left untreated, LGV may result in the tertiary stage characterized by extensive fibrosis of tissue, strictures and genital elephantiasis. LGV is endemic in parts of Africa, Asia, South America and the Caribbean. More recently, LGV has re-emerged among MSM in Europe and North America. Molecular typing has demonstrated that the majority of the European LGV-associated *C. trachomatis* strains are clonal (serovar L2b), whilst the North American strains are more diverse. Accordingly, it has been hypothesized that the L2b variant was recently imported into Europe from North America. Anorectal LGV in MSM has been strongly associated with HIV seropositivity. This observation may be explained by serosorting, increased biological susceptibility to LGV infection, epidemiological synergy wih LGV leading to increased HIV acquisition and, possibly, the effects of the immune restoration inflammatory syndrome associated with the commencement of antiretrovial therapy. Diagnosis of LGV has traditionally relied upon serological techniques; these are only really useful for diagnosing LGV from the secondary stage onwards. Following the re-emergence of LGV in the northern hemisphere, a number of in-house nucleic acid amplification tests (NAATs) have been developed which can diagnose LGV infections from the primary stage onwards. In those situations where LGV-specific NAATs are unavailable, treatment for LGV is recommended in cases of proven anorectal chlamydial infection in MSM patients when proctitis is visualized by proctoscopy, white cells are detected at levels >10 cells per high power field in anorectal smears and when the patient is known to be HIV-infected. LGV is best treated with a 3-weeks' course of doxycyline (100 mg 12-hourly) or, alternatively, with a 3-weeks' course of erythromycin (500 mg 6-hourly).

Conclusions: LGV has re-emerged as an important STI among HIV-infected MSM. Clinicians should consider LGV as a differential diagnosis for proctocolitis and genital ulceration in this patient group. Where possible, LGV-specific NAATs should confirm a presumptive LGV diagnosis.

POSTER ABSTRACTS

Session P-A1 Poster Session
Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

SAMHD1

166 CDK2 But Not CDK1 Phosphorylates SAMHD1 in Primary Macrophages

Alba Ruiz[1], Eduardo Pauls[1], Ester Ballana[1], Albert Gubern[2], Mar Álvarez[3], Luis Menéndez-Arias[3], Francesc Posas[2], Bonaventura Clotet[1], José A. Esté[1]
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Background: SAMHD1 is an HIV-1 restriction factor present in lymphocytes and macrophages that is deactivated by phosphorylation. The mitotic cyclin-dependent kinase (CDK) 1 has been proposed as responsible for phosphorylation-dependent regulation of SAMHD1 activity in immortalized cells. We wanted to study whether other CDK, different from CDK1, may play a role in regulating SAMHD1 in primary monocyte-derived macrophages (MDM).

Methodology: CD14+ monocytes were isolated and transfected with small interfering RNA (siRNA) against different CDK. Transfected monocytes were differentiated in macrophages using M-CSF. RNA interference was assessed by quantitative PCR (qPCR) and western blot. MDM were infected with a VSV-pseudotyped NL4-3 GFP-expressing virus or full-replicative R5 strain BaL. Proviral DNA formation was quantified by qPCR and HIV replication measured by flow cytometry. SAMHD1 phosphorylation and CDK2 activation were analyzed by immunoblotting. Recombinant CDK1, CDK2 and CDK6 were used in an in vitro kinase assay using HA-purified SAMHD1 in the presence of radioactive ATP.

Results: We effectively downregulated (>80 %) CDK1, CDK2, CDK4, CDK5 and CDK6 mRNA compared to mock-transfected cells or cells transfected with a non-targeting siRNA (siNT) in primary monocyte-derived macrophages (MDM). Protein downregulation of CDK1, CDK2 and CDK6 was further confirmed by western blot. siRNA-mediated knockdown of CDK2 and CDK6 but not CDK1, CDK4 or CDK5 led to reduced SAMHD1 phosphorylation measured by western blot. Similarly, siRNA knockdown of CDK2 and CDK6 but not CDK1, CDK4 or CDK5 inhibited proviral DNA formation (~60% and ~80%, respectively) in macrophages infected with a VSV-pseudotyped NL4-3 GFP-expressing virus or the fully replicative R5-tropic strain BaL. Moreover, knockdown of CDK2 and CDK6 significantly reduced HIV-1 replication ($p<0.001$) quantified by flow cytometry. Confirmatory siRNA sequences targeting CDK2 and CDK6 showed similar effects on infection and proviral DNA formation after HIV-1 infection.

We also found that SAMHD1 is a substrate of CDK2 in vitro, being even more efficient than CDK1 in phosphorylating it. In contrast, we could not detect CDK6-mediated phosphorylation of SAMHD1. However, CDK6 siRNA-mediated downregulation led to reduced activation of CDK2, suggesting that CDK6 signals upstream CDK2.

Conclusions: Our results provide additional support to the role of CDK-dependent phosphorylation of SAMHD1 in mediating restriction of HIV-1, but argue against the in vivo relevance of CDK1 as the single kinase responsible for SAMHD1 phosphorylation. CDK2 but not CDK1 regulates SAMHD1 phopshorylation, leading to inhibited proviral DNA formation and reduced HIV-1 replication in primary human macrophages.

167LB p21 Regulates the HIV-1 Restriction Factor SAMHD1

Alba Ruiz[1], Eduardo Pauls[1], Eva Riveira-Muñoz[1], Marc Permanyer[1], Roger Badia[1], Oliver T. Keppler[2], Bonaventura Clotet[1], Ester Ballana[1], **Jose Este[1]**
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Background: CDKN1A (p21) is a cyclin-dependent kinase (CDK) inhibitor controlling cell cycle progression through binding and activation of cyclin-CDK1 or -CDK2 complexes. p21 expression has been shown to restrict HIV-1 replication in macrophages by controlling the expression of the RNR2 subunit of the ribonucleotide reductase that, in turn, controls the intracellular deoxynucleotide (dNTP) pool required for HIV reverse transcription. dNTP levels are also tightly controlled by the dNTP triphosphohydrolase SAMHD1. We have evaluated the role of p21 in SAMHD1-mediated restriction of HIV infection.

Methodology: RNA interference was used to evaluate the role of p21, CDKs and SAMHD1 function in M-CSF monocyte derived macrophages (MDM). Protein expression was evaluated by mRNA qPCR or by Western blot of the corresponding factor. SAMHD1 phosphorylation at residue T592 was used as a marker of SAMHD1 inactivation. HIV-1 infection was monitored by total proviral DNA or GFP expression of a pseudovirus expressing the VSV envelope and the GFP gene in the presence or absence of the SIVmac Vpx. FACS measurement of Ki67+ cells was used as a marker of cell proliferation.

Results: Monocyte stimulation with M-CSF leads to differentiation into macrophages and cell proliferation. RNAi of p21 expression led to an increase in the number of Ki67+ cells. Susceptibility to HIV-1 replication correlated to the degree of SAMHD1 inactivation as measured by SAMHD1 phosphorylation at T592. Delivery of SIVmac Vpx induced SAMHD1 degradation and subsequently increased virus infection. Under these conditions, siRNA-induced downregulation of p21 strongly enhanced the phosphorylation of SAMHD1 followed by an increase in HIV-1 proviral DNA formation and virus infection without affecting the overall SAMHD1 expression. The increased HIV-1 replication observed after SAMHD1 degradation was not affected or further enhanced by downregulation of p21, suggesting that the effect of p21 was indeed dependent on SAMHD1 expression.

SAMHD1 activity in primary cells (MDM and CD4+ T lymphocytes) was dependent on CDK2 as specific pharmacological inhibition or siRNA of CDK2 blocked SAMHD1 phosphorylation, proviral DNA formation and HIV-1 replication.

Conclusions: Our results strongly suggest that p21 positively correlates with the degree of SAMHD1 HIV-1 restriction. The restriction induced by p21 is dependent on CDK2 controlling SAMHD1 function. Cell cycle control must include a coordinated regulation of RNR2 and SAMHD1 as both tightly regulate dNTP availability. CDK2 activity may be the underlying mechanism explaining p21-mediated control of both RNR2 and SAMHD1 and their control of the dNTP pool required for cell proliferation and virus replication, opening new alternatives for the control of HIV-1 infection.

168 Inhibitors of CDK2 and CDK6 Block HIV-1 RT Through the Control of SAMHD1 Activity

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Background: SAMHD1 inhibits HIV-1 reverse transcription by decreasing the pool of intracellular deoxynucleotides in myeloid and lymphoid cells. The activity of the HIV-1 restriction factor SAMHD1 is controlled by cyclin-dependent kinase (CDK)-mediated phosphorylation. However, the exact mechanism of SAMHD1 regulation in primary cells is unclear.

Methodology: Human primary monocytes obtained from PBMC were differentiated into macrophages with M-CSF. CD4+ T lymphocytes were obtained from PBMC and stimulated with PHA/IL-2. Cells were pre-treated with CDK inhibitors and then infected with a GFP-expressing HIV-1 or R5-tropic virus BaL. Proviral DNA formation was measured by quantitative PCR and infection assessed by flow cytometry. SAMHD1 was degraded treating cells with viral-like particles carrying Vpx (VLP-Vpx).

Results: Pan CDK inhibitors roscovitine and purvalanol A show in vitro activity against several CDK, including CDK2 and AT7519 is a preferential inhibitor of CDK2. These CDK inhibitors reduced SAMHD1 phosphorylation in macrophages and CD4+ T lymphocytes as measured by Western blot analysis. HIV-1 replication was blocked in primary macrophages by roscovitine (47.3%±3.9; n=4), purvalanol A (55.7%±15.7; n=4) and AT7519 (66.4%±3.8; n=4) at subtoxic concentrations as measured by the colorimetric MTT assay. CDK inhibitors blocked the formation of proviral DNA formation, indicating an effect on the reverse transcription step. Similar results were obtained in primary CD4+ T lymphocytes. In addition to these broad-spectrum CDK inhibitors, we tested the antiviral activity of palbociclib, a potent and selective CDK6 inhibitor. Palbociclib potently inhibited SAMHD1 phosphorylation, HIV-1 reverse transcription and HIV-1 replication (99.5%±0.2; n=4). Notably, treatment of macrophages with palbociclib led to reduced CDK2 activation, measured as the phosphorylation of the T-loop at the Thr160. The antiviral effect of all CDK inhibitors was lost when SAMHD1 was degraded using VLPVpx, providing further evidence for a role of SAMHD1 in mediating the antiretroviral effect.

Conclusions: Our results indicate that SAMHD1-mediated restriction of HIV-1 infection is controlled by CDK as previously suggested, but point to a preferential role for CDK2 and CDK6 as mediators of SAMHD1 activation. Our study provides a new signalling pathway susceptible for the development of new therapeutic approaches against HIV-1 infection.

169 Vpx Mediated Degradation of SAMHD1 Does Not Render HSCs More Permissive To Lentiviral Gene Transfer

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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 and resting $CD4^+$ T cells that interferes with reverse transcription by decreasing the nucleotide pools. 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.

Methodology: We used Vpx-mediated degradation of SAMHD1, shRNA to SAMHD1, HIV-2- or SIV- based lentiviral vectors or provided an excess of deoxynucleoside triphosphates (dNTPs) or deoxynucleoside (dNs) to relieve a potential block of SAMHD1 in HSCs. In addition, Alu-PCR was used to identify and characterize the integrated provirus in HSCs and monocyte-derived macrophages (MDMs).

Results: Our results show that SAMHD1 is highly expressed in HSCs cultured in a medium enriched with cytokines conventionally used for transduction of HSCs. In contrast, uncultured HSCs have poor SAMHD1 expression. Expression levels of SAMHD1 in cultured HSCs are comparable to those found in myeloid cells, including monocytes and MDMs. However, Vpx+ VLPs, dNs or shRNA for silencing SAMHD1 and HIV-2- or SIV-based lentiviral vectors do not relieve a potential block in reverse transcription in HSCs that would result in a higher transduction rate. Notably, while Vpx+ VLPs resulted in a vigorous decrease of SAMHD1 in HSCs, the remaining SAMHD1 level is still remarkably high. Last but not least, Vpx+ VLPs lead to a striking increase of dNTPs in MDMs but not HSCs.

Conclusions: In summary, HSCs, unlike quiescent cells, express high levels of SAMHD1. However, the Vpx-mediated decrease of SAMHD1 levels was not associated with a higher lentiviral-based transduction rate. These data imply that other restriction factors might be operative in lentiviral transduction of HSCs.

Session P-A2 Poster Session
Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**
Integration/Nuclear Import

170 BET Proteins Mediate Integration Site Selection of MLV Much Alike LEDGF/p75 in HIV Integration

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Background: A hallmark of retroviral replication is stable integration of the viral genome in the host cell DNA. However, retroviruses do not integrate at random. Mediated by LEDGF/p75, lentiviruses preferentially integrate in the body of active transcription units. Gammaretroviruses, including Moloney Murine Leukemia Virus (MLV), favour transcription start sites and CpG islands. It is generally believed that cellular proteins target viral integration complexes to the chromatin resulting in a integration site preference. The consequences of the integration site preference for latency and oncogenicity are still unclear.

Methodology: By co-immunoprecipitation combined with mass spectrometry we identified cellular proteins differentially interacting with HIV-1 and MLV-1 integrase. Hits were ranked and validated resulting in the identification of bromodomain and extra-terminal (BET) proteins (BRD2, BRD3 and BRD4) as gammaretroviral targeting factors.

Results: We discovered that the BET proteins interact with MLV IN and direct integration towards transcription start regions. BET proteins specifically bind and co-localize with the MLV IN in the nucleus of the cell. The interaction is gammaretroviral-specific and mediated by the C-terminal domain of integrase and the extraterminal (ET) domain of BET. Interfering with chromatin interaction of BET proteins via the specific bromodomain inhibitors JQ1 and I-BET decreased MLV replication and MLV vector transduction 5-10-fold, without affecting HIV vector transduction. Quantitative PCR analysis revealed a block at the integration step. In addition, bromodomain inhibitors did not affect the late steps of viral replication. MLV integration site distribution strongly correlated with the BET protein chromatin binding profile. Finally, expression of an artificial fusion protein that merges the BET integrase binding domain with the chromatin interaction domain of LEDGF/p75, retargeted MLV integration into the body of actively transcribed genes, paralleling the HIV integration pattern.

Conclusions: Our results explain the molecular mechanism of MLV integration site selection. Differential integration site selection between HIV and MLV is based on the use of a specific integrase cofactor: BET proteins for MLV and LEDGF/p75 for HIV. Our results provide possibilities to investigate the effect of integration site specificity on the biology of retroviral replication. In addition, our data suggest methods to engineer gammaretroviral vectors with altered integration site specificity which could be used for carrying out gammaretroviral vector-based gene therapy with an increased safety profile.

171 Zinc-Finger Endonuclease Targeting LEDGF/p75 Inhibits HIV-1 Integration

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Background: Human immunodeficiency virus (HIV) requires several host factors to complete viral replication cycle. Genome editing using zinc-finger nucleases (ZFN) has been successfully applied to disrupt CCR5 or CXCR4 host factors, inhibiting viral entry and infection. Lens epithelium-derived growth factor (LEDGF/p75) is a lentivirus-specific cellular cofactor which directly interacts with viral integrase, tethering viral preintegration complex into active transcription units of the cellular chromatin. Gene therapy using ZFN to modify LEDGF gene might restrain a late step of viral replication cycle at the integration level.

Methodology: Knockout ZFNs targeting the LEDGF gene (ZFN-LEDGF) were designed to specifically target the sequence nearby the integration binding domain (IDB) of LEDGF/p75 protein. TZM-bl cells were transfected with ZFN-LEDGF expressing plasmids carrying a ZsGreen reporter gene. Moreover, LEDGF/p75 knock-out cells were infected with HIV-1 R5 tropic BaL and the X4 tropic NL4-3 strains and infection was monitored by proviral and integrated viral DNA at 24h post infection and β-galactosidase assay 3 days after infection. AZT, AMD3100 and raltegravir were used as controls.

Results: A total of 15% of TZM-bl ZFN-LEDGF positive cells were obtained after transfection and cell sorting of GFP expressing cells. Assessment of ZFN-LEDGF efficiency in the deletion of the gene by heteroduplex formation and DNA sequence analysis, revealed two homozygotic cell clones with deletions ranging from 17 to 41 bp surrounding the target sequence of ZFN-LEDGF. We confirmed that ZFN-LEDGF successfully recognized the target region of the LEDGF gene, induced a frame shift of the coding region and resulted in the abolishment of LEDGF expression at mRNA and protein level. Functional assays revealed that infection with R5 BaL or X4 NL43 viral strains was impaired in LEDGF knock-out cells regardless of entry tropism (up to 85% inhibition, $p<0.05$). Disruption of LEDGF gene restricted HIV-1 provirus integration into host genome. However, residual infection was detected in LEDGF knock-out cells. Indeed, LEDGF knock-out restriction was overcome at high virus multiplicity of infection, suggesting alternative mechanisms for HIV-1 genome integration rather than LEDGF/p75. Observed residual integration was, however, sensitive to the integrase inhibitor raltegravir.

Conclusions: Genome editing is an incoming issue for HIV-1 research and treatment. Here, we describe a novel ZFN that effectively targets LEDGF gene which is involved at late steps of viral replication cycle. LEDGF knock-out cells represent potent tools to elucidate the role of HIV integration cofactors in virus replication. The ZFN-LEDGF becomes a potential antiviral agent to restrict HIV-1 integration.

172 Small-Molecule Inhibits HIV-1 Replication by Interacting With HIV Capsid

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Background: HIV-1 capsid (CA) is a viral protein essential for early and late events of the replication cycle and so far CA has been an untapped target, thus providing excellent opportunities for the discovery of new antiretrovirals that act by novel mechanisms of action.

Methodology: We screened a library for compounds that interfere with multimerization of HIV-1 CA and identified a small molecule, 18E8, with antiretroviral activity of 18E8 in single- and multiple-round infection assays. To identify the antiviral target of 18E8 we selected resistance viral variants in *in vitro* serial passage experiments. To determine whether 18E8 affects the late step of the viral replication cycle, we conducted virus production assays, western blot analysis of viral supernatants and electron microscopy. To further gain insight into the mode of action of 18E8 and to determine the affected early step of the viral replication cycle, we performed synchronized time-of-drug-addition experiments that determine how long the addition of 18E8 could be postponed before losing its antiviral activity. To evaluate the effect of 18E8 on levels of different DNA forms, we used qPCR to detect late reverse transcriptase (RT) products, 2-LTR circles and integrated viral DNA.

Results: 18E8 showed broad antiretroviral activity against drug resistant and non-clade B viruses, but not against an HIV-1 core pseudotyped with VSV-G envelop. Experiments for the selection of drug resistance revealed that an A105T CA mutation confers resistance to18E8, suggesting that it exerts its antiretroviral activity by binding to HIV-1 CA. 18E8 did not affect proper assembly of fully processed CA in nascent viral particle. By comparing its relative position in the time scale to that of drugs that target RT and integrase steps we demonstrated that 18E8 targets an early step in the HIV replication cycle, after reverse transcription. Consistent with these results, cell-cell fusion and primer extension by RT assays showed that 18E8 did not affect the viral entry or RT steps. Surprisingly, although 18E8 targeted CA, it decreased the amount of integrated viral DNA. 18E8-resistant virus carrying A105T in CA restored integration efficiency. It has been reported that antiviral host factor CPSF6 interacts with CA and restricts HIV-1 infection by preventing nuclear entry and integration of the viral dsDNA. HIV-1_{N74D}, which is unable to bind CPSF6, maintains 50% infectivity in TNPO3-deficienct cells, and this infectivity is hypersusceptible to 18E8. Docking simulation suggests that 18E8 binds at the CPSF6 binding site and may affect interactions between the N-terminal domains of two CA monomers.

Conclusions: Our data suggest that 18E8 acts during nuclear import and affects integration by interacting with CA.

173 Resistance To HIV-1 Infection in PBLs From LGMD1F Patients Carrying a Genetic Defect in TNPO3

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Background: Recently, a heterozygous single nucleotide deletion in transportin 3 (TNPO3) gene has been characterized as the elusive genetic defect leading to an autosomal dominant form of limb-girdle muscular dystrophy 1F (LGMD1F). TNOP3 is an essential factor in the HIV-1 viral cycle but its precise role in viral replication is a matter of controversy. We evaluated the susceptibility to HIV-1 infection of PBLs isolated from patients with LGMDF1 disease and characterized the mechanism of restriction in the viral cycle.

Methodology: Monocyte-depleted PBLs isolated from four patients with LGMD1F and two healthy relative controls were activated with PHA/IL2 for 48h and then infected with NL4-3_renilla, VSV-αEnv-NL4-3_LUC, or R5 and R5X4 isolates from HIV-infected patients for 18h or 6 days. Viral retrotranscription, proviral integration, and episomic forms (2LTRs circles) were analyzed by TaqMan qPCR. Rate of TNPO3 wild-type (wt) and mutated forms was analyzed by allelic discrimination using TaqMan probes.

Results: PBLs from LGMD1F patients were fully functional. No defect in CD4, CCR5, CXCR4 or activation markers was found and T-cell proliferation remained in normal levels. TNPO3wt and mutated forms were expressed at similar levels. A strong reduction (90%) in HIV-1 replication was observed in 3 out of 4 patients as compared to controls. DNA proviral integration was reduced more than 90% in 3 out of 4 patients and 2LTRs circles were barely detected. The defect on TNPO3 showed lower effect on viral retrotranscription.

Conclusions: In vitro HIV-1 infection was sharply decreased in PBLs from patients carrying a single nucleotide deletion in one allele of TNPO3. Low detection of 2LTRs circles and strong decrease in proviral integration demonstrates that TNPO3 participates in a step previous to the nuclear import of the pre-integration complex. Surprisingly, despite the co-expression of similar levels of normal and mutated mRNA coding for TNPO3, HIV-infection was more than 50% inhibited, thereby suggesting an interaction between the wt and mutated forms of the protein.

174 HIV Integrase$^{R263A/K264A}$ Is Defective for TRN-SR2/IN Interaction and Nuclear Import of the PIC

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Background: Transportin-SR2 (TRN-SR2/TNPO3) is a human karyopherin encoded by the *TNPO3* gene. We identified TRN-SR2 as a binding partner of HIV-1 integrase (IN) and validated TRN-SR2 as an important cellular cofactor for the nuclear import of HIV-1. However, the question still remained whether the direct interaction between TRN-SR2 and IN mediates the nuclear import of HIV.

Methodology: By peptide screening we analyzed the interaction between TRN-SR2 and IN in molecular detail. Protein-protein interactions were verified by co-IP and AlphaScreen. We engineered site specific mutants in the C-terminal domain of HIV-1 IN that display reduced interaction with TRN-SR2 and studied their role in HIV replication using Q-PCR and fluorescence microscopy.

Results: Using the AlphaScreen protein-protein interaction assay we have been able to pinpoint the interacting hot spots in IN to R262/R263/K264 and K266/R269 in the IN C-terminal domain. We also identified a secondary interaction surface involving residues F185/K186/R187 and K188 in the catalytic core domain. Next, we introduced mutations at these positions in the C-terminal domain in the virus to corroborate the biological relevance of the interaction. Several mutations in the C-terminal domain of HIV IN inhibited the IN/TRN-SR2 interaction and rendered the virus replication-deficient. Some mutants affected reverse transcription (RT) compromising analysis of HIV nuclear import. All mutants also affected integrase activity. Still, one mutant, $IN^{R263A/K264A}$, retained full RT activity but displayed a specific block at the level of nuclear import as measured by Q-PCR and fluorescence microscopy. Although this mutant was defective for integration, no increase in 2-LTR circles was detected. Moreover, HIV encoding $IN^{R263A/K264A}$ showed reduced nuclear import when assayed with an eGFP-IN labeled HIV.

Conclusions: The $IN^{R263A/K264A}$ mutation in the C-terminal domain of HIV-1 integrase reduces the interaction with TRN-SR2 and specifically blocks HIV replication at the stage of nuclear import, corroborating the importance of this direct protein-protein interaction in HIV nuclear import.

Session P-A4 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Late Events in HIV Replication

175 SHAPE-Directed Discovery of a Novel Structure in the HIV-1 RNA Polyadenylation Signal

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Background: Although polyadenylation at the 3' end of HIV-1 RNA has been shown to be regulated by sequence elements in U3 and in R, its molecular mechanism remains incompletely understood and has not been studied in the context of the full-length genomic RNA. Selective 2'-Hydroxyl Acetylation analyzed by Primer Extenstion (SHAPE) technology produces RNA structural information at single nucleotide resolution. SHAPE data have previously been used to constrain RNA folding algorithms and model structures with high accuracy. Pseudoknots are RNA structures that occur when nucleotides in a loop region base pair with nucleotides outside of the parent helix. While rare, pseudoknots are often important for biological function in riboswitches, catalytic RNAs, and viral regulatory elements.

Methodology: SHAPE experiments were used to develop structural models for an entire NL4-3 HIV-1 RNA genome. A pseudoknot was predicted to form between sequences in U3 and R adjacent to the polyadenylation signal and was chosen for additional study. Site-directed mutagenesis of the NL4-3 sequence was used to disrupt 3 of the 7 base pairs in the predicted pseudoknot. The mutant and native sequence NL4-3 plasmids were transfected into 293T cells to produce virus that was titered on TZM-bl cells. Equal amounts of infectious virions were used to infect H9 and Jurkat T cells; p24 was measured in culture medium 4-6 days post-infection.

Results: There was little difference in virus production between the U3 mutant and native sequence NL4-3 after 293T transfection and infection of TZM cells. However, after infection of Jurkat and H9 cells with equal amounts of infectious virus, the mutant showed no spread in Jurkat and a slight decline in spread in H9 cells compared to the native sequence. Growth of the mutant virus in H9 cells over 3 weeks led to reversion of the mutations in one-half of the culture. SHAPE analysis of the mixture of mutant and revertant RNA indicated disruption of the putative pseudoknot in the mutant RNA.

Conclusions: SHAPE data can be used to identify biologically functional structures in HIV-1 RNA, including pseudoknots. Mutation of three bases on the U3 side of a putative U3-R pseudoknot led to reduced spread and fitness of the mutant virus, as evidenced by the rapid reversion of the mutations. These data support our model of a pseudoknot around the 3' polyadenylation site of HIV-1 genomic RNA that is important to the replication cycle of HIV-1, likely in the regulation of polyadenylation.

176 HIV-1 Assembly On Intracellular Plasma Membrane-Connected Compartments of Human Macrophages

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Background: In differentiated human monocyte-derived macrophages (MDM), HIV-1 assembles primarily on intracellular plasma membrane (PM) connected compartments (IPMC). It is unclear how the IPMC differs from the cell surface PM, or whether the IPMC is indeed the only site for virus assembly in MDM. As the endosomal sorting complex required for transport (ESCRT) machinery is required for the final scission events that release assembled virus from the PM, we inhibited ESCRT-mediated scission of HIV-1 in macrophages to generate stable budding intermediates in order to identify the main site(s) where virus is assembled in MDM.

Methodology: We used siRNA to deplete expression of the ESCRT pathway proteins Tsg101 and ALIX, or we generated HIV-1 mutants defective in ESCRT recruitment. Cells were either infected with virus or nucleofected with provirus. Virus release was characterised by western blotting, and the distribution of virus was analysed by immunofluorescence (IF). Electron microscopy (EM) was used to identify HIV-1 budding sites.

Results: In siRNA experiments, good knockdown efficiencies were achieved for ALIX and Tsg101, but effects on virus release were only modest, perhaps because many of the infected cells had escaped the knockdown. To address these complications, we mutated motifs in Gag p6 required for recruitment of Tsg101 (PTAP–) and ALIX (YP–), or deleted the entire p6 (Δp6). In MDM, the release of PTAP– and Δp6 viruses was inhibited more efficiently and to the same extent for both mutants, compared to the YP– mutant (63% vs. 29%). This showed that, as in other cells, Tsg101 is more important than ALIX for virus release in MDM. To analyse the global distribution of virus in the cells, we used IF. In a significant number of cells, both the WT and the PTAP– mutant viruses were found to assemble only at the IPMC (Fig 1). To verify these findings, we performed EM on MDM infected with PTAP– mutant viruses. Consistent with the IF data, we observed immature HIV-1 budding profiles mainly associated with the IPMC.

Conclusions: Our study is the first to provide conclusive evidence that the IPMC is the preferred assembly site for HIV-1 in MDM. Because macrophages are long-lived compared to T-cells, this "archiving" of HIV in the IPMC may conceal it from immune surveillance, which may have implications for HIV therapy and disease progression.

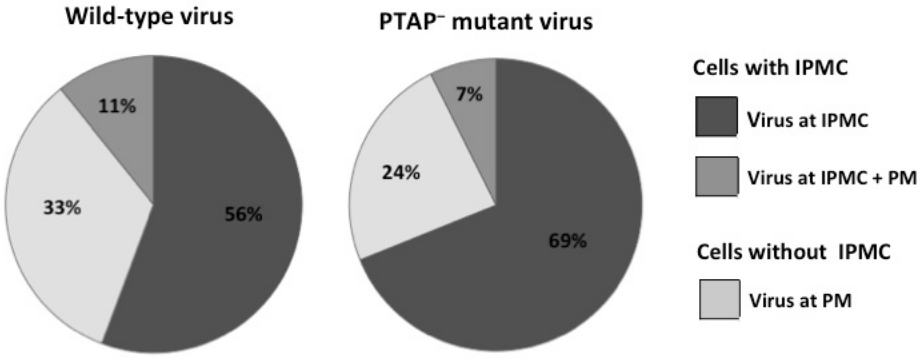

Fig 1: Distribution of assembled HIV-1 in MDM. Viruses were predominantly found at the IPMC. About a third of the MDM had no IPMC and in these cells virus assembly occurred at the cell surface.

177 LEDGIN (ALLINI) Disruption of HIV-1 Assembly Does Not Involve LEDGF/p75

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Background: LEDGF/p75, the product of the PSIP1 gene, is an HIV-1 integration cofactor that tethers the viral pre-integration complex to the site of its subsequent integration. Allosteric integrase inhibitors or ALLINIs (also known as LEDGINs) disrupt the interaction of LEDGF/p75 with the HIV-1 IN dimer and impair integration. However, a considerably more potent (and apparently main) mechanism of ALLINI action was recently identified: disrupting proper particle assembly. It is not clear whether this antiviral effect involves LEDGF/p75. Some studies suggest that it is LEDGF/p75-independent but others suggest LEDGF/p75-dependence and, consistent with this, that LEDGF/p75 incorporation into HIV-1 particles occurs and is necessary for normal HIV-1 infectivity. RNAi-depleted cells still contain some LEDGF/p75 protein, and a fractionally minute LEDGF/p75 residuum can maintain integration cofactor function. Mouse PSIP1 gene knockout cell lines exist but cannot be used for HIV assembly studies. Here we definitively answer two questions: does LEDGF/p75 play a role in HIV-1 assembly and does the ALLINI antiviral mechanism involve LEDGF/p75? To do so, we used TAL effector nucleases (TALENs) to delete the PSIP1 gene from informative human cell lines.

Methodology: We designed and constructed multiple TALEN pairs that site-specifically target PSIP1. We used them to generate clonal Jurkat and 293T cell lines that are -/- for the entire 42 kb gene, and separately, -/- for the only the exons that encode the LEDGF/p75 integrase binding domain (IBD). Correct deletion of all PSIP1 alleles was verified at the DNA and protein levels, precise chromosomal deletion junctions were determined, and comprehensive viral life cycle analyses were conducted in the presence and absence of drug.

Results: HIV-1 integration is impaired, and spreading viral replication is blocked, but HIV-1 production and infectious particle assembly are normal in PSIP1 -/- cells. This is the case whether the entire gene is deleted or only the IBD-encoding gene segment is deleted. We further determined that ALLINI potency for blocking HIV-1 infectious particle formation is unaffected by total removal of LEDGF/p75-encoding capacity from the cell. TALEN gene KO was efficient. For example, a third of single cell clones generated from a single transfection were found to contain bi-allelic gene disruptions due to NHEJ-generated indels at the specific target site, suggesting efficacy for gene targeting cure strategies aimed at this and other HIV dependency factor genes such as CCR5.

Conclusions: The main ALLINI mechanism is independent of LEDGF/p75. This protein also does not play a detectable role in particle assembly. The LEDGF/p75 cofactor role is confined to the integration step of the viral life cycle.

178 Characterization of the Interaction Between Staufen-1 With HIV-1 Rev and HERV-K(HML-2) Rec

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Background: The Rev protein of HIV-1 is an RNA transport factor that enhances nuclear export of intron-containing retroviral transcripts and appears to be critical for various aspects of subsequent RNA utilization pathways. The cellular protein Staufen-1 is in several ways functionally related to retroviral RNA transport proteins. It shuttles RNA out of the nucleus and has previously been shown to become incorporated into HIV-1 particles by direct binding to the genomic RNA and to interact with the Gag protein of HIV-1, promoting Gag oligomerization and RNA encapsidation. Moreover, we have recently demonstrated that it interacts with Rev of HIV-1 and the Rec and Gag proteins of HERV-K(HML-2).

Methodology: Using pull-down and coimmuniprecipitation experiments along with deletion mutants we have mapped the interaction sites of Staufen-1 with Rev and Rec. The effect of Staufen-1 on nucleo-cytoplasmic export and translation was determined with reporter constructs in HEK 293T cells. Stress granules were induced with arsenit and the localization of the proteins in granules was investigated by immunofluorescence.

Results: Having demonstrated a direct interaction between Staufen-1 and HIV-1 Rev we found that the NLS of Rev is the region required for binding. In the Staufen-1 protein, the RBD3 domain is the main mediator of the interaction with Rev. This is in contrast to the situation with Rec, where binding is mediated primarily through the RBD4 domain. While Staufen-1 strongly enhances nucleocytoplasmic export and/or translation of unspliced HERV-K(HML-2) transcripts in the presence of Rec, this seems not to be the case for unspliced HIV-1 transcripts in the presence of Rev. Moreover, we demonstrate that under cellular stress conditions Rec and Rev associate in Staufen-1-positive stress granules. However, Staufen-1 appears to attract only Rec, but not Rev, into stress granules.

Conclusions: Although Staufen-1 interacts with both HIV-Rev and HERV-K(HML-2) Rec, only the nucleocytoplasmic transport and translation of HERV-K(HML-2) is significantly upregulated by Staufen-1. Our data also indicate that Rev and Rec are recruited into stress granules by different mechanisms.

179 The Role of RNA Interference in HIV-1-Infected Primary Human Monocyte-Derived Macrophages

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Background: Micro RNAs (miRNAs) and other small noncoding RNAs (sncRNAs) are key players in post-transcriptional gene regulation. We and other groups have described the presence of HIV-1 derived sncRNAs in different experimental setups; however, so far their biological function remained to a large extent unknown. Here we used a global, comprehensive approach to investigate whether viral small RNAs may play a role in the RNA interference (RNAi) pathway in primary human monocyte-derived macrophages (MDMs). Specifically, we aimed to characterize the profiles of host and HIV-1 derived small RNAs and the possible impact of these RNAs on the viral life cycle.

Methodology: We applied Argonaute 2 (Ago2) photoactivatable ribonucleoside-enhanced crosslinking and immunoprecipitation (PAR-CLIP) to MDMs infected with HIV-1_{JRFL} for 14 days from two different donors. It has been previously demonstrated that this approach enables identification of Ago2-bound miRNAs as well as of the miRNA-targeted mRNAs. Illumina sequencing was performed on PAR-CLIP and small RNA (18 to 30 nt) samples from the same donors, and small RNA sequencing was performed on HIV-1 infected MDMs from two additional donors.

Results: The analysis of PAR-CLIP data demonstrated the absence of viral RNAs in Ago2-RISC, suggesting that viral sncRNAs do not enter the canonical RNAi pathway in MDMs. However, small RNA sequencing on samples from the same MDM cultures confirmed the presence of HIV-1 sncRNAs, although expressed at low levels (< 0.5 % of total small RNA fraction). Most host miRNAs revealed no significant change in expression levels between infected and non-infected MDMs.

Conclusions: Our data indicate that it is unlikely that viral sncRNAs are incorporated as functional miRNAs or resemble targets for host miRNAs in Ago2-RISC. The presence of HIV-1 sncRNA as detected by small RNA sequencing implies alternative functional roles or biogenesis pathways. Future efforts are needed to uncover potential functions of HIV-1 derived sncRNAs in MDMs or other HIV-1 host cell types.

180 Induced Maturation of HIV-1 Virions

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Background: HIV-1 assembles at the plasma membrane of host cells as immature, non-infectious particles. Processing of Gag and Gag-Pol polyproteins catalyzed by the viral protease (PR) activates the viral enzymes and results in dramatic structural rearrangements within the particle. Formation of the mature HIV-1 core is a prerequisite for infectivity; processing and morphological maturation thus represent important targets for antiretroviral therapy. When and how fast the maturation event occurs are two basic questions that surprisingly still remain unanswered. Whereas the architecture of start and end point - the immature and mature virion - is well characterized, structural intermediates delineating the pathway of morphological maturation are missing. Biochemical ensemble measurements and structural analyses are hampered by the fact that HIV-1 release and maturation in tissue culture occur asynchronously between individual cells and between individual particles released from the same cell. We have established a method to synchronize HIV-1 proteolytic maturation in vitro with the aim to allow a more detailed analysis of the maturation process.

Methodology: Immature virions were prepared from cells treated with high concentrations of PR inhibitor and an inhibitor wash-out strategy was developed to induce proteolytic maturation of polyproteins within the assembled particles. Using this approach, we followed the production of mature Gag and Gag-Pol processing products over time. These data were correlated with analysis of viral infectivity, reverse transcriptase (RT) activity and virion morphology.

Results: Preparation of immature virions followed by inhibitor wash-out resulted in complete processing of Gag into its mature subunits with a t1/2 of ~4 h under optimized conditions, suggesting that factors other than PR activity were limiting in this setup. Infectivity of 'in vitro matured' virions was detectably higher than that of the corresponding immature particles; recovery of infectivity was only partial, however, yielding low titers compared to mature virus prepared in the absence of inhibitor. Incomplete recovery of infectivity in spite of complete Gag maturation correlated with pronounced defects in Gag-Pol maturation and RT enzymatic activity.

Conclusions: We conclude that the complex process of HIV-1 maturation, occurring at high protein concentrations in a confined space, cannot be easily reconstituted within an already assembled immature virion. We therefore assume that tight temporal control between immature particle assembly and proteolytic processing is required to allow for correct polyprotein cleavage and arrangement of mature protein subunits. Further studies are directed towards elucidating this complex relationship.

181 Interplay of Cholesterol and Env Protein in the Lytic Deformation of HIV-1 by Peptide Triazoles

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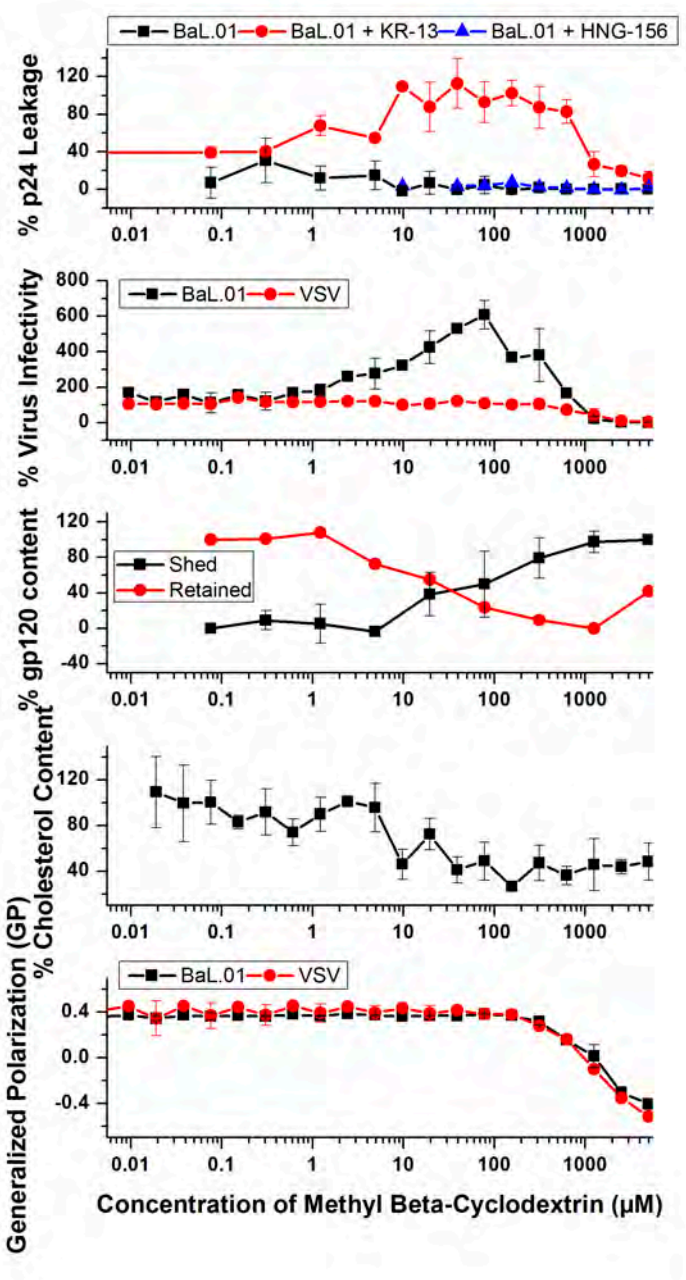
Background: HIV-1 Env spike consists of gp120 involved in binding receptors and gp41 which is embedded in a lipid envelope that is mainly cholesterol (45-mol %) and involved in fusion. Envelope cholesterol affects infectivity of the virus and interacts with gp41. Our lab has developed peptide triazoles that inhibit gp120 binding to CD4 and CCR5/CXCR4 and cause leakage of capsid p24, from the viral lumen. Examining the effects of cholesterol on p24 release allows us to investigate lipid-protein interplay at the Env spike.

Methodology: Cholesterol was extracted from BaL.01 (HIV-1) and Vesicular Stomatitis Virus (VSV-G) spike psuedotyped viruses containing the Luciferase gene using methyl β-cyclodextrin (MβCD). Infectivity was detected by chemiluminescence from Luciferase expression in cells while p24 release and gp41 were measured by spinning virus and testing supernatant and pellet fractions respectively by ELISA. Fluidity was measured with Laurdan. Shed gp120 was detected from western blots. Morphological analysis was done on fixed virus by transmission electron microscopy (TEM). Cholesterol was quantified using Cholesterol Oxidase and the fluorescent Amplex Red dye.

Results: Initial depletion of viral membrane cholesterol strikingly enhanced both KR-13-induced p24 capsid protein leakage and infectivity and decreased virus size (TEM). Further depletion of cholesterol arrested both processes and caused complete shedding of gp120 but gp41 and the virus size remained intact and membrane fluidity increased though this wasn't specific to HIV-1. Under similar conditions, the non-virolytic parent peptide HNG-156 did not induce p24 release and the VSV pseudotyped viruses did not see any enhanced infectivity.

Conclusions: Light cholesterol depletion enhances both KR-13 triggered p24 release and infectivity while heavy depletion arrest both processes, possibly due to shedding of gp120. While fluidity increases during cholesterol depletion, it is not specific to the HIV-1 spike. Correlated trends between infectivity and leakage during cholesterol depletion leading up to the gp120 shedding suggest lipid-protein interplay. To determine the mechanism of enhancement, we will test protease-treated viruses and Env mutations that disrupt the cholesterol interacting (CRAC), transmembrane, and cytoplasmic tail domains interacting with the lipid envelope. Together, this work will help determine the impact of lipid-protein interplay and define approaches to inactivate the virus.



Session P-A5 Poster Session
Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**
Apobec, Apobec, Apobec

182 Characterizing Novel N-Terminal Domains of APOBEC3G

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Background: The human cytidine deaminase APOBEC3G (A3G) has been shown to exhibit antiviral function in the absence of its established catalytic function. A thorough molecular understanding of this deamination-independent mechanism is largely unknown.

Methodology: We sought out to characterize the A3G protein and identify key regions and domains related to its antiviral function. A library of mutants was constructed and these mutants were examined for antiviral function in a vif-deficient system. 293T cells were transiently cotransfected with proviral DNA and the mutant construct of interest. A3G and viral expression was verified by Western blotting. Viral particles were quantitated, normalized, and then used to infect TZM cells in a single round infectivity assay. Finally, virions were purified and assessed for A3G packaging. Concurrently, the catalytic activity of the mutants was examined using a Rifampicin based E. coli assay.

Results: We have identified two novel N-terminal domains that upon mutation confer a significant loss of antiviral function, but not an observable decrease in catalytic function.

Conclusions: These novel domains are quite interesting because they appear to play a significant role in antiviral function but not catalytic function. We are currently looking at the evolutionary conservation of these residues to determine whether these identified domains are in fact conserved or whether these domains fall within regions of the A3G protein that have been subjected to episodes of positive selection.

183 SLBP (Stem-Loop Binding Protein) Regulates the Expression of APOBEC3G

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Background: Combining quantitative proteomics and functional analysis, we have recently demonstrated that SLBP restricts the integration and transcription of HIV-1. In lymphocytic cells, SLBP depletion leads to the concomitant decrease of the restriction factor APOBEC3G (apolipoprotein B mRNA-editing, enzyme-catalytic, polypeptide-like 3G). This decrease was observed at both the RNA and protein levels. Here, we sought to provide mechanistic insight into the novel SLBP/APOBEC3G relationship on the molecular level.

Methodology: First, using EpiQ™ chromatin analysis, we compared promoter accessibility in lymphocytic cells under-expressing SLBP vs control samples. Then, chromatin Immunoprecipitation (ChIP) assay was employed to examine the binding affinity of specific transcription factors to APOBEC3G promoter regions. Finally, interferon PCR Arrays were performed to characterize potential molecules mediating interactions between SLBP and APOBEC3G.

Results: SLBP depletion led to a significant ($p<0.05$) decrease in chromatin accessibility of the APOBEC3G gene in CEM cells. Also under conditions of SLBP depletion, ChIP revealed less binding of SP1, a known APOBEC3G transcription factor, to the -150 to -50 (relative to transcription start site) APOBEC3G promoter region. Finally, using interferon α, β response RT^2 profiler™ PCR Arrays, SLBP depletion resulted in decreased level of IL15 (~10 fold), a known modulator for APOBEC3G.

Conclusions: The synergistic expression of SLBP/APOBEC3G is likely due to the combined effects of SLBP-induced chromatin accessibility and transcription factor binding affinities of the APOBEC3G promoter region. SLBP depletion also impacts the interferon pathway to modulate APOBEC3G levels indirectly. These results identify SLBP as a regulator of APOBEC3G.

184 Incomplete Apobec3G Neutralization by Vif Mutations Facilitates Evolution From CCR5 To CXCR4 Use

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Background: Some Vif mutations favor incomplete Apobec3G (A3G) neutralization. In this setting, the increased burden of G-to-A mutations introduced by A3G can contribute to HIV genetic diversity and to HIV escape from antiretroviral drugs. Here, we investigate whether Vif mutations affect A3G capability to generate G-to-A mutations at V3 positions critical for CXCR4 usage and for HIV antigenic potential.

Methodology: The CCR5-using 81A-Vifwt and the 81A-VifK22E, 81A-VifE45G mutants with suboptimal activity against A3G were used to infect PBMC (experiments in triplicate). Frequency of G-to-A V3 mutations recovered from proviral DNA was analyzed by ultradeep sequencing (UDPS) at 7, 14, 21 days post infection (dpi). After shorah correction, mutations detected in both forward and reverse primers in >5 reads were considered. The False Positive Rate [FPR] by Geno2pheno was used to infer HIV tropism. To assess the correlation between Vif mutations and co-receptor usage, 769 paired HIV B subtype Vif and V3 RNA sequences from Los Alamos DB were analyzed.

Results: In PBMC, 81A-VifK22E and 81A-VifE45G show a decreased p24 production compared to p81A-Vifwt (mean log reduction=3.1 for K22E and 1.2 for E45G).

By UDPS, no G-to-A mutations are detected in 81A-Vifwt-infected PBMC at each time point analyzed (0/14642 reads at 7dpi, 0/22084 at 14dpi, 0/23013 at 21dpi). G-to-A mutations at 2 V3 positions are observed in 81A-VifE45G-infected PBMC (prevalence from 0.03% [5/22448] to 0.06% [8/22448]). Conversely, a progressive enrichment of G-to-A mutations is detected in 81A-VifK22E infected PBMC (2.2% [373/16797] reads at 7dpi, 2.6% [278/10778] at 14dpi, 4.0% [812/20321] at 21dpi). G-to-A mutations account for >98% of the overall genetic variability, and occur at 6 V3 positions with 6/6 resulting non-synonymous (R9K, G15R, G24E, E25K, G28E/R, D29N). The presence of G24E and E25K strongly decreases the FPR (from 24.7 for wt to 6.8 for G24E and 5.0 for E25K), indicating CXCR4 usage acquisition. Consistent with this result, the introduction of G24E or E25K in B-subtype gp120 strongly increases CXCR4 N-terminus binding affinity for V3 (-40.1Kcal/mol for wt versus -510Kcal/mol for G24E and -522Kcal/mol for E25K). G15R resides in V3 crown proposed as vaccine target.

Finally, the analysis of paired V3 and Vif RNA sequences shows that the presence of at least one mutation in Vif22 and/or Vif45 correlates with increased prevalence of CXCR4 usage (44.8% versus 31.5% in Vifwt P=0.031).

Conclusions: A3G incomplete neutralization by single Vif mutations favors the generation of a proviral reservoir with an increased capability to use CXCR4 and to potentially escape neutralizing antibodies. This has implications for the success of CCR5 antagonist-based dual therapy and for immunological HIV control.

185 17β-Estradiol Protects Primary Macrophages Against HIV Through Induction of IFNα and APOBEC3A

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Background: Estrogen has been shown to display a protective role against HIV/SIV transmission. The effect of estrogen on HIV infection of primary cells has recently been reported, but the mechanism underlying estrogen-mediated protection is not well defined. In this study, we examined the mechanism by which estrogen inhibits HIV infection in primary macrophages.

Methodology: Monocyte-derived macrophages (MDMs) were isolated from PBMCs of healthy human donors, and then treated with 17β-estradiol (E2) at different time points during HIV infection. Cells were infected with either replication-defective HIV pseudotyped luciferase reporter viruses for single-cycle infection assays or replication-competent viruses for multiple round infection assays. Level of viral infection was determined by measuring luciferase activity or by quantitating levels of HIV p24 in culture media by ELISA. E2-induced changes in gene expression of IFNs, SAMHD1, and the APOBEC family proteins were examined by RT-PCR analysis.

Results: E2 inhibited HIV replication in MDMs but not activated PBMCs or CD4+ T cells. Pretreatment of MDMs with E2 for 24 h was required to block HIV infection. E2 had no effect on HIV inhibition when MDMs were exposed to virus prior to E2 treatment. Investigation of the mechanism of E2-mediated HIV inhibition revealed E2 did not affect surface expression of CD4 and HIV co-receptors nor HIV attachment. E2 pretreatment also protected MDMs from infection by HIV reporter virus pseudotyped with VSV Env, which can enter cells independent of CD4 and HIV co-receptors. Quantitative PCR analysis of HIV reverse transcribed (RT) products showed E2 blocked the synthesis of late RT products. Investigation into the involvement of host restriction factors in E2-mediated HIV inhibition indicated that E2 induced gene expression of type I IFN and APOBEC3A in MDMs from multiple donors. Importantly, the anti-HIV activity of E2 was abolished in the presence of IFNα neutralizing antibody and was absent in bone marrow-derived macrophages from IFNα receptor deficient mice. Interestingly, HIV exposure suppressed E2-mediated type I IFN induction, suggesting that HIV could antagonize E2-mediated innate immune responses.

Conclusions: IFNα contributed to E2-mediated HIV inhibition in MDMs. E2 blocked HIV infection at the step of late reverse transcription. Induction of IFNα by E2 was associated with an increase in APOBEC3A but not APOBEC3G, APOBEC3F or SAMHD1. HIV can also antagonize E2-mediated type I IFN induction. Our study offers a better understanding of the interplay between HIV and E2-mediated immune responses that will provide insight into an effective strategy for HIV prevention.

186 Nuclear Import of APOBEC3F-Labeled HIV-1 Preintegration Complexes

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Background: APOBEC3F (A3F) and APOBEC3G (A3G) are host factors that incorporate into virions and restrict HIV-1 replication. Although Vpr and integrase tagged with fluorescent proteins have been used to label viral particles, these marker proteins do not remain associated with PICs throughout replication. As a result, it has not been possible to visualize PICs in the nuclei of infected cells.

Methodology: We labeled HIV-1 particles with YFP-tagged APOBEC3 proteins and examined their association with preintegration complexes (PICs) in infected cells using quantitative confocal microscopy.

Results: We observed for the first time that transcription is not required for nuclear import of PICs. We also quantified association of cytoplasmic PICs with nuclear envelope (NE). In addition, we quantified the distance from the NE to the nuclear PICs to determine the nuclear penetration distance by PICs.

Conclusions: Using A3F-labeling as a novel tool to visualize PICs, we determined that 1) reverse transcription is not required for nuclear import of PICs, indicating that a viral core uncoating event associated with reverse transcription, and the central DNA flap that forms during reverse transcription, are not required for nuclear import; 2) viral core stability mutations dramatically reduce association of PICs with the nuclear envelope as well as diminish their nuclear import; and 3) most nuclear PICs remain close to the nuclear envelope and are not distributed throughout the nuclei.

187 Non-Integrating HIV-1 Is Sensitive To Inhibition by Target Cell Apobec3a

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Background: The APOBEC3A (A3A) polynucleotide cytidine deaminase of the human APOBEC3 (A3) protein family was shown to be antivirally active against HTLV-1 but not HIV-1 when expressed in the virus producer cell. In primary monocytes/macrophages, high levels of endogenous A3A activity have been associated with restriction of HIV-1 during infection. So far, ectopic expression of A3A has not been investigated to study the antiviral activity of target cell A3A.

Methodology: HIV-1 and Murine leukemia virus (MLV) luciferase reporter viruses pseudotyped by VSV-G were investigated using human HEK293T cells as virus producer and virus target cells. We compared the infectivity and capacity for gene expression of wild type and integrase mutated (D64V) HIV-1 in cells ectopically expressing A3A. A sensitive PCR method was applied to identify A3A-induced mutations in the viral genome. To prevent unwanted effects of high A3A amounts on the stability of transfected plasmids and on the cell cycle, A3A expression was limited to moderate levels to minimize direct deamination effects of A3A on genomic and transfected DNA.

Results: We confirm that HIV-1 is insensitive to A3A expressed in the viral producer cells, because of a lack of encapsidation of A3A in viral particles. In contrast, HTLV-1 and the gamma retrovirus Murine leukemia virus were inhibited by producer cell derived A3A. To test the role of A3A in target cells, we infected HEK293T cells expressing A3A with MLV and HIV-1. While HIV-1 resisted an inhibition by target cell A3A, MLV transduction was impaired. We hypothesized that HIV-1 may evade the post-entry restriction by target cell A3s by a different timing of integration into the host's genomic DNA. Indeed, when comparing wild type with integrase mutated HIV-1, we observed that the integration-deficient virus was significantly restricted by target cell A3A. Viral inhibition correlated always with detectable mutations in the viral genome. Additionally experiments in target cells showed that not only A3A, but also A3B, A3C, A3G, and A3H, but not A3D and A3F, restricted non-integrating HIV-1 post-entry.

Conclusions: These data demonstrate that HIV-1's sensitivity to target cell-expressed APOBEC3 proteins is modulated by the integration competence of the virus.

188 Degradation of SAMHD1 Specifically Decreases the Efficacy of Thymidine HIV RT Analog Inhibitors

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Background: SAMHD1 has recently been recognized as an antiviral factor that acts by depleting deoxynucleoside triphosphates (dNTPs) availability for HIV reverse transcriptase (RT), via hydrolization of dNTPs. SAMHD1 restriction is counteracted by HIV-2 Vpx, which targets SAMHD1 for proteosomal degradation, resulting in an increased availability of dNTPs and consequently enhanced viral replication. Nucleoside reverse transcriptase inhibitors (NRTIs) are the most commonly agents used in antiretroviral therapy. NRTIs inside the cell compete with cellular dNTPs as substrate for viral RT. Consequently, SAMHD1 activity has been reported to influence NRTI efficacy in inhibiting viral replication. Here, a panel of different RT inhibitors were analysed in views of their different antiviral efficacy depending on SAMHD1.

Methodology: Antiviral activities of different NRTIs (AZT, ddC, 3TC, d4T and TDF), NNRTIs (NVP, EFV) and Raltegravir were assessed in primary cells expressing SAMHD1 (MDM and PBMCs) or the MT-4 cell line. Cells were infected either with a VSV-pseudotyped HIV-1 GFP-expressing virus or alternatively with GFP-expressing HIV-2 virus with or without Vpx. For HIV-1 infections, Vpx expression was achieved by cell transduction with viral like particles containing Vpx (VLP-Vpx). Replication levels were measured by flow cytometry and 50% effective concentrations (EC50) were determined.

Results: Modulation of SAMHD1 cellular levels either with VLP-Vpx or by HIV-2 infection resulted in a significant reduction of SAMHD1 protein expression in MDM and PBMCs that was accompanied of an increase in viral infection (5 and 2 fold increase for MDM and PBMCs, respectively). Contrary, no effect was observed in the MT-4 cell line where SAMHD1 expression was not detectable. EC50 where obtained for all the inhibitors in MDMs and MT-4 cells infected with HIV-1 with or without VLP-Vpx. As expected, no changes in sensitivity to NNRTIs or integrase inhibitors where observed in MDMs with or without VLP-Vpx. In the case of NRTIs, sensitivity significantly changed in the case of the thymidine analogs (10 and 9 fold difference in EC50 for AZT and d4T, respectively), but no differences were observed with 3TC, ddC and TDF. Accordingly, sensitivity to AZT was also reduced in PBMCs infected with HIV-2 compared to infection with HIV-2 DVpx strain, although to a lesser extent. No changes in sensitivity to any of the inhibitors were observed in MT-4 cells in the presence or absence of Vpx.

Conclusions: Reduction of SAMHD1 levels significantly decreases HIV sensitivity to thymidine but not other nucleotide RT analog inhibitors in both macrophages and lymphocytes. Our results suggest a differential contribution of the different dNTPs in HIV replication, being thymidine the most limiting nucleotide.

188A Natural Resistance To HIV-1 by Select APOBEC3H Haplotypes

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Background: HIV-1 pathogenesis requires neutralization of innate immune defenses. For instance, its viral infectivity factor (Vif) triggers the degradation of several members of the APOBEC3 family of DNA cytosine deaminases. Without Vif, HIV-1 succumbs to lethal mutagenesis inflicted by APOBEC3D, F, G, and H. Overexpression studies have shown that polymorphisms in human *APOBEC3H* encode proteins that differ widely in their expression levels

and degrees of HIV-1 restriction. The distribution of APOBEC3H haplotypes is variable in human populations, but expression and activity of endogenous APOBEC3H protein in primary T cells has heretofore been difficult to measure. A major question is therefore whether the natural variation of endogenous APOBEC3H haplotypes in human populations influences HIV-1 infection in primary cells.

Methodology: Naïve CD4+ T lymphocytes were isolated from 24 donors and genotyped to determine APOBEC3H haplotype. Subsets of these donors with haplotypes that encode putatively stable and unstable APOBEC3H proteins were subjected to immunoblotting to compare endogenous protein levels and to ex vivo spreading infections to monitor susceptibility to HIV-1 infection. These experiments used HIV(IIIB) separation-of-function Vif alleles that were all fully able to counteract APOBEC3F and G, but either unable (F39V) or fully able (N48H, G60E, D61K, A62G, K63E) to degrade APOBEC3H haplotype II.

Results: *APOBEC3H* mRNA levels increased with T cell activation and further with HIV-1 infection regardless of haplotype. In contrast, the protein levels of APOBEC3H haplotype II (which encodes a stable protein) but not haplotype I or III (which encode unstable proteins) increased during the course of the infection. APOBEC3H from individuals heterozygous for haplotype II was efficiently packaged into virus-like particles (VLPs) from Vif F39V mutant virus, to a lesser degree in wild-type HIV, and was absent in VLPs from the Vif N48H, G60E, D61K, A62G, K63E mutant virus. Importantly, packaging of stable APOBEC3H caused a near total restriction of the Vif F39V mutant virus, a delay in replication kinetics of the wild-type virus, and had no effect on the Vif N48H, D61K, A62G, K63E mutant virus.

Conclusions: These data demonstrate that naturally occurring variants of APOBEC3H are expressed stably and capable of encapsidating and restricting HIV-1 replication in primary CD4+ T lymphocytes. Vif V39 exists in 25% of HIV-1 subtype B isolates suggesting a dynamic relationship between the evolution of Vif to antagonize APOBEC3H in populations in which some individuals express an active APOBEC3H and others do not. Future work will determine whether APOBEC3H haplotypes, along with viral variation in Vif, might explain some of the variation in HIV transmission or progression.

Session P-A6 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

HIV Entry

189 The Sphingosine-1-Phosphate Receptor 1 Dimerizes With CCR5 and Enhances HIV Infection

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Background: CCR5 is a G protein-coupled receptor (GPCR). GPCR dimerization may result in a change in cell surface density, in ligand specificity and affinity and in the nature and intensity of the signaling pathway. Therefore, we looked for GPCR able to dimerize with CCR5 at the CD4 T cell surface.

Methodology: We identified by multi quantitaiive RT-PCR the GPCR coexpressed with CCR5 in circulating CD4 T cells. GPCR dimerization was evidenced by time-resolved FRET. Using HIV gene transfer vectors, we established two cell lines expressing or not the sphingosine-1-phosphate receptor 1 (S1P1). HIV infectibility by replicative and non-replicative HIV-1 strains was measured in both cell lines. The effect of S1P1 expression on LTR activation was studied in cells stably transfected with a reporter gene driven by HIV LTR and transduced with the S1P1 gene. S1P1 expression at the surface of primary cells was measured by flow cytometry. The effect of the S1P1 antagonist FTY720 was tested on SCID mice reconstituted with human peripheral blood mononuclear cells (PBMC) and infected with the HIV-1 R5 strain JR-CSF.

Results: We identified 250 GPCR coexpressed with CCR5 in circulating CD4 T cells. Among the GPCR the most expressed, we found that S1P1 dimerized with CCR5 at the cell surface. S1P1 coexpression resulted in a decrease in HIV-1 R5 virion entry, but not in cell to cell propagation. By contrast, S1P1 coexpression boosted LTR activation. Altogether these effects resulted in the increase in replicative HIV-1 R5 infection. We detected S1P1 at the surface of monocyte-derived dendritic cells, and FTY720 inhibited R5 infection in these cells. Moreover, this S1P1 antagonist inhibited HIV-1 R5 infection in a mouse model.

Conclusions: S1P1 dimerizes with CCR5 and its expression increases HIV-1 R5 replication. Consequently, an S1P1 antagonist inhibited R5 infection in vitro and in vivo. S1P1 might also impair the chemokine receptor function of CCR5, and vice versa.

190 Purinergic Receptor Antagonists as Potent Inhibitors of HIV-1 Infection by Blocking Early Entry

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Background: Human Immunodeficiency Virus (HIV-1) causes a chronic infection that can be controlled with antiretroviral medications. However, individuals living with HIV are still at increased risk of morbidity form cardiovascular disease, cancer, and neuropathy. Many of these sequelae are proposed to be due to chronic inflammation, however the mechanism has not been determined. Recent studies indicate that adenosine triphosphate (ATP) release and purinergic signaling is required for HIV-1 infection. Purinergic receptors are distributed through a wide variety of tissue types that detect extracellular ATP as a danger signal released from dying cells. Given this important role in immune cell signaling and viral infection, we have explored how these pathways are involved in transmission of HIV-1 virus from cell to cell through virological synapses. We propose that ATP is a key signaling molecule that links HIV-1 infection and HIV-associated inflammation.

Methodology: Our laboratory has devised molecular tools to study virus-host interactions through the use of fluorescent tags, allowing us to visualize discrete stages of infection. Using these infection assays, we are able to determine the step at which purinergic antagonists block cell-cell infection.

Results: Our data demonstrate that purinergic antagonists can potently block HIV-1 infection at an early stage of infection. We find that inhibitors are equally potent at blocking infection by cell-associated HIV and cell-free virus. This inhibition appears to occur before the initiation of viral membrane fusion. We are currently examining whether purinergic signaling is required for the recruitment of the viral co-receptors to the synapse to support viral fusion.

Conclusions: The results imply that co-receptor recruitment requires a purinergic signaling-dependent step to allow fusion. Our studies explore a novel mechanism of therapeutic targeting in HIV-1, that may also act on inflammatory and cell death pathways associated with chronic infection. We propose that targeting this pathway would represent a potent new form of antiretroviral therapy that may reduce both viral burden and associated inflammatory sequelae.

191 Optical Sorting of HIV-1 Reveal the Minimum Number of Spikes Required for Optimal Viral Infectivity

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Background: A fundamental question in HIV-1 biology is how many envelope spikes are required for viral infectivity. This number is also of great pharmacological interest because the lower this number is, the higher occupancy over the total number of functional spikes on a virion is required for entry inhibitors and neutralizing antibodies. The number of envelope spikes required for the optimal infectivity of HIV-1 is a difficult question to address without knowing the apparent heterogeneity of HIV-1 in their envelope content. How heterogeneity in viral envelope content may give rise to differences in viral infectivity is unknown. The distribution of the spike number and the total number of functional spikes per virion are both required for correct mathematical modeling of this process.

Methodology: In practice, the heterogeneity of HIV-1 envelope content can only be probed by using a technique that permits study of individual virions at single-molecule level so that each virion can be quantitated for their protein composition, preferably under native conditions. Here we developed a technique of this kind, which we termed, 'virometry', that was based on optical manipulation of a dielectric particle in liquid. This technique permits multi-parameter analysis of individual HIV-1 virions in culture media under native conditions, and allowed us to directly address the heterogeneity among virions in their protein compositions down to single-molecule level.

Results: By using fluorescent antibody against gp120, we show that the quantity of gp120 proteins per virion varies over one order of magnitude despite the fact that all the viruses were derived from a single clone, which yields substantial heterogeneity in viral infectivity. By characterizing a series of HIV-1 with different contents of envelope glycoproteins, we reveal a clear nonlinear dependence of HIV-1 infectivity on envelope glycoprotein content.

Conclusions: Model-independent analysis of our data revealed that HIV-1 envelope spikes function cooperatively to mediate HIV-1 infection, and a minimum of two envelope spikes is required for optimal viral infectivity (Supported by NIH 1DP20D008693-01; WC).

192 Application of an HIV Entry Assay To Identify HIV Target Cells in the Female Genital Tract

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Background: The HIV pandemic disproportionately affects women, with the majority of new infections occurring through vaginal sex. The cellular targets of HIV infection in the female genital tract (FGT) are poorly defined, although virus replication in mucosal CD4+ T cells is important and correlates of cellular susceptibility may include the early immune activation marker CD69, expression of CCR5 and the mucosal homing integrin $\alpha4\beta7$. Measuring virus replication within CD4+ T cell subsets in the FGT in a biologically relevant ex vivo HIV infection assay is technically challenging. We have developed a biologically relevant ex vivo assay to quantify HIV entry into unstimulated cervical mononuclear cells (CMCs) obtained from cervical cytobrush sampling.

Methodology: Peripheral blood mononuclear cells (PBMCs) and CMCs were isolated from 26 HIV-negative female participants without clinical signs of sexually transmitted infections in Nairobi, Kenya. Cells were treated with R5-tropic virus incorporating β-lactamase-vpr (BlaM-vpr) chimeric protein into the HIV capsid. Two hours post-infection, samples were loaded with cell-permeant CCF2-AM that contains two fluorophores linked by a β-lactam bond. In the absence of β-lactamase, excitation of intact CCF2-AM leads to fluorescent resonance energy transfer (FRET) and green light emission. In infected cells, β-lactamase cleaves the FRET pair, causing blue light emission. The ratio of blue to green emission is a measure of cytosolic entry of HIV. Twenty hours post-infection, CD4 T cell subsets were defined by flow cytometry based on expression of cell surface receptors relevant to mucosal homing and/or HIV acquisition, which included CCR5, CD69, $\alpha4$, and $\beta7$, and HIV entry was analyzed.

Results: HIV entry of the R5-tropic virus was specific to cervical CD4+ T cells, and blocked by CCR5 inhibitor maraviroc but not by CXCR4 inhibitor AMD3100. CD4 T cells demonstrated 2.8-fold greater HIV entry in CMCs compared to PBMCs from matched participants ($p=0.0003$). HIV entry in CD4+ T cells correlated between PBMCs and CMCs ($r2=0.56$, $p=0.0004$). Cervical CD69+ CD4 T cells had 1.9-fold higher HIV entry than CD69- CD4 T cells ($p=0.001$), possibly due to the 2.4-fold higher CCR5 expression ($p<0.0001$). However, despite 2-fold higher CCR5 expression on $\alpha4\beta7$+ cervical CD4 T cells ($p<0.0001$), HIV entry did not differ between $\alpha4\beta7$+ and $\alpha4\beta7$- CD4 T cells ($p=0.723$).

Conclusions: We have developed a rapid and sensitive assay to quantify HIV entry into cervical CD4+ T cells; this assay confirms that activated CD4+ T cells are preferential targets of CCR5-dependent HIV entry, but finds no preferential targeting of $\alpha4\beta7$+ CD4 T cells. This assay has potential as an intermediate endpoint to assess the impact of clinical interventions on the risk of HIV acquisition.

193 Early Non-Mac-Tropic HIV-1 R5 Envs Efficiently Trans-Infect T Cells and Infect Ectocervices

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Background: Non-mac-tropic HIV-1 R5 viruses are preferentially transmitted and persist in immune tissue even in AIDS patients who carry highly mac-tropic variants in the brain. Non-mac-tropic R5 Envs require high levels of CD4 for infection contrasting with highly mac-tropic Envs, which interact more efficiently with CD4 and can infect cells expressing low CD4. Here, we investigated whether transmitted/founder (T/F), early and late non-mac-tropic R5 Envs mediated more efficient trans-infection of primary CD4+ T-cells and/or infection of ectocervical explant cultures compared to highly mac-tropic R5 Envs.

Methodology: We tested non-mac-tropic R5 Envs identified as transmitter/founder (T/F) and others derived from the acute or late stages of infection. We compared these Envs with highly mac-tropic R5 Envs from late disease. We used Env+ pseudovirions that carried a GFP reporter gene to measure trans-infection of CD4+ T-cells after virus transfer from monocyte-derived dendritic cells (MDDCs) and infection of ectocervical explant cultures.

Results: T/F and acute stage R5 Envs conferred low or background levels of macrophage infection. Infectivity was similar to that mediated by non-mac-tropic R5 Envs from late disease and up to 3 orders of magnitude lower than highly mac-tropic R5 Envs from brain tissue. In contrast, non-mac-tropic and highly mac-tropic R5 Envs mediated similar levels of infectivity for CD4+ T-cells following capture and transfer by MDDCs. Infection of ectocervical explants varied for both non-macrophage-tropic and highly mac-tropic R5 envelopes but were not significantly different. Curiously, T/F Envs conferred lower infection of ectocervical explants compared to highly mac-tropic Envs. Cells infected in ectocervical explants by the highly mac-tropic R5 Bal Env were almost exclusively CD4+ T-cells.

Conclusions: T/F, acute and late stage non-mac-tropic R5 Envs mediated efficient infection of primary CD4+ T-cells via immunological synapses.

Highly mac-tropic R5 Envs from late disease do not confer higher levels of infectivity for primary T-cells following synaptic transfer despite their enhanced ability to interact with CD4.

T/F and acute stage R5 Envs confer infection of ectocervical explants but are not more tropic for this tissue compared to non-mac-tropic or highly mac-tropic Envs from late disease.

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194 Transmitter as Compared To Recipient Envelopes Confer Greater Replication and α4β7 Utilization

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Background: Newly infected individuals generally acquire only a limited number of viruses from chronically infected partners with diverse HIV-1 variants. The biological mechanism for this selection remains uncertain.

Methodology: We identified 9 transmission pairs enrolled in the Rakai community cohort study in Uganda. Full-length HIV-1 envelopes generated from pooling multiple bulk PCRs were incorporated into a HIV-1 backbone to create replication competent recombinant viruses. Viruses were examined for receptor usage, gut homing receptor, α4β7, binding, sensitivity to entry inhibitors, and replication capacity in various primary cell cultures, such as CD4+ T cells, immature and mature monocyte derived dendritic cell (MDDC) - CD4+ T cell co-cultures, Langerhans cells (LC) - CD4+ T cell co-cultures and CD4+ T cells expressing high levels of α4β7 integrin. Summary phenotypic characteristics and recipient to transmitter ratios were compared among the partners in a relationship using the Wilcoxon rank-sum test and one-sample Wilcoxon signed-rank test respectively.

Results: The newly infected partner was sampled a median of 70 days (range 17 - 324 days) after estimated infection while all transmitters had HIV-1 for at least 2 years prior to estimated transmission. Recipient compared to the transmitter envelopes showed no significant difference in their sensitivity to entry inhibitors ($p > 0.05$). Virus with the transmitting partner as compared to recipient envelopes replicated more efficiently in CD4+ T cells ($p = 0.03$), mature MDDC - CD4+ T cell co-cultures ($p < 0.001$), Langerhans cells (LCs) - CD4+ T cell co-cultures ($p = 0.02$), and CD4+ T cells expressing high levels of α4β7 ($p = 0.01$), and demonstrated greater binding to α4β7 high / CD8+ T cells ($p = 0.04$). Transmitter versus recipient envelope virus phenotypic differences were not always consistent among the primary cells obtained from a minimum of 4 different blood or skin donation volunteers. There was a non-significant negative correlation between replication in α4β7 high CD4+ T cells and days post-infection suggesting that if these are the transmission phenotype they are lost relatively early after acquisition.

Conclusions: Envelopes found in recently infected subjects as compared to the corresponding transmitting partner have significantly lower replication capacity in primary cells and decreased binding to the α4β7 integrin. Even though the majority of recently infected subjects were not sampled soon after estimated acquisition, our results suggest that if enhanced infectivity and/or greater α4β7 binding are transmission phenotypes then viruses with these characteristics are selected against early after acquisition and subsequently enriched during the chronic phase of disease.

195 Differences in HIV Receptor Activity of CXCR4 Isoforms: Consequences for X4 Strains Emergence

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Background: Two CXCR4 isoforms have been described in humans, CXCR4-A and CXCR4-B, corresponding to an unspliced and a spliced mRNA, respectively. In this study we analyzed the expression of both isoforms, and their functions as HIV coreceptors and chemokine receptors.

Methodology: To this aim, using HIV gene transfer vectors, we established two cell lines expressing each isoform. HIV infectibility by replicative and non-replicative X4 strains was measured in both cell lines, and the amount of early reverse transcripts was quantified as a marker of viral entry. The capacity of both cell lines to support R5 to X4 switch was studied in vitro. Chemotaxis assays were performed. Expression of the two forms of CXCR4 mRNA was evaluated by specific RT-PCR. R5/X4 genotype was defined in HIV-infected persons by determining the False-Positive Rate (FPR) score calculated by the Geno2Pheno algorithm using the sequence of the V3 region of the envelope.

Results: We showed that CXCR4-B, but not CXCR4-A, mediates an efficient HIV-1 X4 entry and productive infection. Yet, the chemotactic activity of CXCL12 on both isoforms was similar. In vitro infection with an R5 strain increased CXCR4-B : CXCR4-A mRNA ratio in peripheral blood mononuclear cells (PBMC), and this ratio correlated with HIV RNA plasma level in R5-infected individuals. In addition, the presence of the CXCR4-B isoform favored R5 to X4 switch more efficiently than CXCR4-A in vitro. Moreover, the capability of circulating HIV-1 strains to use CXCR4, determined after the FPR, was linked to the predominance of CXCR4-B over CXCR4-A expression in PBMC. Finally, we achieved a specific siRNA-mediated knockdown of CXCR4-B.

Conclusions: CXCR4 isoforms present with similar chemokine receptor but different HIV coreceptor capabilities. Our data support the hypothesis that HIV-R5 infection favors CXCR4-B expression over that of CXCR4-A, a phenomenon that could facilitate R5 to X4 switch. We also established a proof of concept for a possible gene therapeutic approach aimed at specifically blocking the HIV coreceptor activity of CXCR4-B.

196 Defining Interactions of HIV With Rectal Epithelial Barriers and Rectal Mucus

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Background: A major mode of HIV transmission is through receptive anal intercourse with an infected individual. How HIV interacts with the rectal mucosal barriers composed of columnar epithelium covered with a protective layer of mucus has yet to be defined. Therapies that affect the rectal mucosal barrier may play an important role in HIV prevention strategies. We sought to investigate how HIV interacts with the rectal epithelium and the role rectal mucus plays in these interactions using a human rectal biopsy model, in vivo challenges in Rhesus macaques, and studies of rectal mucus.

Methodology: We enrolled 5 HIV seronegative adults undergoing routine screening colonoscopy. 5 rectal biopsies were obtained per patient and transferred to our lab. Tissues were inoculated with a photoactivatable GFP Vpr HIV-1 for 1, 2 and 4 hours. Samples were also treated with a mucolytic enzyme, neuraminidase. In vivo challenges used the same virus. Animals were necropsied at 4 hours post-rectal exposure. The tissue was snap frozen in OCT, sectioned, and epifluorescent deconvolution images were taken with a Delta Vision RT system and analyzed with SoftWorx software.

Results: Rectal biopsies incubated at 1 and 2 hours with an intact mucus layer were associated with the highest number of virions, most of which were seen trapped in the mucus. Accordingly, explants treated with neuraminidase (which decreased the amount of mucus at the surface) did not show the associated trapping of HIV. HIV penetration of the rectal mucosal barrier was observed as early as after 1 hour of incubation. Penetration was more commonly seen in areas where epithelial integrity was apparently compromised. Similar results were seen after in vivo challenge validating the short-term explant studies.

Conclusions: These findings suggest that the mucosal barrier of the rectal compartment can influence the ability of HIV to penetrate this barrier to reach underlying target cells. The protective layer of mucus clearly plays an important role in barrier function. The disruption of the barrier allows increased interaction with underlying target cells. Inflammatory conditions that increase transmission are likely influencing the mucus barrier. A better understanding to the interaction of HIV with the rectal mucosal barrier will facilitate future prevention strategies to decrease HIV acquisition.

Session P-A7 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Factor Potpourri

197LB Platelet Factor 4 Oligomeric State Correlates With Antiviral Activity

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Background: The platelet-derived chemokine platelet factor 4 (PF4) promotes blood coagulation and serves as a chemoattractant for immune cells. Recently PF4 has been shown to inhibit HIV-1 infection in vitro at concentrations less than 0.5μM. However, despite plasma and local tissue concentrations of PF4 ranging from 0.25nM to 10μM, HIV is able to successfully replicate and escape the inhibitory effects of PF4 in vivo. The mechanism of this discordance remains unclear. Here, we demonstrate that the inhibitory effects of PF4 are limited to a narrow concentration range, corresponding to the predominance of a monomeric state. At concentrations of greater than 1μM, PF4 multimerizes and viral infection in vitro is enhanced.

Methodology: Wildtype and mutant PF4s with distinct oligomeric properties were tested for their ability to inhibit viral infection in vitro. We examined the ability of HIV-1 pseudotyped viruses expressing the envelope glycoprotein from CCR5- and CXCR4-using HIV-1, MLV, influenza (H5N1), and VSV-G to infect cell lines and primary human CD4+ T cells in the presence of increasing amounts of either wildtype or mutant PF4. Infection data was compared using t-tests and Fisher's exact tests.

Results: All HIV-1 Envs (n = 24) were inhibited (mean = 65%, SD = 30) by PF4 (<1μM) independent of coreceptor tropism. VSV-G and MLV were also inhibited, while influenza H5N1 pseudoviruses were resistant to PF4. Surprisingly, the inhibitory effects of PF4 waned at concentrations greater than 1μM, above which viral entry was enhanced. Moreover, at concentrations above 1μM of the PF4 mutant K50E, which disrupts the formation of tetramers, we observed approximately 70% inhibition of viral infection. This was in contrast to the 2- to 5-fold enhancement observed with the wildtype PF4 at the same concentration. Chemical crosslinking was used to confirm differences in the oligomeric state of the wildtype and mutant PF4s at the different concentrations tested.

Conclusions: While PF4 inhibits diverse HIV-1 strains in its monomeric state, we demonstrate that it enhances infection when it exists as a tetramer. Since PF4 exists in a dynamic equilibrium, with tetramers predominating at physiologic levels, we conclude that the in vitro inhibitory effects of PF4 are less likely to predominate at physiologic PF4 concentrations. A more detailed understanding of how PF4 modulates viral infection may reveal new insights into virus-chemokine interactions that could inform novel therapeutic interventions.

198 CRM-1: A Critical Regulator of HIV Replication in a Quest Towards a Small Animal Model for HIV

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Background: Combination anti-retroviral therapy has markedly improved the prognosis of individuals living with HIV, yet treatment is not curative, and is often limited by major side effects, emerging viral resistance, drug interactions, and high costs. Furthermore, pathogenesis studies, vaccine development and drug testing are severely hampered by lack of small animal models for HIV infection. In the mouse, there are several blocks to HIV replication. Although some of the obstacles were identified, the underlining molecular mechanisms of this barrier remain poorly understood and have not fully characterized.The aim of this work was to identify factors that augment HIV replication in murine cells and to elucidate their mechanism of action.

Methodology: Using an experimental system that allow quantification of infectious virus production in murine cell, we assessed the effect of expression of panel of human proteins upon HIV production.

Results: The expression of human CRM-1 SRp-40 and SRp55 increased HIV pseudotyped particles in murine cells and the co-expression of hCRM-1 and SRp40 had a more than additive effect. Human CRM-1 increased unspliced/spliced HIV RNA ratio, mildly augmented the levels of intracellular Gag protein while the infectious viral production was disproportionally increased. Using human and murine CRM-1 chimeras and hCRM-1 mutants we mapped the functional domain of hCRM-1 to three amino residues. This functional region is different from a domain that was previously identified as the binding grove of hCRM-1.

Conclusions: CRM-1 has a key role in HIV production, and the murine protein has a loss of function. Identifying a new functional domain in this protein suggests the involvement of other factors interacting with CRM-1 that might have an effect upon HIV production. Elucidating these interactions can assist in a) further understanding of mechanisms of murine resistance to HIV infection. b) Identification of new host-related therapeutic targets for HIV. c) Establishment of the first small animal model of HIV infection, allowing for facilitated study and drug testing of this common devastating disease.

199 Analyses of the Sequence-Function Relationships Among HIV-1 Vpr, SIVagmVpr, and SIVmacVpx

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Background: Lentiviral accessory proteins are known for their ability to counteract host immune responses. Despite the sequence similarity shared by Vpr and Vpx, and the fact that both proteins hijack the cellular CRL4 E3 ligase via DCAF1 interaction, they have very different functions. Vpx causes degradation of cellular SAMHD1, making viral replication in myeloid cells permissive. Vpr is the least well-understood accessory protein. Vpr causes G2-to-M arrest in infected cells but the mechanism is not clear. On the other hand, Vpx does not arrest cells and SIVagmVpr causes G2 arrest in AGM cells but not in human cells. In order to understand the domains required for G2 arrest function and SAMHD1 degradation, we generated a variety of chimeras based on the published NMR structure for HIV-1 Vpr. HIV-1 Vpr is composed by a bundle of three alpha helices, flanked by amino and carboxy-terminal unstructured regions, connected by short flexible loops.

Methodology: To map the functionally relevant domains in HIV-1 Vpr, SIVmacVpx and SIVagmVpr that confer the differential abilities to interact with host immune responses, we generated 7 chimeras where we exchanged domains between HIV-1 Vpr and SIVagmVpr and 4 additional chimeras between HIV-1 Vpr and SIVmacVpx. We then tested the abilities of these chimeras to induce G2 arrest in human cells and to cause degradation of hSAMHD1 and agmSAMHD1

Results: We found that the N-terminus unstructured region of SIVmacVpx is not sufficient to target cellular SAMHD1 for degradation. Surprisingly, the exchange of the unstructured C-terminus region of SIVagmVpr to the HIV-1 Vpr confers to SIVagmVpr the specie-specificity domain required to target the human cellular protein, allowing the SIVagmVpr to induce G2 arrest in human cells.

Conclusions: Vpr and Vpx lentiviral proteins are examples of modular viral proteins where functions can be associated with specific domains. Genetic exchange of these domains is a powerful method to analyze the contribution of such domains to protein function and allows for analysis of evolutionary pressures and their impact on sequence variation.

200 Elevated Expression of Anti-HIV-1 Restriction Factors in Effector Memory CD4+ T Cells In Vivo

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Background: Recent observations suggest that there may be less viral outgrowth from effector memory than central memory CD4+ T cells from ART-suppressed individuals, despite similar levels of HIV-1 DNA in these cellular subsets. This may be driven by cell-intrinsic factors suppressing viral production, and/or the disproportionate presence of replication-incompetent HIV-1 variants in effector memory cells. In this study, we compare restriction factor gene expression patterns between effector memory and central memory CD4+ T cells from individuals of different HIV-1 disease states, to address the hypothesis that host restriction mechanisms suppress viral outgrowth in effector memory CD4+ T cells.

Methodology: Flow-based sorting was used to isolate central and effector memory populations in 20 individuals enrolled in the SCOPE cohort (5 ART suppressed, 5 elite controllers, 5 non-controllers, and 5 uninfected individuals). We implemented a custom real-time PCR array to measure the mRNA expression of 35 established anti-HIV-1 restriction factors in T cell subsets. To represent overall cellular anti-HIV-1 restriction capacity, we defined a CuRe (Cumulative Restriction) score as the cumulative fold-difference in restriction factor expression with respect to a control individual. Unpaired t tests were used to compare gene expression levels.

Results: CuRe scores were significantly higher in effector memory as compared to central memory CD4+ T cells in HIV-1-uninfected individuals ($p=0.008$), and in HIV-1-infected individuals ($p=0.009$). 15 out of 35 anti-HIV-1 restriction genes were significantly elevated in effector memory CD4+ T cells from HIV-1-infected individuals: APOBEC3C, APOBEC3D, APOBEC3G, APOBEC3H, BRD4, CRT9, IFITM2, p21, RTF1, schlafen 11, TRIM11, TRIM14, TRIM19, TRIM21, and TRIM26. TRIM32 was the only restriction factor that was significantly elevated in central memory CD4+ T cells. Within the ART-suppressed group, CuRe scores were significantly higher in effector memory CD4+ T cells ($p=0.034$). In particular, five restriction factors were elevated: APOBEC3G ($p=0.04$), APOBEC3H ($p<0.0001$), TRIM11 ($p<0.015$), TRIM19 ($p=0.0002$), and TRIM26 ($p<0.038$).

Conclusions: Expression data from our exploratory analyses of sorted T cell subsets indicate that enhanced host restriction factor expression may contribute to the reduced viral outgrowth observed in effector memory CD4+ T cells. Restriction factors that are elevated in ART-suppressed individuals include particular TRIM family members that attack HIV-1 at the post-integration phase, and APOBEC3 deaminases that hypermutate HIV-1 genomes. These observations warrant validation using larger sample sizes and sequence analysis of proviral DNA from isolated T cell subsets.

201LB TRIM5alpha Determinants for the Activation of Innate Immunity

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Background: Specific recognition of incoming viral capsids by the anti-retroviral factor TRIM5α disrupts progression of the virus life cycle and also triggers the induction of an antiviral state involving the activation of transcription factors NF-κB and AP-1. Additionally, TRIM5α promotes the formation of K63-linked ubiquitin chains which are thought to be important for innate immunity activation. These functions can also be revealed by over-expressing TRIM5α in the absence of virus, providing a convenient experimental model. A RING zinc-binding motif with E3 ubiquitin ligase activity is found at the N-terminus of TRIM5α and is involved in both the direct inhibition of incoming retroviruses and in innate immune activation. Other TRIM5α motifs were found to be related to the sumoylation pathway, specifically a putatively sumoylated lysine (lysine 10) just upstream of the RING domain, and putative SUMO interaction motifs (SIMs) in the C-terminal PRYSPRY domain which also determines interaction with capsid. Here, we analyzed the role of lysine 10 and the SIMs in the activation of innate immunity by TRIM5α.

Methodology: We searched for novel SIMs in Rhesus macaqueTRIM5α by computational analysis. Lysine 10, the RING domain and the various SIMs of the macaque TRIM5α PRYSPRY domain were mutated and the impact on HIV-1 restriction and on markers of innate immunity activation was measured using specific antibodies for K63-linked ubiquitin and reporter plasmids for NF-κB and AP-1 activation. Co-localization of TRIM5α and nuclear SUMO-1 was observed by IF microscopy.

Results: As expected, mutating the RING domain completely abrogated activation of NF-κB, AP-1 or the generation of K63-linked ubiquitin. Mutating Lysine 10 significantly decreased the activation of NF-κB and AP-1, and reduced the generation of K63-linked ubiquitin. The K10R mutation also caused an increase in TRIM5α self-ubiquitination, unlike mutations in the RING domain which also abrogate this activity. We identified a novel putative SIM motif in PRYSPRY, which we named SIM4. Mutating SIM4 strongly decreased activation of NF-κB while having no effect on the capacity of TRIM5α to trigger the formation of K63-linked ubiquitin chains. Mutations in both lysine 10 and SIM4 decreased the transient nuclear association of TRIM5α with SUMO-1.

Conclusions: Motifs in TRIM5α that are linked to the sumoylation pathway are important for the efficient activation of innate immunity. Lysine 10 modulates the ubiquitin ligase activity of the nearby RING domain to promote K63-linked ubiquitination, while SIM4 has no effect on K63-linked ubiquitin but is nonetheless important for the activation of NF-κB. Thus, we have identified motifs of TRIM5α that differentially modulate activation of innate immunity.

202 HIV-1 Vpu Antagonizes Macaque and Chimpanzee BST-2 Through Cytoplasmic Domain Interactions

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Background: The HIV-1 Vpu protein enhances the release of viral particles from infected cells by interfering with host factor BST-2/tetherin, which tethers nascent virions to the cell surface and inhibits virus release. Previous work demonstrated that HIV-1 NL4-3 Vpu can target human BST-2 (huBST-2) but not monkey BST-2 (moBST-2), suggesting a species-specific activity. However, we found that Vpu of a clinical HIV-1 isolate (DH12) counteracted huBST-2 as well as moBST-2. We also found that an NL4-3 Vpu mutant carrying transmembrane (TM) domain of DH12 Vpu (Vpu tmDH12) could antagonize moBST-2. Interestingly, SIVcpz-encoded Vpu neither antagonizes chimpanzee BST-2 (chBST-2) nor huBST-2. We hypothesized Vpu's ability to antagonize BST2 is directly linked to its ability to bind BST-2.

Methodology: We assessed the physical interaction of Vpu with BST-2 using a live cell protein-protein interaction assay based on bimolecular fluorescence complementation (BiFC). We tranfected 293T cells with BiFC-tagged moBST-2 and BiFC-tagged NL4-3 Vpu or Vpu tmDH12 and quantified the BiFC signal using flow cytometry as a measure of how efficient two molecules are interacting. At the same time we assessed functional antagonism of BST-2 by quantifying released virus in a TZMbl-based infectivity assay or by pulse/chase analysis.

Results: NL4-3 Vpu interacted with moBST-2 almost as efficiently as Vpu tmDH12 suggesting that physical interaction of Vpu with BST-2 is not sufficient for functional antagonism. Our results also suggest that Vpu interaction with moBST-2 might involve domains other than, or in addition to, the TM domain. In fact, we found that HIV-1 Vpu interacts with moBST-2 through a DDIWK motif in the cytoplasmic domains of moBST-2 while it interacts with huBST-2 via its TM domain. We found that Vpu tmDH12 antagonized moBST-2 but not moBST-2 mutant lacking DDIWK motif presumably because of a lack of cytoplasmic domain interaction. Our analysis of SIVcpz Vpu revealed that it neither interacted with chBST-2 nor huBST-2 which may explain why it fails to antagonize them. Interestingly, transfer of the NL4-3 Vpu cytoplasmic domain into SIVcpz Vpu was sufficient to allow interaction with chBST-2 and to allow SIVcpz Vpu to functionally antagonize chBST-2.

Conclusions: Taken together, our data reveal that domains important for physical interaction of Vpu and BST-2 are not limited to the TM domains. Indeed, interaction of Vpu with moBST-2 or chBST-2 occurs primarily via their cytoplasmic domains. This interaction is necessary but not sufficient for functional antagonism, which also depends on determinants encoded by the Vpu TM domain.

203 Investigating the Requirement of a NOD-Like Receptor for Early HIV Replication

Manja Burggraf[1], Prashant Jain[2], Crystal Shih[2], Nicole Esly[1], John Marlett[3], John A. Young[3], Sumit K. Chanda[2], **Renate Koenig**[1]

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Background: Human Immunodeficiency viruses rely on host-encoded proteins to facilitate their replication. A previous genome-wide siRNA screening approach (Koenig et al., 2008) resulted in the identification of NLRX1 as a host cellular protein required for early stages of HIV-1 replication. NLRX1 is a member of the Nod-like Receptor family, which collectively play critical roles in innate immune responses. Thus, our data provide a compelling link between an innate immune signaling receptor, NLRX1, and HIV-1 replication.

Methodology: HIV-1 luciferase reporter viruses pseudotyped by VSV-G and HIV-1 replication competent WT viruses were used to investigate the effect of silencing of NLRX1 on replication efficiency in various cell lines and primary cells. In addition, we assessed the infectivity levels of pseudotyped particles with amphotropic envelope using a pH-independant entry route and mapped the stage of viral inhibiton by real-time quantitative PCR. Effects on IRF3-dependant target gene expression were assessed by quantitative PCR and IFN ELISA.

Results: We first validated NLRX1 as a factor required for early-stage HIV infection in various cell lines, including 293T, HeLa and more physiological relevant cells, THP1, Jurkat cells and primary macrophages. NLRX1-inhibition resulted in a failure to initiate reverse transcription and was independent of the viral entry route. NLRX1 was recently reported to act as a negative regulator of mitochondrial antiviral immunity, through binding and inhibition of MAVS, an essential mediator of the RIG-I and IRF3 antiviral response. Based on the hypothesis that the inhibition of NLRX1 may render the innate surveillance machinery competent to respond to HIV infection, we sought to determine the effects of NRLX1 depletion upon IRF3 target gene transcription. We observed that ISG54, IFN-β and IL-6 was robustly induced upon infection with HIV in NLRX1-depleted cells, but importantly, NLRX1 silencing did not induce these genes in the absence of HIV.

Conclusions: These data suggest that restriction of HIV is not due to a generalized and persistent hyper-activation of an innate immune state in NLRX1-depleted cells. In conclusion, we demonstrate the requirement of NLRX1 for early HIV-1 replication. We are currently investigating the molecular basis of NLRX1 dependency in early stage HIV replication.

204 ITIH4: A Cellular Factor Targeted by HIV-1 Vpr

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Background: The immune system has a multitude of innate immune factors that work to counteract many different viruses. For HIV-1, such factors include APOBEC-3G, Tetherin (BST-2), SAMHD1, and, in the case of non-human primates, Trim5α. However, lentiviruses have evolved accessory proteins to counteract most, if not all of these factors. Such accessory proteins include HIV-1 Vif which degrades APOBEC-3G, HIV-1 Vpu and SIV Nef which reduce cell surface expression of Tetherin, and SIV Vpx which degrades SAMHD1. Interestingly, HIV-1 Vpr, an orthologue of SIV Vpx, does not degrade SAMHD1, and no cellular target for VPR has been identified as yet.

Methodology: Recently, a cell line that is non-permissive to ΔVpr HIV-1 infection has been developed. By examining the proteomic content of viral cores from WT and ΔVpr viruses collected from this cell line, we deduced several potential candidates that could be the culprit to this restriction. One such candidate, the Inter-alpha-trypsin inhibitor heavy chain H4 (ITIH4) has been investigated in this study. We tested whether Vpr induces degradation of ITIH4. Western Blot analysis of ITIH4 expression was performed on cell lines/primary cells treated or not with IFNα. We also analyzed the effect of ITIH4 overexpression and downregulation on virion production (protein expression and virion release) and infectivity (indicator TZM-bl cells).

Results: Vpr overexpression resulted in downregulation of ITIH4. Interestingly, ITIH4 overexpression efficiently degraded Vpr, and reduced its incorporation into the virus. Upon siRNA knockdown of ITIH4, VPR expression and incorporation was increased. When viruses were produced in the presence of ITIH4, a clear inhibition of viral replication was observed at two different points of the viral life cycle. First, there was a block at the production step of HIV-1, with viral production being reduced 3-5 fold. Second, there was a block at the early steps of infection after entry, with a 4-20 fold decrease in infectivity. Western Blot analysis of several cell lines and primary cells demonstrated a lack of this factor within T cells, but showed its presence within THP-1 cells and monocyte-derived macrophages, with upregulation in the presence of IFN-alpha.

Conclusions: The presence of ITIH4 within the producer cell greatly reduces both the production and infectivity of progeny virions. Our data thus warrants further investigation into the exact mechanism by which ITIH4 inhibits HIV and how it interacts with Vpr.

Session P-B1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Transmission Networks

205 Ongoing HIV-1 Subtype B Transmission Networks in the Netherlands

Daniela Bezemer[1], Oliver Ratmann[2], Ard van Sighem[1], Bas E. Dutilh[3], Nuno Faria[4], Rob van den Hengel[1], Luuk Gras[1], Peter Reiss[1], Frank de Wolf[2], Christophe Fraser[2], ATHENA observational cohort

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Background: The HIV-1 epidemic amongst men having sex with men (MSM) in the Netherlands has been shown to be resurgent despite the widespread use of effective combination antiretroviral therapy (cART). This epidemic is dominated by HIV-1 subtype B. In this study, using phylogenetic analysis of HIV-1 subtype B polymerase sequences, we identify the transmission networks that constitute the epidemic.

Methodology: As of June 2011, the ATHENA database contained polymerase sequences from 5,852 subtype B infected patients in the Netherlands. For every sequence, the 10 most similar sequences were selected from the Los Alamos database and a phylogenetic tree was created of in total 8,320 unique sequences. Transmission networks were defined as clusters of sequences with a bootstrap value ≥90%, within the 5th percentile threshold of the whole-tree patristic distance distribution including at least 10 patients in the ATHENA cohort.

Results: Amongst the 5,852 patients, 4,288 (73%) were MSM registered in the Netherlands. We identified 106 different transmission networks which included 3,061 (52%) ATHENA sequences. 50% (2,128) of 4,288 HIV cases amongst MSM in the Netherlands and 380 of the 'Los Alamos' sequences were included in 91 MSM majority networks (≥50%). Strikingly, 64 (70%) of these 91 MSM transmission networks were already circulating before 1996, the year that cART became widely available. Of the total 3,507 sequences among MSM with diagnoses after 1996, 41% (1,436) were found in these 64 networks, and 89% (57) of these networks include patients with proof of infection after 1996. Only in three of the 64 networks no new cases were diagnosed after 2006. The people pertaining these three networks had a higher median age at the study end date; 51 years (IQR: 45-57) compared to 46 (IQR: 39-52) in the persisting networks. Further, 68 MSM were in 10 of non-MSM dominated networks, and 1,324 (31%) were in 550 smaller clusters. 768 (18%) sequences amongst MSM in the Netherlands could not be identified as belonging to a network (singletons). Of MSM in a network, 4% have probably been infected abroad (according to their own report), versus 10% in the smaller clusters and 19% of singletons. If we regard every cluster, network, or singleton as a new HIV introduction, this totals to 1,419 HIV-1 subtype B introductions amongst MSM. Roughly indicating that 33% of infections amongst MSM were imported, and that 6% of introductions amongst MSM in the Netherlands gave rise to a local network.

Conclusions: The majority of the identified MSM-dominated transmission networks were already present before the introduction of cART and are still on-going. Our analyses suggest that the resurgent epidemic is sustained by well-established networks, not brought to an end by the widespread use of cART.

206 Using HIV Networks To Inform Real Time Prevention Interventions

Susan J. Little[1], Sergei L. K. Pond[1], Christy M. Anderson[1], Jason A. Young[1], Joel O. Wertheim[1], Sanjay R. Mehta[1], Susanne May[2], Davey M. Smith[1]

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Background: Understanding the dynamics of HIV transmission may provide opportunities for public health interventions.

Methodology: We inferred a partial local transmission network among 478 recently HIV infected persons and 170 of their HIV infected sexual and social contacts in San Diego, California (n=648) using HIV pol sequences collected from 1996 to 2011. We linked two individuals (nodes) in the network whenever their pol sequences were less than 1.5% distant (Tamura Nei 1993 distance). Whenever possible, we assigned a direction to the network edge, based on the duration of infection for each partner. Using only baseline data after 2004, when network sampling was sufficiently dense (n=157), we defined a transmission network score (TNS) to estimate the risk of HIV transmission from a newly diagnosed individual to a new partner and potential impact of prevention interventions. TNS is a function of the total degree of the node at baseline (set to 0 if no connections are inferred), conditioned on the network inferred at the time of each subject's baseline sequence.

Results: HIV-1 pol sequences from 339 of 648 individuals (52.3%) were linked to sequences from at least one other participant (i.e., clustered). The top quintile of the TNS distribution was designated as 'high' (TNS > 0.75, n=33) and all others as 'low' (n=124). Future transmission risk was characterized by identification of a new outbound connection within 1 year of enrollment. High TNS was significantly correlated with baseline risk behaviors (number of unique sexual partners and insertive unprotected anal intercourse [p=0.014 and 0.0455, respectively]). Baseline viral load (VL) and high TNS were not significantly correlated in univariate analysis (p = 0.27), but in a multivariable analysis, both VL and high TNS at baseline were independently correlated with predicted risk of HIV transmission within the first year after presentation (p=0.0164 and p=0.0018, respectively). Retrospective analysis of antiretroviral therapy (ART) use, and simulations of ART targeted to individuals with the highest TNS, suggested significantly reduced network level HIV transmission (p<0.05).

Conclusions: Sequence data from an HIV screening program focused on recently infected persons and their social and sexual contacts enabled the characterization of a highly connected transmission network. When TNS was incorporated into a multivariate model with VL, the prediction of transmission risk significantly improved, suggesting that VL and TNS are informed by independent transmission risk factors. The network-based TNS was significantly correlated with transmission risk behaviors and outcomes, and can be used identify and target effective prevention interventions, like ART, to those at a greater risk for transmitting HIV.

207 Transmission Networks of HIV-1 Subtype B, CRF01_AE and CRF51_01B Among MSM in Singapore

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Background: HIV-1 subtype B and CRF01_AE are the dominating subtypes among men who have sex with men (MSM) in Singapore. However, the evolutionary history, population dynamics and pattern of transmission networks of these genotypes remain unexplored. Here, we elucidated the phylodynamic profiles of HIV-1 subtype B, CRF01_AE and the recently characterized CRF51_01B strains circulating among the MSM population in Singapore.

Methodology: A total of 105 (49.5%) consenting treatment-naïve MSM were recruited between February 2008 and August 2009. HIV-1 RNA was extracted from plasma specimen, reverse-transcribed, followed by amplification of the protease gene (HXB2: 2239 - 2629), gp120 (HXB2: 6942 - 7577) and gp41 (HXB2: 7803 - 8276) of the env gene. The nucleotide sequences were codon aligned, followed by phylodynamic profiling using neighbour-joining reconstruction, maximum likelihood inference and Bayesian coalescence approach.

Results: Five monophyletic transmission networks (two each within subtype B and CRF01_AE and one within CRF51_01B lineages) of different sizes (involving 3 - 23 MSM subjects, supported by posterior probability measure of 1.0) were observed. Bayesian coalescent analysis estimated that the emergence of multiple sub-epidemic networks occurred between 1995 and 2005, driven largely by subtype B and followed by CRF01_AE. Exponential increase in effective population size for both subtype B and CRF01_AE occurred between 2002 to 2007 and 2005 to 2007, respectively. Genealogical estimates suggested that the novel CRF51_01B lineages were generated through series of recombination events involving CRF01_AE and multiple subtype B ancestors. The estimation of the divergence times for each node revealed that the median interval between transmission events within these networks were short, namely 0.9 years (0.1 - 4.7) in subtype B, 0.75 years (0.1 - 1.7) in CRF01_AE and 0.65 years (0.1 - 2.2) in CRF51_01B.

Conclusions: Our study provides the first insight into the phylodynamic profiles and evolutionary history of HIV-1 subtype B, CRF01_AE and CRF51_01B, suggesting the HIV-1 strains circulating among MSM in Singapore were introduced through multiple sub-epidemic networks. This study also unravels the importance of understanding transmission behaviours as well as evolutionary history of HIV-1 in assessing the risk of outbreak or epidemic expansion.

208 HIV-1 Phylodynamics and Phylogeography Among High-Risk and General Populations in Uganda

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Background: Uganda has historically had the highest HIV prevalence in East Africa. From the 1990s, this prevalence has declined sharply, but it has remained high within high-risk groups. Here, we reconstruct the history and spread of HIV subtypes A1 and D in Uganda, and explore the transmission dynamics of some high-risk populations.

Methodology: We analysed 162 HIV pol sequences from 3 Ugandan populations sampled in 2005-2010: female sex workers based in Kampala (n=42); Lake Victoria fisher-folk communities (n=46); and patients from a rural clinic in Masaka, south-west Uganda (n=74). We added GenBank sequences of subtype A1 (n=177) and D (n=235) from Uganda for which sampling city (mainly Kampala, Entebbe and Rakai) and date (1992-2005) were available. We used SCUEAL to identify recombinants. Clusters were defined by high statistical support (>90%) and low genetic distance (<4.5%). We applied Bayesian MCMC inference to these datasets using BEAST and conducted a phylogeographic analysis by using the discrete traits analysis implemented in BEAST.

Results: Of 162 pol sequences from high risk populations, 83 (51.2%) were subtype A1-like, 71 (43.8%) D-like and 8 (4.9%) were subtypes C and G. Subtype A1 was dominant (58%) in the cities (Kampala, Entebbe) but subtype D was more frequent (74%) in the rural areas (Rakai, Masaka). Sixty-seven recombinants were discarded. Most (84%) of the 71 observed clusters were pairs, and few (10.5%) included individuals from different populations. Half of the sequences from rural regions were included in clusters, while sequences from other populations or locations were more interspersed in the trees. The dates of the most recent common ancestors were 1945.4 (1923.5 - 1962.6) for pure subtype A1 and 1965.6 (1958.5 - 1972.3) for pure subtype D, consistent with results published for other HIV gene segments. The Bayesian Skyride showed a matching temporal trend in the population size for both

subtypes, with an exponential growth in the 1970s and 1980s and a decrease since the early 1990s. For both subtypes, the origin of the epidemic was located to rural southwest Uganda (Masaka, Rakai) with further radiations from Kampala to other locations as Entebbe and Lake Victoria.

Conclusions: The subtype A1 epidemic in the region appeared very old (originating in the 1940s), with subtype D entering in the 1960s. The phylogenies showed a star-like topology attributed to the great root-to-tip distances due to the old age of these clades. Sequences from rural areas were more likely to cluster, while sequences from fishermen and sex workers were interspersed in the trees. Finally, our results pointed to the south-western rural areas as the probable origin of the Ugandan epidemic, in contrast to other hypotheses that inferred the origin of HIV in large cities.

209 Sustained Spread of HIV-1 Drug Resistance in Treatment-Naïve Patients in the United Kingdom

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Background: Transmitted drug resistance (TDR) in the UK peaked at about 15% of those tested between diagnosis and initiation of ART in 2002 but has since declined to 8-9%. Originally, the proportion of specific TDR mutations mostly mirrored those observed in treated patients when ~80% of resistance tests undertaken on treated patients showed drug resistance mutations (DRMs). In recent years 60-70% of resistance tests from treated patients show no resistance mutations and there is a marked discordance between the mutation patterns observed in failing patients and those seen in new diagnoses. This suggests onward transmission of TDR from untreated and possibly undiagnosed patients.

Methodology: We extracted all subtype B HIV-1 *pol* gene sequences from treatment-naïve patients within the UK HIV drug resistance database sampled between 1997-2011 with any of DRMs: L90M - protease; K103N, T215Y and T215 revertants - reverse transcriptase (n=1140). These DRMs were chosen as the most common associated with PI, NNRTI and NRTI TDR in the UK database. Sequence alignments with DRMs removed were used to identify transmission clusters (n≥2) by maximum-likelihood phylogeny using a genetic distance cut-off of ≤1.5% and high bootstrap support. The time of origin of the large clusters containing ≥8 sequences (n=10) was estimated by Bayesian Markov chain Monte Carlo approach and a birth-death model was employed to estimate the basic reproductive numbers (R_0) of individual clusters (subepidemics).

Results: The most common TDR DRM seen in 1140 patients was T215rev which was present in 47% (n=540) of the sequences, followed by K103N (31%; n=359) and L90M (10%; n=109). The remaining sequences contained T215Y or combinations of L90M, K103N and T215rev. Fifty five percent (n=624) of the sequences formed highly supported transmission clusters (n=193) containing between 2 and 15 sequences with 115 clusters containing 3 or more sequences. The time of origin of the 10 large clusters containing 8 or more sequences was estimated to be between 2000 [1999-2002; 95% highest posterior density (HPD)] and 2006 [2005-2007; 95% HPD]. The oldest subepidemic was formed of 10 sequences containing the K103N mutation and was found to have persisted for nearly 9 years. All 10 clusters were shown to have R_0s ranging between 1.3 [0.4-2.5; 95% HPD] and 2.8[0.6-6.5; 95% HPD] meaning that on average each person in the clusters is responsible for infecting more than one person over the sampling period. This suggests the likelihood of sustained spread of the TDR lineages within treatment-naïve patients.

Conclusions: A high proportion of observed TDR is derived by onward transmission in treatment-naïve patients. This could be decreased by enhanced testing to reduce late diagnosis.

210 Transmission Clustering Among Newly Diagnosed HIV+ Patients in Chicago, 2008 To 2011

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Background: Despite wide availability of diagnostic testing and effective therapy, United States HIV incidence has remained stable. Assessing for transmission clusters via comparison of HIV *pol* sequences provides HIV epidemiologic data that can be used to inform prevention efforts. We describe the first such assessment for transmission clustering among HIV positive patients in Chicago.

Methodology: The Ruth M Rothstein CORE Center, as part of the Variant, Atypical, and Resistant HIV Surveillance project for the Center for Disease Control, obtained HIV genotypes on patients presenting within 90 days of diagnosis. We assessed for transmission clustering using HIV *pol* sequences collected between January 2008 and May 2011. Sequences were compared via progressive pairwise alignment. We used the Tamura-Nei neighbor joining method to determine genetic distance and construct an un-rooted phylogenetic tree. We defined a cluster as >2 sequences among which each sequence had at least one partner within a genetic distance of <0.015. We used multivariate regression to assess for correlates of membership in a transmission cluster. Kulldorff's spatial scan statistic was used to assess geographic clustering using Satscan software version 9.0.

Results: We included HIV *pol* sequences from 920 CORE Center patients. Of those, 77% were <25 years old (median age of 34.5 years); 75% were male; 67% were Black, 23% Hispanic, and 9% White. 8% had an RPR titer >1:16 at the time of HIV diagnosis. Risk factor data were available for 59%; 46% of those reported MSM behavior as their HIV risk factor. Phylogenetic analysis demonstrated that 124 patients (14%) grouped into 26 clusters, the largest having 21 members. In multivariate regression, age <25 (OR=2.67; 95% CI 1.74-4.09), Black race (OR=4.37; 95% CI 2.41-7.91), male gender (OR=1.83; 95% CI 1.83-6.92), and RPR >1:16 (OR=2.09; 95% CI 1.16-3.77) were associated with membership in a transmission cluster. When the analysis was stratified for MSM risk factor, only Black race (OR=6.58; 95% CI 3.17-13.7) remained associated with cluster membership for MSMs. For non-MSM patients, Black race (OR 3.71; 95% CI 1.16-11.8) and RPR >1:16 (OR 13; CI 2.96-57.6) remained associated with cluster membership. Geographic clustering by home address was not observed for clustered patients.

Conclusions: These results confirm surveillance data demonstrating high rates of HIV transmission among young Black males in Chicago. Applied prospectively, phylogenetic clustering analysis could guide targeted contact tracing activities, helping to break the cycle of transmission within active clusters. Exploration of the social networks of clustered patients may reveal high yield areas for venue based prevention and guide test and treat initiatives in Chicago.

211 Can Molecular HIV Surveillance Identify Groups To Prioritize for Prevention?

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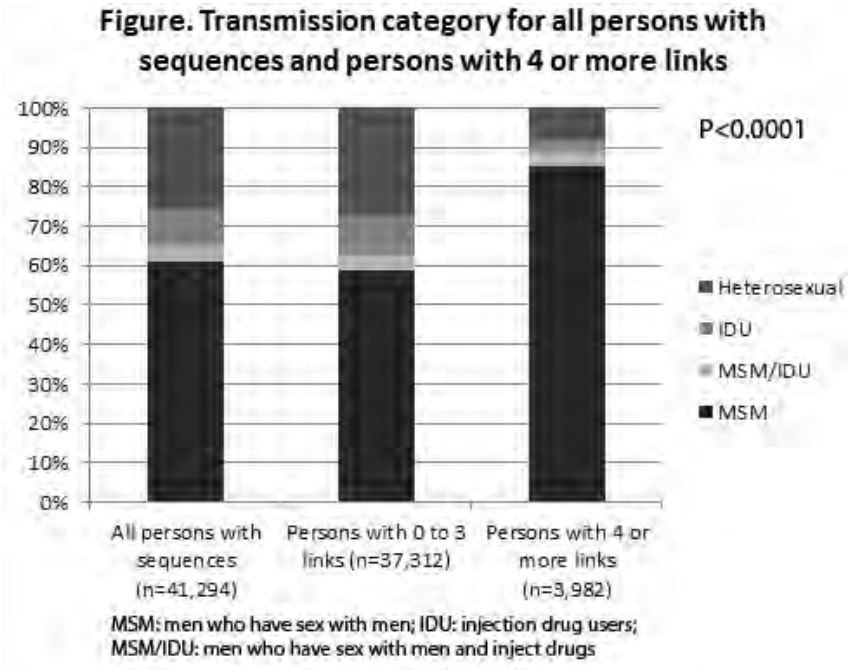
Background: Because mutation causes strains of HIV to diverge fairly quickly, two persons with highly similar HIV sequences are likely to have been involved in recent acquisition or transmission. Those persons whose HIV strains are similar to many other sequences are of particular interest for prevention, as they may be part of a dense region of a transmission network. The findings from this type of molecular analysis can be triangulated with other data to identify groups for intensive prevention efforts. Our goal was to describe persons with many potential transmission connections.

Methodology: We analyzed HIV-1 *pol* sequences (one/person aged ≥13 years) collected through the U.S. National HIV Surveillance System during 2001-2012. Sequences were aligned to a reference sequence (HXB2), and pairwise Tamura-Nei 93 genetic distance ≤1.5% was considered evidence of possible linkage. We constructed an HIV transmission network and analyzed demographic and transmission category data for persons who linked to ≥4 other sequences (i.e., those in the highest quartile of those with any links). Furthermore, we created a logistic regression model to determine whether these associations persisted after adjusting for sex, age, race/ethnicity, and transmission category.

Results: Of 41,294 sequences, 12,910 (31%) linked to ≥1 other sequence (range: 1-83), and 3,982 (10%) linked to ≥4 sequences. Males represented 78% of the sample and 93% of persons with ≥4 links. Persons aged 20-29 years represented 34% of the sample and 51% of persons with ≥4 links. White persons represented 26% of the sample and 34% of persons with ≥4 links. Although black persons represented almost half (47%) of the sample, they represented a smaller percentage of persons with ≥4 links (41%). Men who have sex with men (MSM) represented 61% of the sample and 86% of persons with ≥4 links (Figure). In multivariable analysis, age, race/ethnicity, and transmission category were independently associated with having ≥4 links (p<0.0001), although sex was not.



Conclusions: MSM and young persons are overrepresented among persons with many potential links, suggesting that they are disproportionately involved in networks associated with HIV transmission; this finding corroborates other analyses demonstrating high HIV incidence among these groups. Efforts to interrupt HIV transmission and reduce incidence must reach these groups. Implementation of intensive and other effective interventions should prioritize MSM and young persons.

212 Investigation of HIV Transmission Dynamics Reveals "Active" Clusters of Men Who Have Sex With Men

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Background: New HIV infections in the US continue to increase, driven in part by local transmission networks among at-risk populations. Phylogenetic characterization of clusters and examination of their dynamics can provide information on HIV transmission and identify actively growing clusters which may be targeted for intervention.

Methodology: To investigate transmission cluster dynamics, HIV *pol* sequences from 2004-2011 at a large outpatient clinic were analyzed. Phylogenetic trees were constructed in MEGA and clusters were identified in PhyloPart. We examined (1) Associations between risk behavior and cluster size using latent class analyses and ordinal logistic regression; (2) Homogeneity of risk factors within clusters using general estimating equations (GEE2); and (3) Active clusters, defined as those with increasing growth rates over time. Cluster dynamics were characterized using a Bayesian model of the number of observed diagnoses with a latent logistic growth transmission process. Ongoing transmission activity in clusters (i.e. active clusters) was assessed based on the probability of one or more new diagnoses in the year after the data collection period.

Results: At least one HIV-1 subtype B *pol* sequence was available for 1,166 patients diagnosed from 1980-2011. Thirty-one percent (358/1,166) of sequences formed 114 distinct clusters (cluster size range 2-15). Men who have sex with men (MSM) were more likely to be in clusters than not (52% vs. 35%, p<0.01) whereas injection drug users were less likely to be in clusters (11% vs. 25%, p<0.01). One latent class was comprised primarily of MSM diagnosed after 2003. Members of this class were more likely to be in larger clusters compared to the other 3 classes (odds ratio [OR] range 1.69-11.63, p<0.01) and were more heterogeneous in terms of risk factor for HIV infection. Compared to a cluster size of 2, the likelihood of a cluster being comprised only of MSM was reduced for cluster sizes of 3 (OR 0.5 [0.01-20.9 95% CI], p=0.7), 4-5 (OR 0.08 [0-1.4 95% CI], p=0.08) and >6 (OR 0.12 [0-3.33 95% CI], p=0.21). In the logistic growth modeling, cluster growth rates were estimated for 24/114 clusters with >3 individuals. Seventeen percent (4/24) of clusters containing 24% (38/161) of individuals were identified as active with >15% probability of harboring undiagnosed infections. Of the 38 members of the active clusters, 100% were male, 90% MSM and 45% were diagnosed with primary HIV infection.

Conclusions: In our community, the HIV epidemic is driven by local transmission networks among MSM which should be further explored. Phylogenetic examination of cluster dynamics can reveal active clusters that have the potential of harboring undiagnosed infections and represent targets for intervention.

213 HIV Transmission in the United States: The Roles of Risk Group, Race/Ethnicity, and Geography

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Background: The study of HIV transmission networks provides insight into the spread of HIV, and thus into opportunities for intervention. By identifying genetically similar HIV variants in large datasets, we can construct such transmission networks. Two persons infected with highly similar HIV variants are likely to have a direct or indirect epidemiologic connection and represent potential transmission partners. Transmission dynamics between people who are similar or different with respect to race/ethnicity, risk characteristics, and geography are unclear. To identify demographic and risk characteristics of potential transmission partners, we constructed a U.S. HIV transmission network.

Methodology: We analyzed 41,294 HIV-1 *pol* sequences collected through the U.S. National HIV Surveillance System (NHSS) during 2001-2012. We aligned sequences (one/person aged ≥13 years) to a reference sequence (HXB2) and performed pairwise comparisons among all sequences. Possible linkages were defined by Tamura-Nei 93 genetic distance ≤1.5%. We constructed a transmission network and analyzed data on risk group (MSM, IDU, MSM/IDU, heterosexual), race/ethnicity, and state of residency at diagnosis for pairs of potential transmission partners.

Results: The network contained 12,910 nodes (31% of all sequences) and 29,493 connections. MSM comprised 61% of persons with sequences but 76% of the network. In the vast majority of transmission pairs containing at least one MSM, the second person was also MSM (MSM: 82%, MSM/IDU: 7%) (Table). Heterosexual women were more commonly connected to MSM (44%) than to heterosexual males (18%) or IDUs (13%). MSM/IDU were far more commonly connected to MSM (88%) than to IDUs (2%). Transmission pairs containing blacks/African Americans were more racially homogeneous (63%) than pairs containing whites (47%) or Hispanics (27%). Of pairs, 82% consisted of two persons living in the same state at diagnosis; this percentage was higher for pairs with female IDUs (90%) and heterosexual women (91%).

Table. Risk group and race/ethnicity of potential transmission pairs.

	Partner risk group										
	MSM		MSM/IDU		IDU		Male heterosexual		Female heterosexual		Total
For pairs containing at least one person who is:	n	%	n	%	n	%	n	%	n	%	n
MSM	22645	82%	1935	7%	853	3%	829	3%	1208	4%	27478
MSM/IDU	1935	88%	101	5%	47	2%	42	2%	83	4%	2210
Male IDU	654	68%	28	3%	88	9%	48	5%	109	11%	957
Female IDU	199	33%	19	3%	121	20%	66	11%	203	33%	608
Male heterosexual	829	54%	42	3%	114	7%	54	4%	486	32%	1524
Female heterosexual	1208	44%	83	3%	342	13%	486	18%	597	22%	2718

	Partner race/ethnicity										
	White		Black		Hispanic/Latino		Asian/NHOPI		Other*		Total
For pairs containing at least one person who is:	n	%	n	%	n	%	n	%	n	%	n
Asian/NHOPI	640	54%	95	8%	359	30%	65	5%	34	3%	1193
Black	2790	19%	9121	63%	1861	13%	95	1%	525	4%	14392
Hispanic/Latino	3951	45%	1861	21%	2382	27%	359	4%	220	3%	8773
White	6892	47%	2790	19%	3951	27%	640	4%	536	4%	14809
Other*	536	40%	525	39%	220	16%	34	3%	22	2%	1337

MSM: men who have sex with men; IDU: injection drug user; NHOPI: Native Hawaiian or Other Pacific Islander
*Other race includes American Indian/Alaska Native, other race, multiple races, or unknown race

Conclusions: This analysis is the first use of NHSS data to infer an HIV transmission network. Geographic and racial/ethnic mixing in HIV transmission were present, although the extent varied by population. The majority of potential transmission partners connected to MSM were also MSM, but other risk groups were also commonly connected to MSM. Interventions that reduce transmissions by MSM are likely to reduce HIV acquisition among other risk groups as well.

214 Risk Factor Predicts Geographic Spread Within New York City HIV-1 Transmission Network and Beyond

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Background: HIV transmission networks inferred from sequence data can be used to identify risk groups for intervention. Transmission clusters spread over larger geographic areas may require different methods of intervention than localized clusters. We investigated how individual transmission risk factor predicted the geographic spread of HIV within and outside NYC.

Methodology: We analyzed 39,135 individuals' earliest HIV pol sequence reported to NYC through routine laboratory surveillance during 2005-2012. . All sequences were aligned to the reference genotype HXB2. Potential transmission partners were defined as two individuals whose sequences had a pairwise genetic distance ≤2%; groups of linked partners formed transmission clusters. We applied multivariate logistic and ordinal logistic regression to identify characteristics associated with clustering and geographic spread. NYC geographical information was derived from zip code of residence at diagnosis as grouped into standard multi-zip NYC neighborhoods. We also included 86,216 non-US sequences from the Los Alamos National Laboratory (LANL) HIV sequence database to investigate global transmission links.

Results: The network contained 8801 nodes (22.5% of all individuals) and 19,637 edges (connections between potential transmission partners). Propensity for clustering within the NYC network was not uniform: men who have sex with men (MSM) were more likely to cluster than heterosexuals (OR = 2.4; $p < 0.001$), and injecting drug users (IDU) were less likely to cluster than heterosexuals (OR = 0.52; $p < 0.001$). Both MSM and IDU had transmission partners spread over a greater median distance than heterosexuals (10.3 and 9.0 vs. 7.8 km; $p < 0.01$). Of all individuals clustered within the NYC network, 28.3% have a potential partner diagnosed within, but residing outside of, NYC. Among individuals connected in the NYC network, MSM were more likely to cluster with individuals residing outside of NYC than heterosexuals (36.6% vs. 8.2%; $p < 0.001$), but not with individuals from other countries in the LANL reference dataset. IDU were unexpectedly more likely than heterosexuals to have an international connection in LANL (18.5% vs. 6.2%; $p < 0.001$).

Conclusions: Risk factor plays an important role in predicting the geographic spread of HIV transmission clusters. MSM have the most geographically expansive clusters. However, IDU clusters are not as geographically constrained (locally or internationally) compared with heterosexual clusters. Interventions targeting specific risk groups should take the geographic spread of these clusters into account.

215 Large MSM Group and Local Heterosexual Transmission Are Major Concerns in the HIV Epidemic in Japan

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Background: To clarify HIV transmission dynamics from a large collection of viral sequences, a useful tool is phylodynamic analysis. We used this tool to analyze HIV pol sequence data from our nationwide surveillance network to reveal the dynamics of HIV transmission in Japan.

Methodology: Nucleotide sequences of the protease-reverse transcriptase (RT) gene were obtained from 4393 newly diagnosed HIV patients in 2003-2011. These sequences were then aligned with subtype reference sequences retrieved from the HIV database, and subtypes belonging to each sequence segment were determined using similarity plot analysis against subtype references. Domestic transmission clusters (infection networks) were identified by combined monophyly evaluation using three different phylogenetic methods: neighbor-joining method with interior branch test, maximum likelihood method, and Bayesian Markov chain Monte Carlo (MCMC) method. Chronological phylogeny, median time of the most recent common ancestor (tMRCA), and basic reproductive number (R0) were also inferred by Bayesian MCMC coalescent analysis using BEAST1.7.4.

Results: The predominant subtypes in Japan (with number of patients and prevalence) were subtype B (n=3899: 88.8%) and CRF01_AE (n=344: 7.8%). Other minor subtypes were found: C (n=46), CRF02_AG (n=36), G (n=15), F (n=9), CRF06_cpx (n=3), CRF07_BC (n=2), and CRF12_BF (n=2), and CRF33_01B (n=2). Subtypes D, CRF08_BC and CRF28 or 29_BF were detected in one patient. Another 32 patients had unknown forms of intra-subtype recombinants. Phylodynamic analysis yielded four major findings. 1) Although tMRCAs of a few infection networks of subtype B dated to the 1980s, many had spread between men having sex with men (MSM) from the second half of the 1990s. 2) CRF01_AE was also transmitted into Japan through heterosexual and intravenous drug user routes in the 1990s. 3) In the 1990s, minor subtypes and recombinant viruses also colonized in some groups that mingled with foreigners. 4) In the 2000s, CRF01_AE was also transmitted to MSM communities and might have generated some domestically circulated recombinants between subtypes 01_AE and B. R0 of subtypes B, C, F and CRF01_AE in Japan (3.3, 3.2, 2.1, and 3.7, respectively) did not differ significantly, but the R0s of subtypes G and CRF02_AG (7.7 and 6.9) were significantly higher than those of other subtypes.

Conclusions: These results suggest that a large MCM community with intra-subtype recombinants and a local population network with high infectivity females are major concerns in Japan.

Session P-B2 Poster Session
Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**
Application of NGS To Viral Profiling

216 Full-Length HIV-1 Haplotype Reconstruction From Heterogeneous Virus Populations

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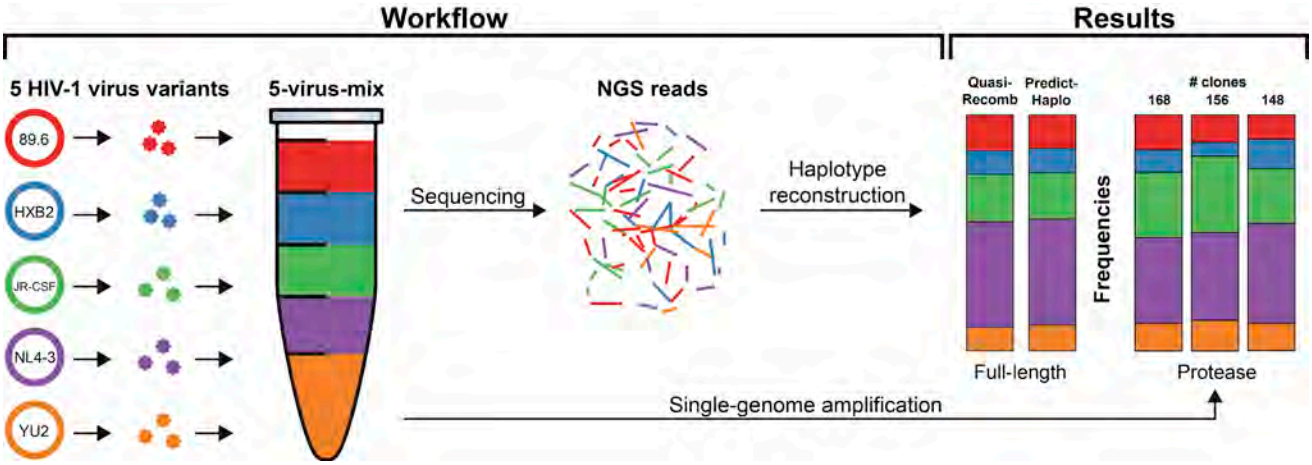
Background: Next-generation sequencing (NGS) can provide in-depth resolution of heterogeneous intra-patient viral populations, composed of one or more genetically distinct haplotypes. However, such analyses are complicated by small read length, up to two orders of magnitude shorter than the genome size, and by the error rate of amplification and sequencing. Identification of co-occurring resistance mutations, composition, and ongoing evolution of intra-patient viral populations on the basis of full-length genomes are of great interest, but remain unsolved. New approaches and tools are needed to reconstruct individual full-length haplotypes and to estimate their frequency in the population.

Methodology: We combined five molecular HIV-1 strains to create a heterogeneous mixture of viral haplotypes. RNA was isolated and whole genomes amplified with three different protocols for the NGS technologies 454/Roche, Illumina, and PacBio. For each data set, we performed full-length haplotype reconstruction over the complete coding region of 8,627 bp, using the software packages QuasiRecomb and PredictHaplo. To determine the ground truth sequences and frequencies, we sequenced the HIV-1 strains individually and performed single-genome amplification (SGA) on the protease gene.

Results: Applying the NGS platforms 454/Roche, Illumina, and PacBio, we amplified and sequenced 35, 5, and 11 amplicons, with average read length (mean±sd) 410±41 bp, 237±26 bp, and 1499±77 bp, and average coverage (range) 7,712 (2,237-22,661), 23,010 (5,084-47,232), and 1,741 (450-3,147) reads per nucleotide, respectively. We reconstructed all five full-length haplotypes error-free from p17 in gag to nef. Estimated frequencies were almost identical between the independent reconstruction methods QuasiRecomb and PredictHaplo, in agreement with SGA, and very stable for 100 bootstrap samples with a mean variance of 0.4% across strains and technologies. Full-length frequency estimates were more reliable than gene-wise estimates.

Conclusions: Full-length haplotype reconstruction from a heterogeneous HIV-1 sample is technically feasible. It depends critically on amplicon layout and successful amplification, sufficient read length, and homogeneous coverage. Our protocols and methods to decompose a heterogeneous population into individual full-length haplotypes can be used to identify quasispecies structures and study evolution of viral populations.



217 Limited HIV-1 Superinfection in Seroconvertors From the CAPRISA 004 Microbicide Trial

Andrew Redd[1], Caroline Mullis[2], Daniel Sheward[3], Carolyn Williamson[3], Lise Werner[4], Nigel Garrett[4], Stephen Porcella[5], Quarraisha Abdool Karim[4], Thomas Quinn[1], Salim Abdool Karim[4], TRAPS Study Team

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Background: HIV superinfection (SI) occurs when an infected individual acquires a new viral strain that is phylogenetically distinct from all previous viral strains. This study examined if HIV SI as identified by next-generation sequencing (NGS) occurred at a rate similar to the rate of primary incidence in the CAPRISA 004 trial.

Methodology: Viral sequences were successfully generated for 76 of the 96 women screened who acquired HIV during the trial and had available plasma samples within the first 3 months of infection and a second sample prior to initiation of anti-retroviral therapy (median time from infection=111 weeks). Viral RNA was extracted from plasma, reverse-transcribed, and amplified for regions of the viral p24 and gp41 genes, and was sequenced using the 454 platform. All similar sequences were combined into a single consensus sequence, which were used for all subsequent phylogenetic analyses.

HIV superinfection was defined when an individual's second sample demonstrated two or more distinct consensus sequences forming a phylogenetically distinct cluster unlinked from the individual's consensus sequences in the initial sample. Recent sexual partner status for the 96 women screened was examined as possible risk factor for SI.

Results: Two women were found to have been superinfected from all women screened (2.6%). There was one case of SI identified in each arm, and in each case the women experienced a spike in their viral loads of at least 0.5 log10 between visits when the SI was first detected. The rate of SI for the seroconvertors screened was calculated to be 1.5/100pys [95% confidence intervals (CI) =0.2-5.4], which was significantly lower than the observed primary infection rate of 7.3/100 pys as observed for the total trial population [IRR=0.20, 95% CI=0.02-0.75; p=0.003].

80% of women screened reported having sex in the last thirty days with a stable partner pre-infection, but a significantly higher percentage of these women (99%) reported having sex with a stable partner at the timepoint near the initial SI screening sample (p = <0.001).

Conclusions: The observed frequency of SI appears lower than primary HIV incidence in this population. This was unexpected and in contrast to a previous finding by our group in Uganda where the rate of SI was similar to the rate of primary infection in a general population cohort. A study of high-risk women in Kenya also found a significantly lower rate of SI compared to primary incidence, which agrees with these findings. Interestingly, the percent of women who reported sex with a stable partner increased after seroconversion. More research in a variety of populations is needed to fully clarify the relationship between HIV-SI risk and primary incidence, which could have important implications for HIV vaccine efforts.

218 Analysis of PCR Bias Using Primer IDs and Illumina Sequencing of HIV RNA Populations

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Background: The study of HIV population genetics and pathogenesis is greatly improved by deep sequencing of HIV-1 genomic DNA and RNA. To achieve sequences that accurately represent the virus population, primer IDs containing 10 random bases have been used to label each molecule with a unique sequence during cDNA synthesis. However the use of primer IDs reveals an apparent PCR bias in which a large fraction of the resulting sequences obtained are represented only once in the dataset. This effect has hampered progress. Here we describe a source of this bias.

Methodology: We hypothesized that carryover into the PCR reaction of unused primer IDs from the cDNA synthesis step could give the appearance of inefficient amplification of templates. To test this idea, cDNA was synthesized from wild-type HIV-1 BH10 *pol* transcripts using one primer ID to tag all molecules in the reaction identically. Separately, and using a different known primer ID sequence, cDNA was synthesized from transcripts containing drug resistance mutations. The two dissimilarly tagged cDNA reactions were purified, mixed and amplified together with illumina primers. Products were sequenced using paired-end Illumina MiSeq technology. In parallel, plasma HIV RNA from a chronically HIV-infected patient was labeled with primer IDs containing 10 random bases, amplified and sequenced the same way. The sequencing data were used to build consensus sequences from reads that shared the identical primer IDs and analyzed for PCR bias.

Results: We observed substantial carryover of the primers containing IDs used for cDNA synthesis into the PCR reactions resulting in frequent mislabeling of sequences giving the appearance of PCR bias. Of 234,680 sequences obtained from the samples that were tagged individually, 23.8% of the molecules sequenced were labeled with the wrong primer ID; 18.5% of WT molecules were labeled with the mutant ID and 5.3% of the mutant molecules were labeled with the WT ID. In addition, 25% of the sequences from the plasma HIV RNA sample were mislabeled (assuming each HIV RNA molecule would be unique after long-term chronic infection), as many identical sequences were tagged by more than one primer ID. Interestingly, in the same patient sample, two different HIV RNA molecules were never labeled with the same primer ID.

Conclusions: Our results show that up to 25% of sequences derived from HIV RNA may be artifacts from carryover of primer containing IDs into the PCR reaction. This problem limits the accuracy of the current primer ID approach for studying HIV populations. New methods can now be developed to eliminate the carryover of primer IDs while maintaining the unique tagging of individual templates and subsequent sequences to achieve results that accurately represent the virus population being studied.

219 HIV Surveillance and Parallel Virome Analysis Using Unbiased Next-Generation Sequencing

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Background: Next-generation sequencing (NGS) has the potential to revolutionize strategies for HIV surveillance, genome characterization, and minor variant analysis. Moreover, application of this technology in an unbiased manner offers the promise of simultaneous detection and characterization of viral co-infections. In this study, we examined the utility of high-throughput sequence analysis for characterization of HIV and detection of known and novel viruses.

Methodology: Thirty-five plasma specimens from HIV-1-infected Cameroonian blood donors were selected for analysis based on partial genome characterization (*gag* p24, *pol* IN and *env* IDR) using traditional Sanger sequencing**.** NGS cDNA libraries prepared using nuclease pre-treatment followed by RNA extraction and random-primed reverse transcription were multiplexed (4-5 libraries/run) and run on a MiSeq instrument. Sequence data was analyzed using a customized bioinformatics pipeline for rapid pathogen identification, SURPI, to identify and bin all viral sequences. Phylogenetic analysis was performed with PHYLIP and HIV-1 recombinants were characterized using SimPlot.

Results: HIV-1 related sequences ranged from 0.002% to 4.11% of total sequences yielding >90% coverage for 83% of samples. Complete genomes were assembled for 26 strains including 7 CRF11_cpx and 2 CRF13_cpx, 1 CRF18_cpx, 2 CRF22_01A1, and 1 CRF37_cpx, circulating recombinant forms with relatively limited data available as well as 8 unique recombinant forms. Average depth of genome coverage ranged from 121- to 8972-fold. Bioinformatics analysis revealed the presence of numerous other viruses. Notably, GBV-C (HPgV) co-infection was detected in 65% of samples. Eight samples yielded complete GBV-C genomes with read numbers ranging from 0.19% to 4.40%. These GBV-C genomes formed a unique cluster in genotype 1 with Ghanian sequences distinct from S. African reference strains. Additional detected viruses included hepatitis B virus, adeno-associated virus, hepatitis delta virus, human parvovirus B, human rhinovirus C, and viral sequences with distant homology (<70% aa identity) to small circular DNA viruses (circoviruses, cycloviruses, and geminiviruses).

Conclusions: These data demonstrate the utility of unbiased NGS for HIV-1 surveillance, rapid viral genome characterization, and for simultaneous screening of known and potentially novel viruses. Moreover, the extent of HIV-1 genome coverage substantially increases confidence in phylogenetic classification of strains. This technology coupled with powerful bioinformatics represents an unparalleled opportunity to characterize the virome and decipher interrelationships between HIV-1 and other viral infections.

220 Primer ID Deep Sequencing of HIV-1 env Region To Reveal Genetic Structure of Viral Population

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Background: HIV env gene consists of several highly variable regions and is a major determinant of pathogenesis, disease progression, and entry phenotype. However, deep sequencing env gene by next generation sequencing (NGS) is challenging. By using a stretch of randomized bases (Primer ID) at cDNA synthesis step prior to NGS to reduce PCR and sequencing errors and provide accurate frequencies of minority variants in the viral population, we developed an approach to deep sequence the V1-V3 region of the env gene to detect X4 variants and define the genetic structure of the viral population within individual subjects.

Methodology: Viral RNA was extracted from plasma samples obtained from 10 late-stage and 6 early-stage HIV-1 infected patients. Primers with Primer ID were used for cDNA synthesis. We used MiSeq 250 bp pair-end sequencing to sequence an amplicon covering most of V1/V2 region, all of the V3 region, and part of C2 region. In-house bioinformatics pipelines were used to create consensus sequences of the same Primer IDs. Entry tropism was predicted by V3 sequences using the Gene2Pheno[coreceptor] (False Positive Rate, FPR) algorithm. A control plasmid was amplified, sequenced, and analyzed along with clinical samples. We also used single genome amplification (SGA) to obtain env sequences from the same samples, and in vitro entry-phenotype was examined using cloned env gene.

Results: Sequencing data from the control plasmid showed that the residual error rate of this approach was 1 error in 4,000 bases. The number of consensus sequences was linearly correlated with template numbers (R2 = 0.999). We obtained an average of 1,084 and 1,532 consensus sequences for late-stage and early-stage subjects, respectively. X4 viruses were detected in 8 out of 10 late-stage samples. Phylogenetic analysis of C2/V3 sequences revealed that the most stringently called X4 viruses (Geno2Pheno, FPR <= 2%) formed distinct lineages in all the samples containing X4 viruses. Entry phenotype analysis suggested that all lineages gave phenotypic results consistent with FPR <= 2% being true X4 lineages. Analysis of both V1/V2 and C2/V3 regions showed that there was very little recombination between the X4 and R5 lineages, while some of the multiple R5 lineages or X4 lineages themselves had extensive recombination between these regions.

Conclusions: Primer ID combined with NGS provides a novel approach to deep sequencing highly variable region of HIV-1 with low error rate and accurate allelic frequency. Clustering of sequences with low FPR of X4 is an additional type of information to predict X4 calls based on sequence analysis. Restricted recombination of X4 and R5 viruses suggest these variants are genetically isolated either producing nonviable recombinants or replicating in distinct cell types.

221 Using RNASeq To Characterize Viral Genetic Diversity in a Cohort of HIV-2 Monoinfected Individuals

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Background: HIV-2 disease progression appears to be bimodal. Approximately 20% of patients progress to AIDS in a manner similar to HIV-1 infection, whilst a significant proportion (37% in the Caió cohort) maintain high CD4+ T cell counts and plasma viral loads below detection in the absence of ART, equivalent to a "functional cure". Previous work on HIV-2 plasma genetic diversity has been limited and mostly focused on single genes from patient derived clones. A bias-free method of whole genome sequencing may help to elucidate whether there is a correlation between HIV-2 viral diversity and disease progression, and shed light on whether continuing viral replication occurs in subjects with long-term viral control.

Methodology: Plasma samples were collected from HIV-2 mono-infected individuals representing each end of the clinical spectrum in a well-characterized community cohort in Caió, Guinea Bissau. Lab strains were grown in vitro and supernatant collected. RNA was extracted using a modified version of the UltraSens method. RNA samples were prepared for sequencing on the HiSeq platform with a standard RNAseq library preparation protocol. Reads were assembled into whole genomes using the VICUNA package (Broad institute) alongside in-house scripts. PCR primers were designed to amplify the whole

HIV-2 genome and the HIV-2 specific accessory gene Vpx in overlapping amplicons. Amplicons were sequenced using Sanger sequencing technology to verify HiSeq data.

Results: Full Genome sequence data will be presented from 3 HIV-2 clinical samples and 2 laboratory HIV-2 strains. We have, for the first time, used RNASeq methods to generate whole HIV-2 genome sequences directly from patient plasma with an average of 10x coverage. Our results show RNASeq can be used to generate data from small volumes (500ul) of plasma or cell culture supernatant, a crucial aspect when working with limited samples from remote cohorts. Alongside complete HIV-2 genomes, we also present the first HIV-2 Vpx sequences derived directly from patient plasma rather than patient-derived clones.

Conclusions: We have demonstrated that RNASeq is a feasible and valuable tool for generating HIV-2 whole genome sequences directly from patient plasma without the need for sequence-specific amplification or clonal expansion, reducing biases introduced during sample-preparation. As these samples were collected from a well-characterized community cohort with a long follow up time, we will outline methods to combine patient clinical data and HLA-type with RNASeq data to look for associations with disease progression. Whole genome HIV-2 sequences provide a powerful tool to elucidate the mechanisms of viral suppression in HIV-2 controllers, a natural model of attenuated HIV progression.

222 Next Generation Sequencing of Full-Length HIV-1 env During Primary Infection

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Background: The use of next generation sequencing (NGS) to examine circulating HIV *env* variants has been limited due to *env*'s length (2.6kb), extensive indel polymorphism, GC deficiency, and long homopolymeric regions. We developed and standardized protocols for isolation, RT-PCR amplification, single-molecule real-time (SMRT®) sequencing, and haplotype analysis of circulating HIV-1 *env* variants to evaluate viral diversity in primary infection.

Methodology: HIV RNA was extracted from 7 blood plasma samples (1mL) collected from 5 subjects (one individual sampled and sequenced at 3 time points) in the San Diego Primary Infection Cohort between 3-33 months from their estimated date of infection (EDI). Median viral load per sample was 50,118 HIV RNA copies/mL (range: 22,387-446,683). Full-length (3.2kb) *env* amplicons were constructed into SMRTbell® templates without shearing, and sequenced on the PacBio RS II using P4/C2 chemistry and 180 minute movie collection without stage start. To examine viral diversity in each sample, we determined haplotypes by clustering circular consensus sequences (CCS), and reconstructing a cluster consensus sequence using a partial order alignment approach. We measured sample diversity both as the mean pairwise distance among reads, and the fraction of reads containing indel polymorphisms.

Results: We collected a median of 8,775 CCS reads per SMRT® cell (range: 4243-12234). A median of 7 haplotypes per subject (range: 1-55) were inferred at baseline. For the one subject with longitudinal samples analyzed, we observed an increasing number of distinct haplotypes (8 to 55 haplotypes over the course of 30 months), and an increasing mean pairwise distance among reads (from 0.8% to 1.6%, Tamura-Nei 93). We also observed significant indel polymorphism, with 16% of reads from one sample later in infection (33 months post-EDI) exhibiting deletions of more than 10% of *env* with respect to the reference strain, HXB2.

Conclusions: This study developed a standardized NGS procedure (PacBio SMRT®) to deep sequence full-length HIV RNA *env* variants from the circulating viral population, achieving good coverage, confirming low *env* diversity during primary infection that increased over time, and revealing significant indel polymorphism that highlights structural variation as important to *env* evolution. The long, accurate reads greatly simplified downstream bioinformatics analyses, especially haplotype phasing, increasing our confidence in the results. The sequencing methodology and analysis tools developed here could be successfully applied to any area for which full-length HIV *env* analysis would be useful.

Session P-B3

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Viral Subtype: Expansion, Migration, and Recombination

223 Spread of CRF33_01B and Emergence of Novel Recombinants Among People Who Inject Drugs in Malaysia

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Background: In Southeast Asia, continuous genetic diversification and active recombination involving circulating recombinant form, CRF33_01B and other circulating genotypes in the region including CRF01_AE and subtype B' of Thai origin, may lead to the emergence of novel CRFs and unique recombinant forms. The history and magnitude of CRF33_01B transmission among various risk groups including people who inject drugs (PWID) however have not been investigated despite the possible epidemiological impact of CRF33_01B. Here, we update the most recent molecular epidemiology of HIV-1 among PWIDs and elucidate the epidemiological history of CRF33_01B among both high and low risk populations in Malaysia.

Methodology: Plasma samples were collected from a total of 356 consented HIV-positive PWIDs recruited among the prison inmates and attendees of a needle syringe exchange program in Malaysia between 2010 and 2011. The study population comprised 336 males and 20 females (mean age range: 31.3-44.7 years old). Population sequencing and phylogenetic analysis of gag-pol sequences were used to assess HIV-1 molecular epidemiology among

PWIDs. In addition, the past population dynamics of CRF33_01B was elucidated using maximum likelihood and the Bayesian Markov chain Monte Carlo (MCMC) sampling of CRF33_01Bpol sequences.

Results: HIV-1 CRF33_01B was circulating among 72% of PWIDs whilst a lower prevalence of other previously dominant HIV-1 genotypes [subtype B' (11%) and CRF01_AE (5%)] and CRF01_AE/B' unique recombinants (10%) were detected, indicating a significant shift in genotype replacement. Three clusters of CRF01_AE/B' recombinants displaying divergent yet phylogenetically-related mosaic genomes to CRF33_01B were characterized, suggestive of an abrupt emergence of multiple novel CRF clades among PWIDs. We showed that the founder lineages of CRF33_01B were likely to have first emerged among PWIDs in the early 1990s before spreading exponentially to various populations (including children who acquired infections from their mothers) and became endemic around the early 2000s.

Conclusions: Our findings provide notable genetic evidence indicating the widespread expansion of CRF33_01B among PWIDs and into the general population. The emergence of novel recombinant clades highlights the escalating genetic complexity of HIV-1 in the Southeast Asian region.

224 AHI Detection Among People Who Inject Drugs in Russia Reveals the HIV-1 Transmission Bottleneck

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Background: The expansion of the HIV-1 epidemic in Russia is mostly among people who inject drugs (PWID) due to unsafe injection practices with parenteral transmission. A pilot study to determine the feasibility of detecting acute HIV infection in PWID in St. Petersburg, Russia was conducted in 2011. Here we report the results of the molecular analysis of longitudinal blood samples obtained from the acutely infected IDUs and their risk network partners.

Methodology: We performed phylogenetic and BEAST analysis of the SGA-derived full-length env genes of acutely infected IDUs to estimate the multiplicity of HIV-1 infection. The AHI participants were also followed for up to 12 months with the weekly blood draws in the first month post-infection. We included single blood samples of the network members into the analysis to determine possible in-network transmission events. We analyzed the behavioral data provided by the subjects to suggest the parenteral over sexual transmission. We also created a panel of pseudoviruses derived from the HIV-1 strains of AHI and chronically infected subjects to test for the neutralization sensitivity of the virus.

Results: We obtained single env genes for 32 cDNAs samples from the blood of 7 AHI subjects and 8 members of their risk network. All sequences represented region-specific subtype A strains. We identified 3 potential transmission clusters: two included the chronically infected subject, and one was an AHI-to-AHI case. For all of the AHI subjects including those who were suggested to have predominantly injection risk of HIV-1 acquisition we confirmed that a single variant established each HIV-1 infection. We detected superinfection and subsequent recombination of the diverse strains in one subject. Combining these data with our previously described findings, we have found that in 14 out of 19 (74%) IDU cases HIV-1 infection was initiated by the single viral variant, including all the suggested injection-related transmission cases (total of 8). The neutralization sensitivity assay of transmitted vs persistent strains of HIV-1 subtype A is under study.

Conclusions: Similar to the sexual route of infection, injection drug use in St. Petersburg, Russia, is associated with single-variant HIV transmission. High HIV-1 incidence and prevalence, low genetic diversity and a transmission bottleneck make this population a good candidate for preventive HIV-1 vaccine trials.

225 Migration of HIV-1 Subtypes in East Africa Is Associated With Proximity To Highway Corridor

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Background: Epidemiological processes such as migration and population structure leave a measurable imprint into HIV gene sequences that can be recovered using phylodynamic approaches. Empirical evidence suggests that HIV-1 migration in east Africa is determined by spatial accessibility, a measure of human mobility that summarizes transport availability and quality.

Methodology: Here, we use a large comprehensive set of nucleotide sequences that span most HIV-1 genetic diversity in this region and apply a recently developed Bayesian phylogeographic model to assess and quantify the contribution of several potential drivers underlying viral migration. We further investigate the most significant pathways of HIV-1 dispersal and examine spatial structure among locations along the northern highway, the most active transportation axis in this region.

Results: We tested the contribution of potential predictors of HIV-1 migration among 17 east African locations along Burundi, Democratic Republic of Congo, Kenya, Rwanda, Republic of Tanzania and Uganda. We find that spatial proximity to the northern highway is the single best predictor of HIV-1 migration in the region, with substantial statistical support in favour of including this predictor in the process model (Bayes Factor=6.41). Viral migration was not significantly associated with spatial accessibility, pairwise geographic distances, train transportation network data, population changes nor with distances to the central highway, another transportation axis in the region. These findings were robust to the inclusion of sampling efforts for each location.

Also, nearly half of the significant viral migration pathways (47%, 30/64) involved locations situated along or nearby the northern highway. For all subtypes, viral exchange between locations along this highway was significantly higher as compared to locations remote from this highway axis.

Conclusions: We offer a statistical quantification of HIV-1 drivers in a high prevalence sub-Saharan region. Our high-resolution phylodynamic approach allowed to fine-tune previous findings and supports that HIV-1 migration in east Africa is mostly determined by viral exchange among populations that travel or live along or in the vicinity of the northern highway transport corridor. This approach is applicable to other scales or regions and highlights the potential for quantitative large-scale phylodynamic analyses in public health.

226 Ongoing Cross-Species Transmission of Simian Retroviruses and High HIV Prevalence in Cameroon

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Background: Recent studies have shown ongoing exposure of humans to a wide variety of simian retroviruses, including SIVs, HTLVs and SFVs. Moreover, the recent descriptions of HIV-1 group P in Cameroon, and HIV-2 group I in Ivory Coast, confirm that our knowledge on HIV diversity is still incomplete. Here, we studied retroviral infections in humans living in rural forest areas in southern Cameroon, to further explore other transmissions to humans as well as the extent of the HIV epidemic in these areas.

Methodology: A total of 3288 blood samples were obtained from adults in 26 villages. All samples were tested for the presence of HIV antibodies using commercial assays, and a subset of individuals with highest probability of exposure to non-human primates were tested for the presence of SIV and SFV antibodies by an in-house xMAP assay. HTLV antibodies were detected by commercial Elisa. HIV, SIV, SFV and HTLV antibody positive samples were tested by PCR and sequence analysis to confirm and characterize retroviral infection; RT and protease (1800 bp) for HIV, integrase for SIV (300 bp) and SFV (425 bp), tax (200 bp) and/or LTR (450-900bp) for HTLV.

Results: In this rural forest areas, the overall HIV prevalence ranged between 6% and 9%, and was at least two times higher in women as compared to men, reaching 20% in women aged between 25 and 34 years. All HIV infections were HIV-1 group M. Genetic characterization of 188 HIV-1 strains showed predominance of CRF02-AG (58%), 12 other subtypes/CRFs, URFs (10%) and two new possible CRFs. Importantly, 13 transmission clusters (20% of HIV-1 strains) including 2 to 10 strains were observed. Only 3 clusters comprised HIV-1 strains from 1 women and 1 man. In the other clusters, strains derived from women predominated, with one cluster of 10 strains exclusively from women, residing in 4 different villages on a major road for logging transport. HTLV infection was confirmed by PCR in 30/2501(1.2%) individuals in Cameroon, prevalences were similar among women and men but increased with age from 0.7% (18-24y) to 1.8% (>45y). HTLV-1 subtype B predominated, but a new HTLV-1 subtype F and HTLV-3 B variant related to STLVs from local NHPs were observed. Although, 23 on a subset of 813 samples reacted weakly with SIV antigens, no virus was amplified by PCR. Among 69 SFV antibody reactive samples, only one SFV infection with a chimpanzee virus, was confirmed by PCR in a 65 years old male reporting hunting.

Conclusions: Although no SIV infections were observed in rural forest areas from Cameroon where humans are exposed to NHPs, our study clearly shows contemporary transmission of simian retroviruses. The high HIV prevalence and high rates of transmission clusters in these rural areas indicate that, if a new SIV crosses the species barrier, conditions for rapid spread are present.

227 An Emerging HIV-1 Recombinant (CRF58_01B) Disseminating Among People Who Inject Drugs in Malaysia

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Background: The HIV epidemic is characterised by the circulation of HIV-1 group M (main) comprising of 11 subtypes and sub-subtypes and to date 55 circulating recombinant forms (CRFs). In Southeast Asia, active inter-subtype recombination involving three main circulating genotypes - subtype B (including subtype B'), CRF01_AE and CRF33_01B, have contributed to the emergence of novel unique recombinant forms. Here we report the characterisation of a novel CRF candidate among people who inject drugs in Malaysia, designated as CRF58_01B by the Los Alamos National Laboratory.

Methodology: A molecular epidemiological surveillance of HIV-1 gag-RT genes were conducted among 258 people who inject drugs (PWIDs) in Kuala Lumpur, Malaysia between 2009 and 2011 whereby a novel CRF candidate was identified among six epidemiologically unlinked male subjects (mean age range: 33.6-47.4 years old) from various ethnic groups. HIV-1 near full length genome (~9kb) was amplified by nested PCR in ten overlapping fragments using primers as previously described, sequenced and assembled prior to alignment, phylogenetic and bootscanning analyses to define the recombinant structures. Sub-region tree analysis was further used to determine the parental origin of each region.

Results: Near full length genomes sequenced in six epidemiologically unlinked individuals (09MYPR37, 10MYKJ036, 10MYPR87, 11MY1ZK731, 11MY1RJ704 and 11MY1EP794) showed identical mosaic structures consisting of subtype B' and CRF01_AE, with six unique recombination breakpoints in the gag-RT, pol and env regions. Among the high-risk population of PWIDs in Malaysia which was predominantly infected by CRF33_01B (>70%), CRF58_01B circulated at a low but significant prevalence (2.3%, 6/258). Interestingly, the CRF58_01B shared two unique recombination breakpoints with other established CRFs in the region: CRF33_01B, CRF48_01B and CRF53_01B in the gag gene, and CRF15_01B (from Thailand) in the env gene. Discrete Bayesian Markov chain Monte Carlo sampling analysis showed that CRF58_01B and other recently discovered CRFs were most likely to have originated in Malaysia, and that the recent spread of recombinant lineages in the country had little influence from neighbouring countries.

Conclusions: Our recent findings signify the increasingly complex HIV-1 diversity in Southeast Asia that may hold an implication on disease treatment, control and prevention.

228 Exploring the Hidden Interrelationship of HIV-1 Epidemics in Asia and Beyond

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Background: Along with the resurgence in HIV infection among men who have sex with men (MSM) in the Western world, there have been reports of emerging or newly-identified HIV epidemics among MSM in Asia. Especially, epidemics among MSM in China continued to expand rapidly. Recently, China witnessed the dramatic shift in HIV-1 genotype distribution among MSM from subtype B to CRF01_AE. CRF01_AE strains responsible for China's MSM epidemics were found to be classified into two distinct variants (designated CN.MSM.01-1 and CN.MSM.01-2). Both variants accounted for 95% of CRF01_AE infections among MSM in China. We aim to examine the possible effect of China's expanding epidemics among MSM in the surrounding regions and the rest of world.

Methodology: Using Los Alamos HIV sequence database (HIVDB) and the in-house HIVDB for Tokyo-Kanagawa metropolitan area in Japan, we explored the possible interplay of the epidemics in the region and the rest of the world, by means of Basic Local Alignment Search Tool (BLAST) search coupled with subsequent phylogenetic tree analyses with the nucleotide sequences of 1.1-kb pol (pro-RT). The timescale of the emergence of various MSM lineages was estimated by Bayesian molecular clock analyses.

Results: Extensive database survey revealed that Chinese CRF01_AE variants occurred in surrounding regions in Asia [Hong Kong (n=19); Thailand (n=3); Japan (n=4)] as well as in the rest of the world [Germany; USA (n=1 each)]. The variants detected among MSM in Japan (4 of 4) and Hong Kong (17 of 19) formed distinct phylogenetic subclusters within CN.MSM.01-1 (JP-CN.MSM.01-1) and CN.MSM.01-2 (HK-CN.MSM.01-2), revealing remarkable founder effects. Evolutionary analyses indicated that the emergence of CN.MSM.01-1 and CN.MSM.01-2, JP-CN.MSM.01-1 and HK-CN.MSM.01-2 was estimated to be ~1997, ~1999, ~2009 and ~2005, respectively.

Conclusions: Our study demonstrates for the first time the effect of the expanding HIV epidemic among MSM in China on transmission in neighbouring countries and the rest of the world. This finding highlights the importance of strengthening HIV monitoring efforts in a global scale and the urgent need for implementing effective measures to reduce HIV transmission among high risk groups in Asia, especially as HIV prevalence in China grows and socio-economic links between China and the rest of the world continue to expand.

229 CRF01_AE and Subtype B Transmission Networks Cross Over; A New AE-B Recombinant Emerges in Japan

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Background: The major circulating HIV-1 subtypes in Japan have been B followed by CRF01_AE, with prevalences of 86% and 7% in newly diagnosed HIV/AIDS cases, respectively. These two strains have distinct epidemiological characteristics; B predominates in men who have sex with men (MSM), whereas AE is observed mostly in heterosexuals (Hattori 2010). However, transmission networks of these two risk populations appear to be crossing over and diffusing. We have recently seen more AE cases among MSM, suggesting an increasing chance of recombination between the two strains in Japan. Indeed, newly diagnosed populations have had more discrepant subtyping results between pol and env regions. In this study we explored possible AE-B recombinations and transmission networks in Japan.

Methodology: Newly diagnosed HIV/AIDS cases that visited Nagoya Medical Center from June 1997 to March 2012 were enrolled in the study. We sequenced and analyzed three regions, gag p17 (396bps), protease-rt (1017bps), and env C2V3 (222 bps). Subtypes of each region were determined by phylogenetic analysis with reference sequences from Los Alamos database. Cases with discordant subtype results among the 3 regions were suspected as recombinant strains, and their near full-length sequences were determined. To clarify recombinant structures, we performed similarity plotting, boot-scanning and informative site analysis.

Results: Among 1070 cases diagnosed as HIV/AIDS during the study period, suspected AE-B recombinant form, where gag was identified as AE, pol as B, and env as AE, were found in 7 cases with their time of diagnosis ranging from 2003 to 2010. Of these, 5 were Japanese MSM and 1 was a heterosexual male. Detailed analysis clarified that 6 cases shared identical recombinant structure, different from any previously reported AE-B recombinant strains and was designated as CRF69_01B by the Los Alamos HIV sequence database. tMRCA analysis estimated CRF69_01B emerged between 1993 and 1997, soon after CRF01_AE was introduced from neighboring countries in mid 1990s.

Conclusions: A new recombinant strain composed of CRF01_AE and subtype B, CRF69_01B, was identified in Japan. Although the majority of AE- and B-infected cases belong to different risk populations and transmission networks, the emergence of the recombinant strain indicates the two networks are not sequestered and connections exist. As nine circulating recombinant forms composed of AE and B (CRF15, 33, 34, 48, 51, 52, 53, 54, and 55) have been reported in neighboring countries, it appears that the two strains have higher affinity of recombination. Thus, stakeholders can anticipate the emergence of further recombinant strains, emphasizing the need for continuous surveillance to understand HIV transmission in Japan and neighboring countries.

230 Phylodynamic Analysis of a Regional HIV Epidemic

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Background: Understanding the processes shaping epidemics is critical for their prediction and management. Phylogenetic inferences drawn from viral sequence data can provide a window into the temporal dynamics of regional epidemics, allowing estimation of rates of incidence, infection accumulation, and viral population demographic history. Within such regional epidemics, different risk factors in transmission dynamics and health care engagement predict corresponding different viral evolutionary dynamics measureable from the shape of phylogenetic trees.

Methodology: We inferred 1,000 time-scaled phylogenetic trees for 27,296 HIV protease and RT sequences sampled from 7,747 patients in the BC Centre for Excellence in HIV/AIDS database in BC, Canada. All sequences were doubly anonymized to protect patient privacy. Estimates of epidemic age were calculated using the root age of each phylogenetic tree in our distribution. We visualized the accumulation of infections through time using lineage through time plots (LTT). We utilized maximum likelihood approaches for estimating rates of incidence and effective population size by fitting birth-death models across our distribution of phylogenetic trees for the epidemic as a whole and within risk factors.

Results: Our analysis suggested 1897 (IQR: 1883-1923) as the estimated median time for the origin of the HIV epidemic overall, and 1941 (IQR: 1923-1958) for the subtype B clade. LTT plots reveal that within and between HIV subtypes, the BC epidemic is composed primarily of variation originating prior to 1990 (the advent of health care intervention). Birth-death models show the subtype B epidemic has undergone a recent decrease in the estimated rate of incidence. Skyline plots show corresponding declines in effective population size towards the present. Results are consistent with an epidemic founded by multiple sources and subsequent spread along local networks corresponding to different HIV risk factors, with later declines in spread.

Comparative phylogenetic analyses among risk exposure categories reveal substantial differences in the timing of the HIV epidemic between intravenous drug users (IDU) and MSM. IDU experienced a dramatic increase in rate of lineage accumulation; incidence and effective population size in the mid-1990s whereas the MSM epidemic underwent rapid growth in the 1980's followed by subsequent tapering off.

Conclusions: Concordance of our population-level phylogenetic results with epidemiological data validates the use of phylogenetic methods in assessing the past and present dynamics of the HIV epidemic. Further, we show the potential of comparing inferences drawn from phylogenetic trees partitioned by different HIV risk exposure categories.

Session P-C1 Poster Session
Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

The Gut and Lymph Nodes in HIV Pathogenesis

231 Damage of Gut Junctional Complexes Features HIV-Infected Immunological Non Responders

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Background: Gastrointestinal (GI) integrity/permeability were investigated as mechanisms for T-cell activation and poor immune recovery during cART (Immunological Non Responders, INR).

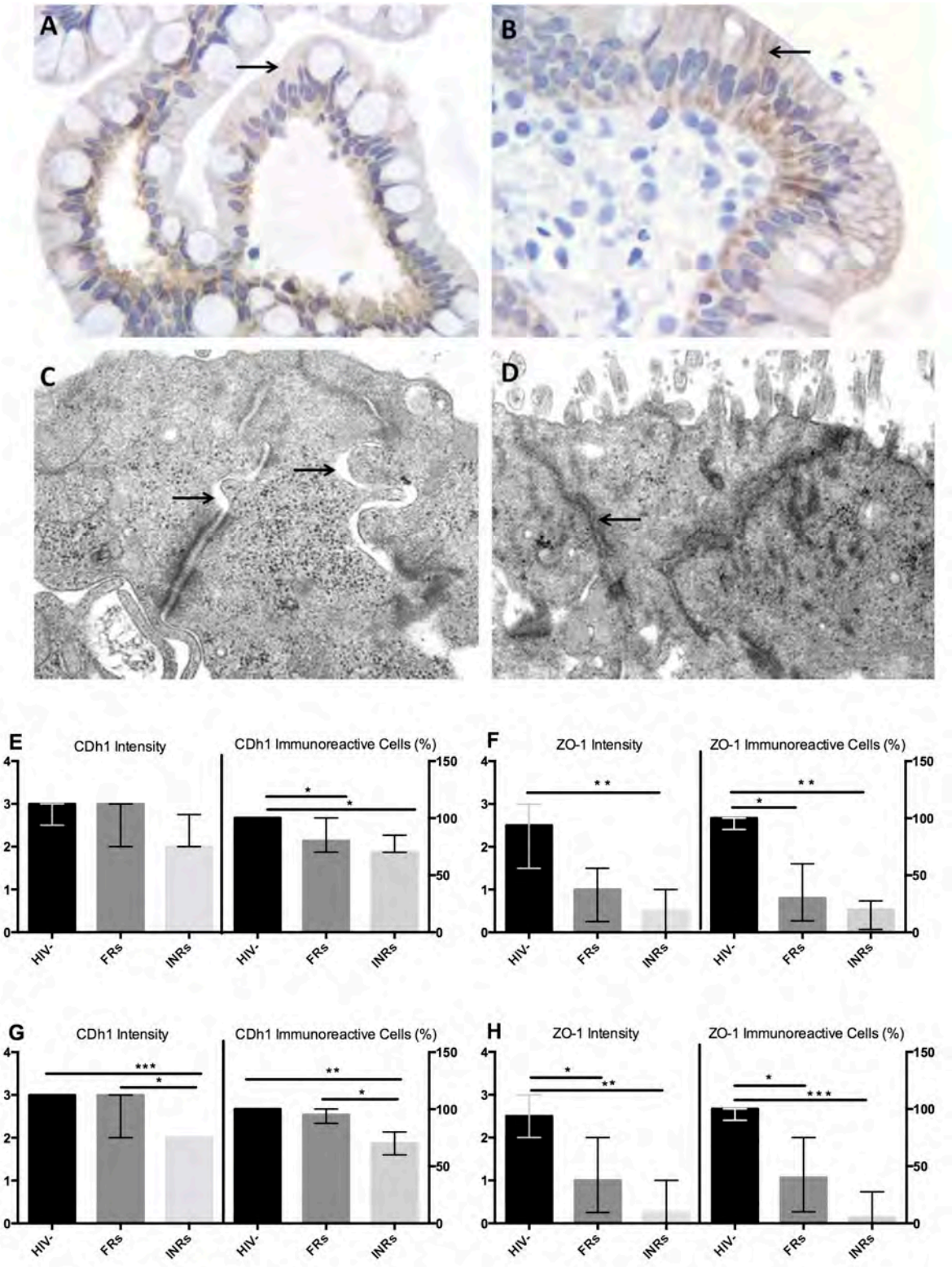
Methodology: HIV+ patients (pts) on suppressive cART for at least 12 months were enrolled. 21 INR (ΔCD4 <30% and/or CD4 <350/uL) were compared to 29 Full Responders (FR). GI permeability (LAC/MAN test), stool microbiome (DGGE), plasma MT (LPS, sCD14, EndoCAb) and T-cell distribution (flow cytometry) were analyzed. 13 FR and 8 INR also underwent colonoscopy with colon and ileum biopsies for immunohistochemical (ICH) evaluation of adherens/tight junction proteins (CDh1, ZO-1, Claudin1 and 7), cell proliferation (Ki67), T-cell tissue count (CD3, CD4, CD8) and electron microscopy (EM) study of paracellular spaces. Anatomopathological (AP) findings were compared to those of 5 HIV- controls. Total (tHIV-DNA), integrated HIV-DNA (iHIV-DNA) and 2-LTR circles were quantified by Real-Time PCR in colon/ileum biopsies and in blood isolated CD4 T-cells.

Results: INR presented reduced naïve CD4+CD45RA+ (p=.01) and CD4+CD127+ (p <.001) and increased activated CD8+CD38+ (p=.03) and CD8+CD38+RO+ (p=.03).

INR and FR displayed comparable ileum and colon expression of CD3, CD4 and CD8. INR showed higher Ki67 colon expression (35%, IQR 30-40 vs 25%, IQR 9-30; p=.02). CDh1 and ZO-1 immunoreactivity were impaired in HIV+ pts vs controls. CDh1 immunostaining was distributed around the entire epithelial plasma membrane in controls, at the basolateral surface in FR and only at the basal level in INR. The lowest levels of CDh1 cells were detected in colon biopsies from INR. Moreover, ZO-1 expression was frequently negative in ileum and colon tissue from INR. EM evaluation of the colon confirmed wider intercellular spaces in INR (Fig). DGGE demonstrated clustering stool microbial communities in INR not detected in FR. Both INR and FR showed a heightened LAC/MAN ratio (>.045) suggesting increased GI permeability; however, no significant differences in LAC/MAN and plasma LPS, sCD14, EndoCAb were noted between groups.

No differences in tHIV-DNA, iHIV-DNA and 2-LTR in circulating CD4 and colon/ileum tissue were registered between FR and INR.

Conclusions: Patients failing CD4 recovery on effective cART present damage of gut junctional complexes seemingly not due to increased viral burden. Such defects may translate into impaired mucosal and peripheral immunity, hampering CD4 reconstitution, albeit GI CD4 repopulation.



A, C: Colon biopsy from a representative INR patient. A: CDh1 antibody, arrow points to negative lateral edge of enterocytes. 40X original magnification (OM). C: arrows point to dilated intercellular space. 30,000X (OM). **B, D: Colon biopsy from a representative FR patient**. B: CDh1 antibody, arrow points to lateral immunoreactivity of enterocytes. D: arrows point to normal intercellular space. 30,000X (OM). **E, F: CDh1 and ZO-1 expression in the ileum of study patients**. **G, H: CDh1 and ZO-1 expression in the colon of study patients.** Immunoreactivity was evaluated by staining intensity (1 to 3) and percentage of positive cells.

232 Gut Homing and HIV-1 Permissiveness Are Specifically Regulated by Retinoic Acid in CCR6+ T-Cells

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Background: The majority of HIV-infected CD4+ T-cells are localized in gut-associated lymphoid tissues (GALT). The integrin β7, CCR6, and CCR9 mediate the gut-homing and their expression is induced by retinoic acid (RA), a metabolite of vitamin A produced by the GALT dendritic cells. We previously identified CCR6 as a marker for memory CD4+ T-cells permissive to HIV and demonstrated that RA selectively increased HIV replication in CCR6+ T-cells by interfering with yet uncharacterized mechanism at entry and/or post-entry levels. In search for the identification of new molecular determinants of HIV permissiveness, we performed a genome-wide analysis of gene expression in RA-treated CCR6+ versus CCR6- T-cells.

Methodology: CD4+ T-cells were sorted from PBMCs by negative selection using magnetic beads (Miltenyi). Memory (CD45RA-) CCR6+ and CCR6- T-cells were sorted by flow cytometry (BDAriaII). Cells were stimulated via CD3/CD28 and cultivated in the presence or absence of ATRA (10 nM) for 4 days. Total RNA was extracted for microarrays analysis (HT 12v4 BeadChip, Illumina; >46,000 probe sets per chip) and real-time RT-PCR quantification. In parallel, cells were used for flow cytometry validation of gene expression. Finally, a fraction of cells was exposed to HIV. Viral replication and integration was measured by HIV-p24 ELISA and real-time PCR, respectively.

Results: Among 15,303 "present calls", 1,538 and 1,285 probe sets were modulated by RA in CCR6- and CCR6+ T-cells, respectively, with only 466 probe sets being regulated by RA in both subsets (p-value <0.05). Gene classification using Gene Ontolog revealed that RA-treated CCR6+ T-cells expressed a specific transcriptional signature that included known HIV permissiveness factors, while RA-treated CCR6- T-cells expressed genes linked to HIV resistance. A number of transcripts were validated by real-time PCR and flow cytometry as being differentially expressed in RA-treated CCR6+ (e.g., RARESS3, KLF2, CCR5, CCR9, CXCR6) and CCR6- T-cells (e.g., ABCA1).

Conclusions: We identified a molecular signature associated with HIV permissiveness in RA-treated CCR6+ T-cells. This signature includes RARESS3 or RA-induced gene 1 (RIG-I); the transcription factor KLF2 that regulates CCR5 transcription; CCR5, a major HIV co-receptor; CXCR6, a minor HIV co-receptor also involved in cell-to-cell transmission of HIV; CCR9, a chemokine receptor essential for the migration in lamina propria. At the opposite, RA-treated CCR6- T-cells upregulated expression of ABCA1, a known HIV restriction factor. Our studies reveal that transcriptional changes induced by RA in CCR6+ T-cells are associated with HIV permissiveness and gut-homing potential thus, providing a molecular mechanism for preferential HIV replication in GALT CD4+ T-cells.

233 Dysregulated Gut Dendritic Cells Correlate With T-Cell Activation During Untreated HIV Infection

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Background: The gut mucosa is a major site of HIV-1-associated pathogenesis. Dendritic cells (DCs) play crucial roles in innate and adaptive immunity, in gut homeostasis and in pathogen defense, but the impact of HIV-1 infection on gut DCs has not been extensively studied. We investigated the impact of chronic, untreated HIV-1 infection on colon DC frequency and activation and evaluated associations with virological and immunological parameters.

Methodology: Colonic mucosal cells (CMC) and peripheral blood (PB) mononuclear cells were obtained from 24 untreated HIV-1 infected (HIV-1^{+}; median viral load (VL): 51,350 HIV-1 RNA copies/ml; median CD4 T cell count: 445 cells/µl) and 14 uninfected (HIV-1^{neg}) subjects. Participants gave informed consent. Flow cytometry was used to determine frequencies (number per gram of mucosal tissue) of colon CD11c^{hi} HLA-DR^{+} myeloid DC (mDC) subsets (CD1c^{+} and CD1c^{neg}) and CD303^{+} plasmacytoid DCs (pDC), DC maturation (% CD83^{+}) and activation (CD40 MFI) state, and colon and PB CD4 and CD8 T cell activation (HLA-DR^{+}CD38^{+}). Cytokine production in cultured (16hrs) CMC was assessed using a multiplex assay. Mucosal HIV-1 VL was quantified by real time PCR. Non-parametric statistical tests were used for all analyses.

Results: HIV-1^{+} and HIV-1^{neg} donors had similar numbers of CD1c^{+} and CD1c^{neg} mDCs and pDCs. However, HIV-1^{+} donors had a lower fraction of CD83^{+} CD1c^{+} (p=0.02) and CD1c^{neg} (p=0.001) mDCs in conjunction with increased levels of CD40 on CD1c^{+} (p=0.006) and CD1c^{neg} (p=0.005) mDCs. The fraction of CD83^{+} pDCs were also reduced (p=0.03), but levels of CD40 on pDCs were similar to HIV-1^{neg} donors. In HIV-1^{+} donors, CD40 expression on CD1c^{+} mDCs correlated with mucosal VL (r=0.49, p=0.04), with the number of activated colon CD4 (r=0.70, p=0.0009) and CD8 (r=0.59, p=0.008) T cells, with CMC production of pro-inflammatory IL-1β (r=0.72, p=0.003), IL-23 (r=0.67, p=0.008), IL-6 (r=0.68, p=0.006), TNF-α (r=0.66, p=0.009) and regulatory IL-10 (r=0.54, p=0.04), and with the percent of activated PB CD4 (r=0.61, p=0.006) and CD8 (r=0.53, p=0.02) T cells. No associations between activated DCs and PB CD4 count or plasma VL were observed.

Conclusions: Untreated, chronic HIV-1 infection results in a dysregulated colon mDC phenotype characterized by a lower percentage of CD83^{+} mDCs, but increased expression of CD40. Increased CD1c^{+} mDC activation was associated with local T cell activation, higher mucosal HIV-1 viral load, and with mucosal cytokine production. Further, CD1c^{+} mDC activation was associated with higher levels of systemic T cell activation, thereby linking colon mDC activation to a marker of HIV-1 disease progression. Taken together, these findings suggest gut mDCs likely contribute to mucosal inflammation and HIV-1 pathogenesis.

234 HIV-1 RNA+ Cells Are Concentrated in the Germinal Centers of Activated Lymph Nodes In Vivo

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Background: Follicular dendritic cells (FDC) are located within germinal centers (GC) of follicles and harbor large amounts of extracellular virus that are potently infectious to CD4+ T cells in vitro. Although most HIV-producing T cells are located within B cell follicles in secondary lymphoid tissues, it is unknown whether HIV RNA+ cells are concentrated within GC *in vivo*. The purpose of this study was to quantify HIV RNA+ cells in GC, non-GC follicular (non-GC F) and extra-follicular (EF) compartments of lymph nodes (LN) of HIV-infected individuals. We hypothesized that if FDC are a major source of infectious virus in vivo, then HIV RNA+ cells will be concentrated primarily within GC.

Methodology: Frozen LN cross-sections from 22 chronically HIV-infected untreated individuals without AIDS and 10 HIV-seronegative individuals were evaluated. For each LN, *in situ* hybridization for HIV-1 RNA combined with immunohistochemical (IHC) staining for CD20 and IgD were performed in a minimum of 3 cross-sections located ~60 µm apart. GC was defined as CD20+ IgD- stained areas, non-GC F as CD20+ IgD+, and EF as CD20- IgD-. Visual inspection and quantitative image analysis were used to determine the number of HIV RNA+ cells per mm^2. IHC for HIV p24 Ag was used to identify the FDC reservoir of virions in follicles (CD20+). Wilcoxon two-sample *t* test was used for comparisons. Spearman σ was used to describe correlations.

Results: LN cross-sectional area was larger in HIV+ (median, 35.8 mm^2) compared to HIV- subjects (median, 15.4 mm^2; p=0.06). Percent LN that was GC was 16-fold higher in HIV+ (median, 8%; range 0.8-41%) than HIV- (median, 0.5%; range, 0-1.6%). Frequencies of HIV RNA+ cells in LN were higher in GC (median, 2.95 cells/mm^2) than in non-GC F (median, 1.38 cells/mm^2; p= 0.0008) and EF (median, 0.13 cells/mm^2; p< 0.0001). A median of 55% of HIV RNA+ cells within LN resided in GC, which was 2.5-fold higher than both non-GC F (median, 22%; p=0.0012) and EF (median, 22%; p= 0.0005). Plasma HIV RNA correlated with HIV RNA+ cells/mm^2 in GC (σ=0.62, p=0.002), non-GC (σ=0.65, p=0.001) and EF (σ=0.83, p<0.0001). Percent p24 Ag+ area within follicle ranged from 0.1 to 4.1 (median, 0.8), but did not correlate with either plasma HIV RNA (p=0.13) or frequency of HIV RNA+ cells in GC (p=0.56).

Conclusions: This study is the first to quantify the distribution and frequency of HIV-1 producing cells within GC of LN. HIV RNA+ cells are concentrated within GC of activated follicles where FDC and their extra-cellular burden of HIV virions are located. Results are consistent with the hypotheses that FDC are major sources of infectious virus in vivo and/or GC T follicular helper cells are highly permissive to HIV.

235 Duodenal and Rectal Mucosa Immune Reconstitution Differ After ART Initiation

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[1]Molecular Immune-Biology Laboratory, Hospital General Universitario Gregorio Marañón, Madrid, Spain, [2]Infectious Diseases Department, Hospital Universitario Ramon y Cajal, Madrid, Spain, [3]Veterans Administration Northern California Health Care System, Sacramento, CA, United States, [4]University of California Davis Medical Center, Sacramento, CA, United States, [5]UCSF, San Francisco, CA, United States, [6]UCDMC and VANCHCS, Sacramento, CA, United States

Background: Despite peripheral immunological recovery, incomplete restoration of the gut associated lymphoid tissue (GALT) during treated HIV infection is likely a major determinant of disease progression. The association between blood and GALT T-cell changes following ART initiation, and whether these changes correlate across the different gastrointestinal tract segments remain unknown.

Methodology: Peripheral blood (PB), duodenal and rectal biopsies were obtained from 11 HIV- controls and 33 ART naïve HIV+ subjects participating in a randomized clinical trial comparing three different ART initiation strategies, at baseline and after 9 months of treatment. Tissue was digested into single-cell suspensions for measurements of T-cell subsets and activation phenotype by immunophenotyping

Results: Twenty-six HIV+ subjects completed the follow-up. Median age was 37 years [25-42] vs 34 [28-43] in the control group, and median CD4 T-cell count 435 cell/mL [283-572]. Eight subjects received EFV, 10 MRV and 8 MVC+RAL, each in combination with FTC/TDF, and all achieved viral suppression.

Overall, ART resulted in a significant repletion of CD4 T-cell in GALT at month 9, greater in rectum (24% to 38%) than in duodenum (12% to 17%) (all P<0.01). Also, CD8 T-cells decreased in rectum (62% to 53%) and duodenum (81% a 70%) (all P<0.01). However, the levels of both CD4 and CD8 T-cells remained very impaired relative to controls (beyond 2 SD). Changes in %CD4 in PB (24% to 40%, P<0.01) predicted %CD4 changes in colon (Beta 0.54, P=0.023) but not in duodenum (Beta -0.19, P=0.272).

The %HLADR+CD38+ of CD8 T-cells was significantly higher at baseline in PB and rectal mucosa in HIV+ compared to HIV- subjects, but not in duodenum. CD8 T-cell activation significantly decreased in blood (57% to 28%, P<0.001), duodenum (65% to 52%, P=0.015) and rectum (71% to 58%, P=0.429,] and the change in PB was reflective of the smaller mucosal changes [duodenum Beta=0.39, P<0.01, and rectum Beta=0.23, P<0.01). However, the % of activated CD8 T-cells in PB and in colon did not reach normal levels. In addition, the % of PB activated CD8 T-cells at baseline predicted the extent of CD4 depletion in duodenum (Beta=-0.7, P<0.001) and colon (Beta=-0.7, P<0.001).

HIV+ subjects showed similar % of naive CD8+ T-cells in colon and duodenum than controls, but not in PB. The CD8 naïve/memory ratio significantly improved in blood but did not reach normal levels.

Conclusions: Following ART initiation we observed incomplete recovery of GALT CD4 T-cells. Immune reconstitution of the duodenal mucosa was impaired compared to changes in blood and rectum. The duodenal compartment may represent a portal for systemic immune activation and CD4 depletion during HIV infection and further studies of this compartment are warranted.

236 Gut Microbiota of HIV Infected Subjects Induce Inflammatory Cytokines But Not T Regulatory Cells

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Background: We co-exist with an abundant microbiota that cooperate with and help regulate our immune system. However, during HIV infection the microbial community in the gut is altered to a distinctive composition which is not consistently restored to that of seronegative subjects by ART. Recently, our group illustrated that in contrast to uninfected patients, the microbial community in HIV infected subjects exhibits increased phylogenetic diversity and is Prevotella-rich and Bacteroides-poor. Here we seek to understand the impact of the change in gut microbiota on HIV infection by characterizing innate and adaptive immune responses, including T regulatory cells, to selected gut bacteria that changed with HIV infection.

Methodology: Based on our 16S rRNA sequencing from HIV+ and HIV- subjects we chose four characteristic bacteria; Bacteroides dorei, Bacteroides fluxus, which were decreased, and Prevotellaceae copri, Erysipelotrichaceae biforme, which were elevated with HIV infection. PBMCs of 15 HIV-positive and 18 HIV-seronegative subjects were incubated with lysate of these bacteria. Levels of inflammatory cytokines were evaluated at 24 hours post inoculation by bead array assay, and T regulatory cells and CD4+ T cell proliferation were enumerated by flow cytometry at either 3 or 6 days. Statistical significance was determined using Mann-Whitney T tests.

Results: HIV-infected subjects had significantly elevated levels of both TNF-α and IL-10 to all bacteria in comparison with HIV-seronegative ($p<0.05$). Levels of T regulatory cells also increased with all bacteria although levels were not significantly different in regard to HIV status. Median levels of T regulatory cells from PBMC cultured with B. fluxus (2.24%) and B. dorei (2.08%) were greater compared to that of P. copri (0.44%; $p=0.03$, $p=0.05$, respectively) and E. biforme (0.06%; $p=0.02$, $p=0.03$, respectively). All bacteria induced CD4+ T cell proliferation regardless of HIV status. However, with HIV infection CD4+ T cell proliferation to B. fluxus (1.30%) and B. dorei (0.47%) was reduced compared to HIV-seronegative subjects (4.77% and 1.78%; $p=0.03$, $p=0.08$, respectively), while responses to P. copri and E. biforme were not significantly different.

Conclusions: These results illustrate that HIV infection is associated with a distinct microbial signature that is more pro-inflammatory. Furthermore, Bacteroides species which are lost during HIV infection are better adapted for inducing T regulatory cells than P. copri and E. bioforme that are enriched in the gut during infection. By evaluating bacterial mediated immune responses these studies will provide important new understanding about the mechanisms and functional aspects of these bacteria in regulating the immune system and their role in HIV disease.

Session P-C2 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Immune Activation and Pathogenesis

264LB An SMS Intervention To Improve HIV Linkage To Care: A Randomized, Comparative Effectiveness Trial

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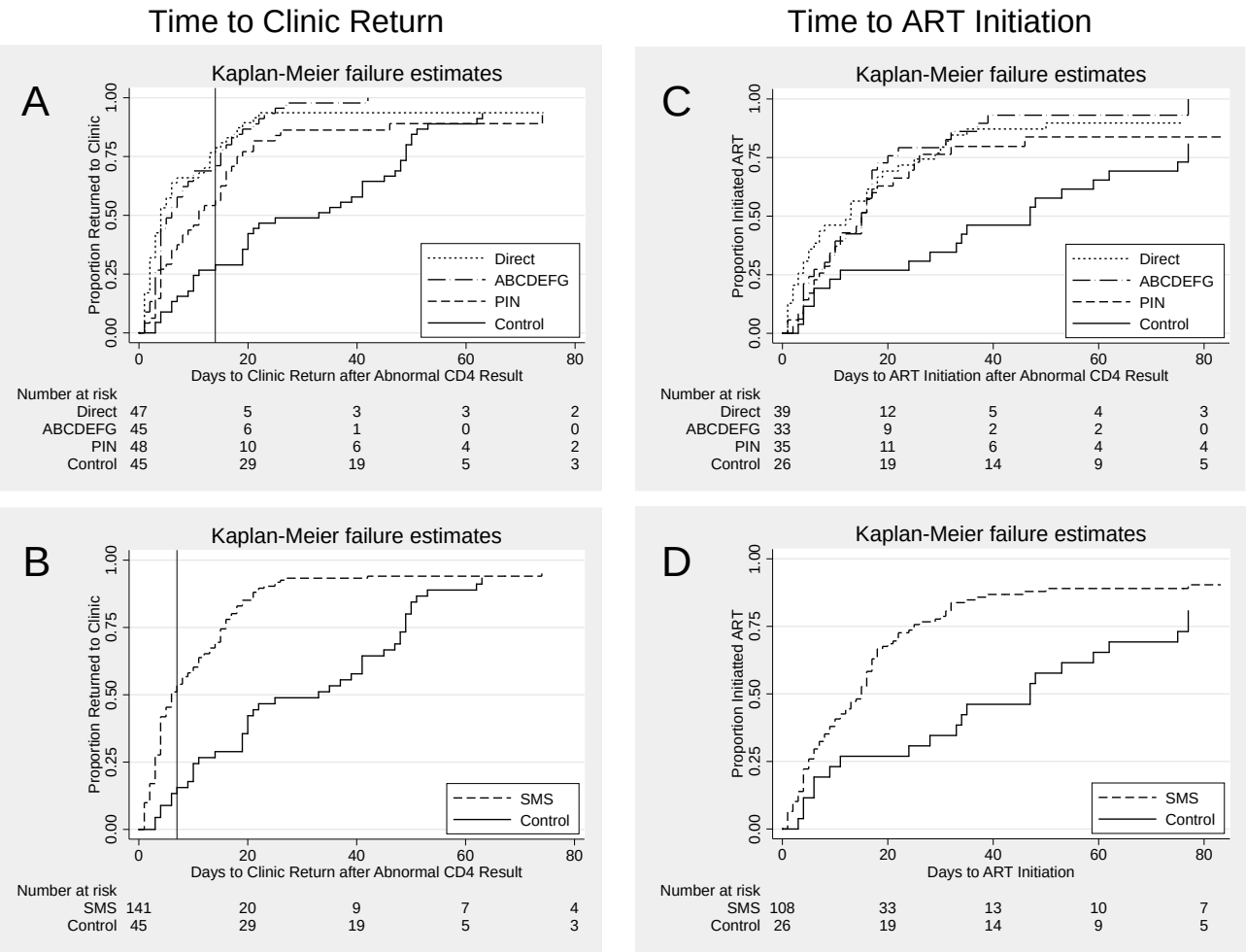
Background: Up to 50% of HIV-infected persons in sub-Saharan Africa are lost from care between HIV diagnosis and ART initiation.

Methodology: We enrolled participants in a comparative effectiveness trial to improve linkage to care at a publicly operated HIV clinic in Mbarara, Uganda. Clinicians identified patients undergoing high-risk CD4 testing, defined as a test for which an abnormal result would prompt early return to care. Participants enrolled in the pre-intervention period (January-August 2012) served as a control group. Participants enrolled in the intervention period (September 2012-November 2013) received an SMS message notifying them of normal results or, if results were abnormal, were randomized to one of three messages: 1) an unprotected SMS reporting an abnormal result (direct message); 2) a personal identification number-protected (PIN) message; or 3) a message reading "ABCDEFG", coded to convey an abnormal result confidentially. We provided transportation reimbursements (~$6USD) to those returning within 7 days of their first abnormal result SMS. We conducted survival analyses and fit Cox proportional hazards regression models to estimate differences between groups for outcomes of interest: 1) time to return to clinic after an abnormal result and 2) time to initiation of ART among the ART naïve.

Results: Of 553 participants enrolled, 533 (96%) had a valid laboratory result, and 187 (35%) of results were abnormal. There were 46, 48, 47, and 45 participants with abnormal laboratory results in the control, direct, PIN, and coded message groups. Median days to clinic return after abnormal results in the control, direct, PIN, and coded groups was 29, 4 ($P<0.001$ for logrank test vs. control arm), 11 ($P=0.02$), and 6 days ($P<0.001$). Median time to ART initiation was 47, 13 ($P=0.03$), 15 ($P=0.10$), and 15 days ($P=0.001$). In multivariable regression models adjusted for age, gender, district of residence, education, and CD4 result, receipt of an SMS was associated with earlier return to clinic (adjusted hazard ratio [AHR]=2.4, 95%CI 1.6 - 3.6, $P<0.001$) and shorter time to ART initiation (AHR=1.7, 95%CI 1.0 - 2.7, $P=0.04$). Among those with normal results, a greater proportion who received an SMS message returned within 7 days of their scheduled return date (81 vs 62%, $P=0.001$).

Conclusions: An SMS-based laboratory result communication system coupled with transportation incentives significantly decreased time to clinic return and time to ART initiation after abnormal CD4 test results.

Figure. Kaplan-Meyer survival curves demonstrating time to clinic return after an abnormal CD4+ T-lymphocyte count result (Panels A-B) and time to ART initiation after an abnormal CD4+ T-lymphocyte count result (Panels C-D).



265 CD4 T-Cell Responses in Relationship With Immune Activation and Viral Load in Primary HIV Infection

Mathieu F. Chevalier[1], Céline Didier[1], Gaël Petitjean[1], Pierre-Marie Girard[2], Françoise Barré-Sinoussi[1], Daniel Scott-Algara[1], Laurence Weiss[3, 4]

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Background: Early events during primary HIV infection (PHI) are thought to influence disease outcome. Although few studies have characterized HIV-specific CD4 T cells during PHI, a growing body of evidence suggests a beneficial role of functional CD4 T-cell responses in different aspects of protective immunity in HIV infection. It is unclear how viral replication and systemic immune activation may shape these responses. Here, we longitudinally investigated polyclonal and HIV-specific CD4 T-cells in relationship with the immuno-virological status of patients with PHI.

Methodology: 27 patients with early PHI were included in a prospective longitudinal study and followed-up for 6 months. T-cell activation, natural Tregs, Th1, Th17 and Th1/Th17 cells were assessed by cytometry on fresh PBMC. Cytokine-producing effector CD4 T cells were quantified by intracellular cytokine staining on isolated peripheral $CD3^+CD4^+$ cells stimulated with PMA/ionomycin for 5h or with the HIV-1 gag p24 antigen for 72h in the presence of autologous monocytes. Statistical significance was assessed using the Mann-Whitney or the Wilcoxon matched-paired non-parametric tests.

Results: Two groups of patients were segregated based on the level of CD8 T-cell activation at baseline (the groups with lower immune activation (LIA, n=13) and higher immune activation (HIA, n=14) were defined as % $HLA\text{-}DR^+CD38^+$ CD8 T cells < median and ≥ median, respectively). Following PMA/ionomycin activation, compared to patients with HIA, patients with LIA exhibited higher frequency of CD4 T cells producing IFNγ (p=0.039) or IL-17 (p=0.018). Also, patients with LIA exhibited higher effector/regulatory T-cell balance (p=0.001 when considering the Th1/Treg ratio; p=0.039 when considering the Th17/Treg ratio). No differences were found in the frequency of HIV-specific CD4 T cells between both groups. However, patients with plasma viral load (pVL) > median had higher IFNγ^+ (p=0.031), IL-2^+ (p=0.018), $IL17^+$ (p=0.037) and IFNγ^+IL17^+ (p=0.009) HIV-specific CD4 T cells compared to patients with pVL < median. Of note, the frequency of IFNγ^+ (but not of IL-2^+) HIV-specific CD4 T cells significantly diminished between baseline and month 6 only in patients receiving ART during the follow-up (p=0.014).

Conclusions: Immune activation in PHI is associated with low polyclonal effector CD4 T cell responses but not related to levels of HIV-specific responses suggesting that immune activation is mainly driven by the virus and innate responses rather than by HIV-specific responses. In addition, the frequency of HIV-specific Th1, Th17 and Th1/Th17 cells is positively associated with plasma viral load, suggesting that these cells are driven by viral replication but not able to contribute to its control in the early phase of infection.

266 Herpesvirus Infections in HIV+ Individuals On ART Are Not Associated With Immune Activation

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Background: We assessed whether systemic reactivation of herpesviruses contributes to innate immune activation and inflammation observed in treated chronic HIV-1 infection.

Methodology: We obtained whole blood, plasma, throat washings, urine, semen, and stool specimens from HIV-1(+) MSM in the Multicenter AIDS Cohort Study (MACS) who were <50 years old, on suppressive ART for at least 2 years, and with CD4+ T cell counts >500 cells/mL (HIV+; N=15) as well as in matched, CMV IgG(+), seronegative MSM controls (NC; N=12). HSV 1 and 2, CMV, EBV, HHV6, and HHV8 DNA were measured using multiplex real time PCR. ELISA was done on plasma samples to assess levels of monocyte (sCD14) and macrophage (sCD163) innate immune activation, and soluble markers of inflammation and coagulation (IL-6, hsCRP, and D-dimer). Immunologic and virologic parameters were compared between the two groups using the Mann Whitney test, and for correlations using the Spearman rank test.

Results: 14/15 HIV+ and 11/12 NC showed evidence of herpesvirus reactivation, in a median of 2 body compartments in HIV+ compared to 1 in NC. Herpesviral DNA was detected mostly in throat washings of both groups. HHV6 was the most common virus detected in both groups (73.3% in HIV subjects and 66.7% in controls). HIV+ had reactivation in more body compartments ($p=0.0371$) and a trend for multiple types of herpesviruses ($p=0.074$), with up to 5 different herpesviruses reactivating in different body compartments during suppressive ART. CMV reactivated more in HIV+ (6/15;40%) than in NC (1/12;8.3%), and was mostly detected in semen. HIV+ had significantly higher levels of plasma sCD14 than NC ($p=0.0058$). However, these levels did not correlate with the number of herpesvirus DNA copies, the number of herpesvirus types reactivating, or the number of body compartments where the herpesviruses were reactivating. Similarly, there was no correlation between these virologic parameters and the levels of pro-inflammatory biomarkers, IL-6 and hsCRP. There was no significant difference in the levels of macrophage activation (sCD163) or in the levels of pro-inflammatory biomarkers. Levels of D-dimer were also similar between the two groups.

Conclusions: HIV(+) MSM who are virally suppressed on ART and with immune reconstitution (CD4>500) exhibit more systemic herpesvirus reactivation than age and risk-factor matched HIV seronegative controls. However, this viral reactivation was not associated with increased levels of innate (monocyte) activation markers that are observed in these individuals.

267 Chronic Inflammation in HIV-1 Infected Individuals Reduces T-Cell Responsiveness To Vaccines

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Background: Chronic Inflammation remains a problem for HIV-1 infected individuals despite stable anti-retroviral therapy (ART). These low levels of inflammation, an imbalance in the cytokine/chemokine milieu, continue to exacerbate the immune deficiency of HIV+ individuals. And, therefore, these individuals may not mount an adequate immune response to vaccines, such as influenza.

Methodology: We assessed the level of inflammatory molecules in the sera of volunteers who were HIV-1 infected. We also examined cellular activation and responsiveness to HIV-1 and influenza antigens using multi-parameter flow cytometry flow cytometry and ELISPOT.

Results: We found the HIV-1 infected subjects on ART had significantly higher serum IP-10 levels as compared to healthy HIV-negative controls. Additionally, subjects showed a positive relationship between serum IP-10 levels and the percentage of activated (CD38+ HLA-DR+) central memory (CD27+ CD45RO+) CD4+ T-cells. In our in vitro studies we also found that PBMCs exposed to non-normal IP-10 levels for 24 hours demonstrated a decrease in the number of cells capable of secreting IFN-γ production when stimulated with HIV and influenza antigens. To determine the mechanism of suppression of high levels of IP-10 on the lymphocyte responsiveness we cultured PMBCs from healthy HIV-negative subjects with or without IP-10 (0.5, 10, 100ng/mL). PBMCs were either un-stimulated or stimulated with viral antigens. We again observed a decrease in IFN-γ production as well as a decrease in phosphorylation of p38 MAPK.

Conclusions: Chronic exposure to high levels of IP-10 lead to a reduction in IFN-γ production to both HIV-1 antigens as well as influenza antigens. The reduction in the T cell response to viral antigens appeared to be due a loss of p38 MAPK phosphorylation. Therefore, even with stable ART, low level chronic inflammation could lead to continued immune dysfunction, which in turn can impact responsiveness to anti-retroviral therapy, disease progression, and response to vaccination. These findings demonstrate that anti-inflammatory drugs may need to be administered to HIV-1 infected subjects on ART in order to reduce damage from low level inflammation. Such treatment could preserve and enhance T-cell immune responses to vaccination.

268 Persistently Activated CD27+CD80+ B Cells Following ART Correlate With Macrophage Activation

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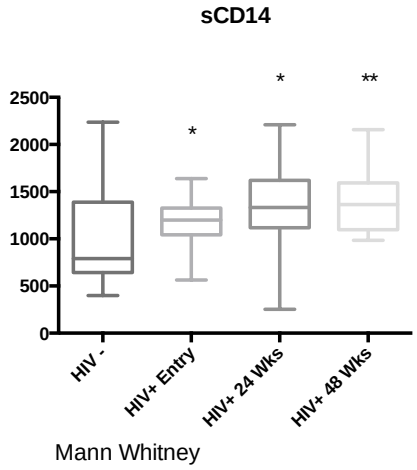

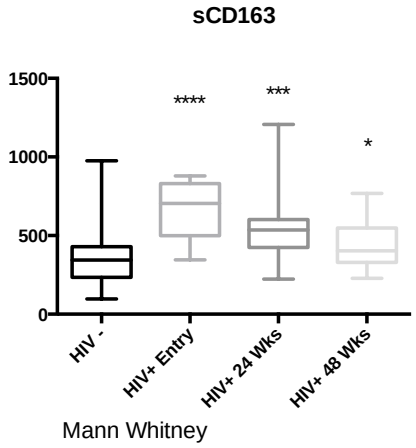

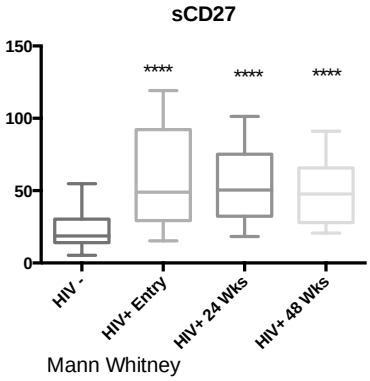

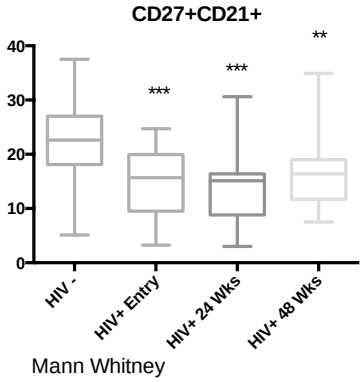

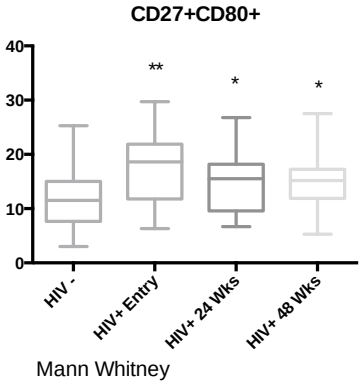

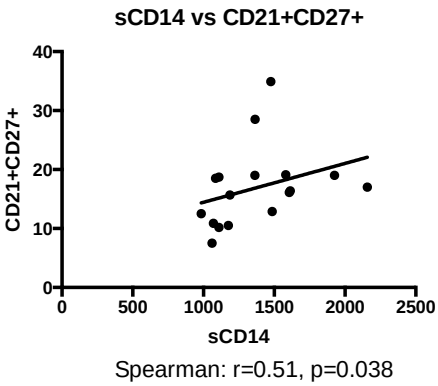

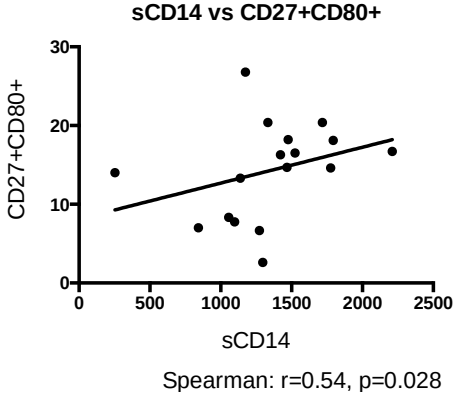

Background: Antiretroviral therapy (ART) and control of HIV replication does not fully restore perturbations within resting (CD19+CD27+CD21+) and activated (CD19+CD27+CD80+) memory B cell compartments. This study was based on the hypothesis that ongoing macrophage activation and HIV-associated inflammation contributes to B cell abnormalities.

Methodology: Longitudinal cellular and soluble plasma markers for inflammation were evaluated in 43 healthy controls (HC) and 17 behaviorally-infected HIV-1+ subjects ages 18-25 years. Multicolor flow cytometry analysis of B cell subsets and assessment of markers of macrophage (sCD163 and sCD14) and lymphocyte (sCD27) were measured by ELISA. Assays were performed prior to and at 24 and 48 weeks following ART. All HIV-1 subjects suppressed HIV to < 50 copies/ml. Healthy controls and HIV+ treated subjects were also compared pair-wise and longitudinally at study entry (prior to ART), 24 weeks and 48 weeks on therapy by non-parametric rank sum.

Results: Compared to HC, resting memory B cells were lower and activated B cells were higher among HIV+ subjects at all time points before and after ART {22.6 ± 8.1% (HC) versus 16.4 ± 6.7% (HIV+ at 48 weeks) for resting memory, p=0.0081, and 11.5 ± 5.3% (HC) versus 15.2 ± 5.1% (HIV+ at 48 weeks), for activated B cells, p=0.0415, Mann-Whitney}, Control of viral replication failed to decrease the proportions of activated B cells or increase memory B cells after 48 weeks on therapy. Compared to HC, sCD14, sCD27 and sCD163 all remained significantly elevated in HIV+ subjects at 48 weeks following therapy (p=0.0027, p<0.0001, and p=0.0142, respectively, Mann-Whitney). Regression analysis revealed a positive correlation between the decrease in resting memory B cells and levels of sCD14 at 48 weeks on therapy (r=0.51, p=0.038, Spearman test) but sCD163 and sCD27 did not correlate with the extent of B cell activation. Results also showed a positive correlation between the increase in activated B cells and the elevation of sCD14 24 weeks following therapy (r=0.54, p=0.028 Spearman).

Conclusions: Elevated levels of sCD14, a biomarker of macrophage activation, is the result of LPS binding to TLR4. Our results show that chronic B cell activation also reflects ongoing inflammation due to microbial translocation that may contributes to ongoing B cell dysfunction, even in HIV-infected subjects who control viral replication with ART.

269 Novel Exosomal HIV miRNAs may Contribute To Chronic Immune Activation

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Background: Chronic immune activation may be in part attributable to translocation of microbial TLR ligands from the GI tract into the systemic circulation, but may involve direct effects of viral proteins and nucleic acids and activation of bystander host immune cells. We investigated whether novel HIV-derived miRNAs can directly induce macrophage proinflammatory cytokine release via non-canonical pathway.

Methodology: HIV miRNAs including vmiRNA-TAR and two novel HIV miRNA designated as vmiR88 and vmiR99 (determined by UNAfold RNA folding software, from R/U5 and U5 regions of HIV LTR, each with requisite short hairpin structure and highly conserved sequence vs. several clinical HIV isolates) were synthesized by IDT (Coralville, IA). Human macrophages U937 and HIV+U1 cell lines (differentiated with PMA), and human alveolar macrophages (AM) from consenting healthy or asymptomatic HIV+ volunteers (hospital IRB-approved bronchoscopy protocol) were isolated by adherence. For select experiments, healthy AM were infected *in vitro* by HIV-Bal isolate x 2 weeks. For select experiments, RNAi targeted TLR8 gene silencing performed by Amaxa. HIV miRNA detected by ultrasensitive qRT-PCR on cell lysates, and exosomal fraction of macrophages cultured supernatants and archived sera from healthy and asymptomatic HIV+ persons. TNF release in cultured supernatants determined by ELISA.

Results: Exosomal fraction of sera from asymptomatic HIV+ persons with CD4+ T-lymphocyte counts <200 cells/mm^3, undetectable viral load, prescribed cART demonstrated abundant HIV vmiR-TAR in 92% of persons, in addition to both novel vmiR88 and vmiR99 each in 54% of persons, often exceeding levels of vmiR-TAR. In addition, vmiRNA-TAR, vmiR88 and vmiR99 were detected in cell lysates, released by HIV-infected macrophages upon PMA stimulation, released by AM following *in vitro* HIV infection, and associated with exosomal fractions. Exogenous vmiR88 and vmiR99 (but not vmiR-TAR) directly stimulated TNF release by human macrophages, dependent on macrophage TLR8 and vmiRNA GU-content. Finally, HIV vmiR-mediated TNF release was neutralized by specific complimentary antagomirs duplexing with HIV vmiRNAs.

Conclusions: Novel HIV-derived vmiRNAs stimulate macrophage TNF release through non-canonical pathway and may contribute to chronic immune activation in HIV-infected persons. HIV miRNAs may represent novel therapeutic targets to limit HIV disease pathogenesis.

270LB Interleukin-21 Reduces Residual Immune Activation in ART-Treated SIV-Infected Rhesus Macaques

Luca Micci[1], Emily Ryan[1], Colleen McGary[1], Sara Paganini[1], Guido Silvestri[1], Jason Brenchley[2], Francois Villinger[1], **Mirko Paiardini[1]**
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Background: Current HIV antiretroviral therapy (ART) successfully inhibits virus replication, improves health, and prolongs life expectancy in people living with HIV. Although HIV replication is suppressed, residual immune activation persists and critically contributes to non-AIDS-related morbidity and mortality in ART-treated individuals. Interleukin (IL)-21 regulates three immunological functions - Th17 cell homeostasis, differentiation of memory B cells, and long-term maintenance of functional CD8+ T cells - that are compromised following HIV infection. Previously, we showed that when administered during acute infection, Interleukin (IL)-21 reduces microbial translocation and systemic immune activation in SIV-infected rhesus macaques (RMs). In this new study we investigated if administration of IL-21 to chronically SIV-infected, ART-treated RMs is effective in limiting the extent of on-ART residual immune activation.

Methodology: Sixteen RMs were infected with SIVmac239 i.v. and, starting at day 60 post-infection, were treated for seven months with PMPA, FTC, Raltegravir, Darunavir and Ritonavir. Eight RMs received IL-21-Fc (100 µg/kg, s.c., weekly for six weeks) at the beginning and at the end of ART, with the other eight serving as ART-treated controls. Longitudinal collections of blood, lymph nodes and rectum were performed. IL-21 effects on immune activation, T cell subset levels and functions were assessed by flow cytometry. 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 treated RMs showed better restoration of mucosal immunity, with higher levels of intestinal IL-17 (Th17), IL-22 (Th22), as well as IL-17 and IL-22 (Th17/Th22) producing CD4+ T cells (P<0.01 for all three subsets). Furthermore, while ART alone was sufficient to restore Th22 functions, the ability of Th17 cells to produce multiple cytokines, as assessed by co-staining of IL-17, IL-2, IL-22, TNF-α, and IFN-γ, was restored at levels significantly higher in IL-21 treated RMs as compared to controls. Remarkably, the combined ART+IL-21 treatment reduced immune activation significantly more than ART alone, with IL-21 treated RMs showing lower levels (P<0.01) of activated (HLA-DR+CD38+), proliferating (Ki-67+) and PD-1+ T cells in rectum and blood.

Conclusions: IL-21 administration in ART-suppressed SIV-infected RMs more rapidly restores intestinal IL-17 and/or IL-22 producing CD4+ T cells while limiting residual immune activation. Thus, IL-21 may provide important therapeutic benefits when used as an immunomodulator in ART-treated HIV-infected individuals.

271 Immune Activation and Risk of HIV-1 Transmission Among HIV-1 Serodiscordant Couples

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Background: Immune activation is a hallmark of chronic HIV-1 infection. A heightened pro-inflammatory state has been hypothesized to enhance HIV-1 transmission - both susceptibility of HIV-1-exposed persons and infectiousness of HIV-1-infected persons.

Methodology: Using data collected prospectively from heterosexual HIV-1 serodiscordant couples from 6 countries in eastern and southern Africa, we conducted a nested case-control analysis to assess the relationship between immune activation and risk of HIV-1 acquisition and transmission. Cases (N=120) included incident HIV-1 transmissions; controls (N=321) were couples in which HIV-1 transmission did not occur. Immune activation was measured in both HIV-1 susceptible and infected partners by a panel of 30 cytokines.

Results: For both HIV-1 infected and susceptible partners, cases and controls had significantly different mean responses in cytokine panels (Hotelling T2 p<0.001), suggesting a broadly different pattern of immune activation for couples with HIV-1 transmission events compared to those who did not transmit HIV-1. When considering elevations in specific cytokines, log10 mean concentrations were found to be significantly higher for HIV-1 susceptible cases when compared to controls for IL-10 (p=0.001) and IP-10 (p=0.002). Similarly, for HIV-1 infected partner cases and controls, log10 mean concentrations were significantly higher for IL-10 (p<0.001) and IP-10 (p<0.002). In multivariate analysis, HIV-1 transmission was significantly associated with elevated IP-10 concentrations in HIV-1 susceptible partners (p=0.001) and elevated IL-10 concentrations in HIV-1 infected partners (p=0.02).

Conclusions: Immune activation - particularly elevated levels of IL-10 and IP-10 - are associated with both increased HIV-1 susceptibility and infectiousness.

272 Inflammation in Acute HIV Infection Correlates With Blood and Gut CD4 T-Cell Loss and Viral Burden

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Background: Biomarkers of inflammation, coagulation and fibrosis are associated with morbidity and mortality in HIV infected persons. Understanding the changes in these biomarkers during sequential stages of acute HIV infection (AHI) before seroconversion could illuminate the course of early HIV pathogenesis.

Methodology: Plasma levels of D-dimer, hyaluronic acid (HA), C-reactive protein (CRP), soluble CD14 (sCD14), IL-6 and TNFα were measured from 78 AHI and 109 HIV uninfected (HIV-) Thai participants by ELFA (D-Dimer) and ELISA methods, respectively. 42 AHI participants had sigmoid biopsies. Cell-associated HIV DNA and RNA in peripheral blood and sigmoid colon were measured by PCR and RT-PCR. Subjects were divided by 4thG staging: 1 (4th generation (G) EIA-, 3rdG EIA-), 2 (4thG +, 3rdG -) and 3 (4thG +, 3rdG +, Western blot - or indeterminate). Median values were compared between groups by non-parametric methods and Spearman correlations were used for associations between variables.

Results: The median age in AHI versus control subjects was 28 vs. 27 years. Median time since HIV exposure was 12, 16 and 18 days in stages 1, 2 and 3, respectively. The table illustrates key data. Plasma levels of biomarkers of inflammation, microbial translocation (MT), fibrosis and coagulation correlated positively with plasma HIV viremia: TNFα (r=0.62, P<0.001), sCD14 (r=0.25, P=0.03), HA (r=0.28, P=0.01) and D-dimer (r=0.33, P=0.003) and with sigmoid HIV DNA levels: TNFα (r=0.66, P=0.002) and CRP (r=0.44, P=0.02). Increased inflammation and MT correlated with low circulating CD4 T cell counts: TNFα (r=-0.31, P=0.04) and CRP (r=-0.25, P=0.03), and low sigmoid CD4 T cell numbers: TNFα (r=-0.40, P=0.03), CRP (r=-0.31, P=0.05), sCD14 (r=-0.42, P=0.005) and IL-6 (r=-0.37, P=0.05). High HA levels (r=-0.42, P=0.006), reflecting fibrosis, correlated with low sigmoid CD4 T cell numbers. Subjects with detectable peripheral blood integrated HIV DNA at week 24 had higher baseline TNFα (8.9 vs. 6.4 pg/mL, P=0.02), sCD14 (2.2 vs. 1.3 µg/mL, P=0.01) and D-dimer (0.41 vs. 0.24 µg/mL, P=0.01) levels.

Conclusions: Biomarkers of inflammation, coagulation and fibrosis are elevated in AHI before seroconversion. The temporal course of these biomarkers suggests that peak viral burden and inflammation trigger a pro-thrombotic and pro-fibrotic response. Stage 2 may represent the peak of immunologic destruction and thus a critical point for early intervention to prevent further immune decay and ultimately HIV disease.

Comparison of key measures (*P<0.05, **P<0.01 vs stage 1, + P<0.05 vs stage 2)					
Baseline levels Median	HIV- (n=109)	All Acute HIV Stages (n=78)	4thGstage 1 (n=20)	4thGstage 2 (n=15)	4thGstage 3 (n=43)
CD4 T cells(cells/µL)	-	384	451	304	386
Plasma HIV RNA (log10copies/mL)	-	5.6	4.8	5.8**	5.8**
Peripheral Blood HIV DNA (copies/10^6 PBMC)	-	87 n=74	7.5 n=19	366** n=13	189** n=42
Sigmoid colon CD4 T cells (10^6 cells/gram)	16.5 n=9	7.8 n=42	11.1 n=14	2.3* n=3	6.6* n=25
Sigmoid colon HIV DNA (copies/10^6 cells)	-	319 n=27	0 n=8	7484* n=2	570**+ n=17
IL-6 (pg/mL)	-	0.64 n=43	0.51 n=14	2.76* n=6	0.6+ n=23
CRP (µg/mL)	0.26**	1.35	0.85	3.08*	1.34+
TNFα (pg/mL)	-	6.57 n=43	4.99 n=15	8.51** n=5	7.72** n=23
sCD14 (µg/mL)	0.79**	1.53	1.29	1.7	1.56
HA (ng/mL)	9*	18.4	13	16	23*
D-Dimer (µg/mL)	0.17	0.28	0.19	0.28*	0.33*

Session P-C3 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

NK Cells in HIV Pathogenesis

273 NK Cell Subsets Responding To HIV-Infected Autologous CD4 T Cell in Protective KIR/HLA Genotypes

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Background: Genetic and epidemiological studies implicate NK cells in HIV resistance and slow disease progression in infected individuals. This protective effect is achieved by interactions between NK cell surface receptors called KIRs and their ligands, HLA molecules. These interactions are important for NK cells to gain functional potential during a developmental process known as education. The receptor KIR3DL1 with its ligand HLA-B*57 (*h/*y+B*57) has the strongest effect on slow time to AIDS and HIV viral load control compared to Bw6 homozygotes (Bw6hmz). *h/*y+B*57 carriers have a stronger effect on these outcomes than do carriers of *l/*x+B*57. Levels of KIR3DL1 on NK cells from *l/*x+B*57 carriers are lower *h/*y+B*57 carriers. NK cells from *h/*y+B*57 carriers receive potent educational signals through HLA-B*57 KIR3DL1 ligation leading to high functional potential. Since Bw6 antigens do not interact with KIR3DL1, NK cells from Bw6hmz are not educated through KIR3DL1. Here we investigated whether KIR/HLA genotype influences the potency of NK-mediated inhibition of viral replication and NK cell subset responses to autologous HIV-infected CD4 cells.

Methodology: The study population included carriers of *h/*y+B*57 (n=7), 3DS1+*80I (n=9), *l/*x+B*57 (n=4) and Bw6hmz (n=11). We measured NK cell mediated inhibition of HIV replication in autologous infected CD4 T cells by assessing the supernatant levels of HIV p24 longitudinally. We measured CC-chemokine secretion following stimulation with autologous infected CD4 cells by ELISA and multi-parametric flow cytometry.

Results: NK cells from *h/*y+B*57 carriers inhibited HIV replication in autologous infected CD4 T cells as well as those from 3DS1+*80I carriers (p>0.05) and better than those from Bw6hmz and *l/*x+B*57 positive subjects (p<0.05 for all comparisons Mann-Whitney test). Infected CD4 cells stimulated NK cells from *h/*y+B*57 and 3DS1+*80I carriers to produce higher levels of CC-chemokines than those from Bw6hmz (p<0.05). Intracellular cytokine staining of stimulated NK cells and NK subsets confirmed that NK cells were the source of CC-chemokines. A higher frequency of NK cells from carriers of *h/*y+B*57 than Bw6hmz secreted these CC-chemokines and in *h/*y+B*57 carriers more KIR3DL1+ than KIR3DL1- secreted these chemokines.

Conclusions: NK cells from carriers of *h/*y+B*57 inhibit HIV replication in autologous CD4 T cells more effectively than those from *l/*x+B*57 carriers and Bw6hmz. This suggests that NK cell education influences the potency of NK cell mediated inhibition of HIV replication. The inhibition of viral replication in autologous infected CD4 T cells involves responses by KIR3DL1 subset and is partially due to secretion of CC-chemokines.

274 Siglec-7 Binds HIV-1 GP120 and Facilitates Infection of CD4pos T Cells and Macrophages

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Background: Sialic acid-binding Ig-like lectin-7 (Siglec-7) expression is strongly reduced on natural killer (NK) cells from HIV-1 infected viremic patients. To investigate the mechanism(s) underlying this phenomenon, we hypothesized that Siglec-7 could directly interact with the HIV-1 envelope (Env) glycoprotein 120 (gp120), thus contributing to the infection of target cells.

Methodology: The binding of Siglec-7 fusion protein to HIV-1 GP 120 was detected by flow cytometry by using a protein-bead conjugation technology. The Siglec-7-induced rates of infection of CD4+ T cells and monocytes-derived macrophages (MDMs) were assessed by detecting HIV-RNA in cell supernatants and by HIV-1 entry assay. The amounts of soluble Siglec-7 (sSiglec-7) in HIV-1infected patients' sera were measured by ELISA.

Results: We found that Siglec-7 binds gp120 Env in a sialic acid-dependent manner. Pre-incubation of HIV-1 with sSiglec-7 increases the infection rate of CD4+ T cells, which do not constitutively express Siglec-7. Conversely, selective blockade of Siglec-7 markedly reduces the degree of HIV-1 infection in Siglec-7+ MDMs. Finally, the amount of sSiglec-7 is increased in the serum of AIDS patients compared to that of healthy donors and inversely correlates with CD4+ T cell counts.

Conclusions: Our results show that Siglec-7 binds HIV-1 and contributes to enhance the degree of infection of CD4+ T cells and MDMs. Indeed, our study demonstrates that Siglec-7 increases HIV-1 viral entry in CD4+/Siglec-7- T cells in its soluble form while it reduces infection in CD4+/Siglec-7+ MDMs if masked/blocked on cell surface. Together with our previous data showing a pathologic expansion of highly dysfunctional CD56-/Siglec-7- NK cells in AIDS patients also carrying higher levels of sSiglec-7 in their sera, our findings provide evidence that that this lectin-type molecule plays an important role in HIV-1 pathogenesis by being associated with an higher susceptibility of CD4+ target cells to be infected by HIV-1 and with disease progression. The disclosure of these novel insights suggest that Siglec-7 might serve as potential biomarker to monitor the clinical course of HIV-1 infection and can also represent a therapeutic target to inhibit viral replication/spreading thus limiting the depletion of CD4+ T cells.

275 Monocyte and NK Cell Dysfunctional Responses To Mycobacteria During Chronic HIV-1 Infection

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Background: Coinfection with M. tuberculosis (Mtb) and other Mycobacteria is a leading cause of morbidity and mortality in HIV+ patients. While neither monocytes nor NK cells are directly infected with HIV, several of their phenotypic and functional properties become altered during chronic infection, and both cell types are important to the control of Mtb. We hypothesized that HIV-related NK cell dysfunction may result from impaired monocyte dysfunction and impaired crosstalk with NK cells, which we will evaluate in the context of Mycobacteria infection.

Methodology: To assess monocyte cytokine production, whole blood from HIV+ ART-naïve patients and healthy donors was stimulated with Mycobacteria for 6 hours (in the presence of Brefeldin-A) and followed by intracellular cytokine staining. For cellular functional assays, cells were isolated from PBMC via maganetic bead isolations. Monocytes were infected with fluorescent (mCherry) BCG (opportunistic pathogen) or Mtb at MOI10 for 6 hours to assess phagocytosis. Autologous NK cells were utilized to assess cell killing.

Results: We observed a decrease in IL-12 ($p=0.017$), but similar TNF-alpha production, by blood monocytes from HIV+ individuals following a 6 hour stimulation with M. Bovis BCG (opportunistic pathogen), compared to uninfected donors. As IL-12 is known to regulate NK cell functionality, we were also interested in evaluating NK cell function in our cohort. While developing a flow-based functional assay to measure NK cell killing of autologous Mtb-infected monocytes, we found that NK cells from HIV+ donors exhibited decreased killing of target K562 cells compared to controls ($p=0.04$). Further evaluation established that monocytes from the same HIV+ patients in which we identified lower NK cell killing also exhibited decreased phagocytosis of fluorescently-labeled BCG ($p=0.016$) but similar phagocytosis of Mtb compared to uninfected donors.

Conclusions: Our data demonstrate a reduction in both monocyte and NK cell functionality in the same HIV-infected patients and is suggestive of synergism in the dysfunction of two innate cell types in our patients. The assays described have the potential to identify novel therapeutic targets to enhance innate (both monocyte and NK cell) cellular function in HIV-infected patients.

276 Identification of a New Isoform of MLL5: A Surrogate Marker of the CD4 Depletion in HIV-1

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Background: NKp44 is a unique member of the natural cytotoxicity receptor family, which is exclusively expressed on activated NK cells. We had previously shown that the cellular ligand of NKp44, called NKp44L, is specifically expressed on bystander non-infected CD4+ T cells during HIV infection. Thus, over the ensuring years, we showed that NKp44L expression is induced by a remarkably conserved motif of the HIV-1 gp41, and correlated to CD4 depletion, T cell-activation, inflammation and apoptosis. To better understand the relations between NKp44 and the HIV-pathophysiology, we undertook studies to identify and characterize its cellular ligand _ NKp44L. We report here that NKp44L is a new isoform of the mixed-lineage leukemia-5 (MLL5) gene.

Methodology: NKp44L has been cloned using the yeast 2-hybrid system, and then confirmed by immunoprecipitation with anti-MLL5 or anti-NKp44L Abs followed by immunoblotting with NKp44-Ig fusion protein. Expression of NKp44L was tested by Northern blot, immunofluorescence and flow-cytometry. Functional assays were performed using a standard 51Cr release assay.

Results: In an important advance, NKp44L, initially cloned by the yeast two-hybrid system and then confirmed in mammalian experiments, was proven to be a novel isoform of the human MLL5 gene, maps to chromosome 7q22 and characterized by a specific C-terminal motif implicated in its cell-surface translocation. Strikingly, this new protein called NKp44L is not detected on circulating cells isolated from healthy individuals, but it is expressed on CD4+ T cells from HIV-infected patients, and AIDS-associated tumor cell lines. The cell-surface translocation of NKp44L is mediated through a signaling cascade that involves sequential activation of PI3K, and NADPH oxidase, as well as TC10 inactivation Besides its cell-surface expression, NKp44L is expressed in the endoplasmic reticulum, but, unlike the other members of the MLL family, is excluded from the nucleus. In addition, we demonstrated that the blocking NK lysis efficacy anti-NKp44L antibodies is unrelated to the expression of class-I MHC molecules, but correlated with cell-surface expression of NKp44L on the target cells.

Conclusions: Altogether, these results provide clues to better understand the key role of NKp44L during the HIV immunopathogenesis and call for prompt investigation of the regulation of its expression.

277 Do KIR3DL1/HLA-B Combinations Influence ADCC Responses of HIV-1 Infected Slow Progressors?

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Background: The *h/*y+B*57 genotype, which encodes high expression Killer Immunoglobulin-like Receptor (KIR)3DL1 variants and HLA-B*57 is the KIR/HLA combination with the strongest effect on slowing time to AIDS and controlling HIV viral load, as compared to Bw6 homozygotes (Bw6hmz). The interaction of 3DL1 with HLA-B*57 is a potent natural killer (NK) cell licensing combination. NK cell licensing plays a role in the potency of antibody dependent cellular cytotoxicity (ADCC) activity.

The percentage of functional NK cells induced by HLAnull or autologous HIV-infected CD4 cells is higher when from *h/*y+B*57 carriers than from Bw6hmz or carriers of several other 3DL1hmz/HLA-Bw4 combinations. Using cells from HIV-infected slow progressors (SP) we investigated whether KIR3DL1/HLA genotypes that support licensing (3DL1+Bw4) generate NK cells with higher ADCC activity than those that do not (3DL1+Bw6hmz). Our hypothesis is that NK cells from HIV-infected SP mediate ADCC activity.

Methodology: We studied 48 3DL1hmz SP with plasma viral loads <3000 cells/mm3, including HLA-Bw4+ HLA-B*57- (n=34), HLA-Bw6hmz (n=12) and *h/*y+B*57 (n=6) carriers. Anti-HIV ADCC was measured using a GranToxiLux (GTL) assay, which assesses the ability of NK cells (effectors) to deliver granzyme B (GzB) to HIV gp120-coated CEM.NKr.CCR5 targets (%GzB+ cells) in the presence of a common pooled source of anti-HIV immunoglobulin G. The significance of between group differences was assessed using the Mann-Whitney test.

Results: NK cells from all HLA-Bw4+ and Bw6hmz 3DL1hmz mediated equivalent levels of ADCC (21.1 ± 13.9 vs 24.05 ± 20.7 %GrB cells+, p=0.87). NK cells from *h/*y+B*57 carriers also mediated similar levels of ADCC activity (20.7 ± 16.1) as those from Bw6hmz (p=0.96) and carriers of other Bw4 alleles (21.1 ± 13.8, p=0.85).

Conclusions: NK cells from HIV infected SP mediate ADCC. Carrying KIR/HLA combinations, that play a role in NK cell licensing through KIR3DL1 ligation, does not influence the potency of ADCC activity of NK cells from HIV-infected SP. These results contrast with previous studies by us and others using NK cells from uninfected individuals, where KIR3DL1/HLA-B genotype does appear to influence levels of ADCC activity. Further investigation will be needed to determine whether HIV infection even in this well controlled SP population abrogates the influence of licensing on NK mediated ADCC activity.

278 CD8+ NK Cells in HIV-1 Infection Are Associated With Slower Disease Progression Towards AIDS

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Background: NK cells are part of the innate immune system and provide one of the first lines of immune defense and its regulation. Although increasing evidence suggests a protective role of NK cells in HIV-1 infection the phenotypical and functional NK cell parameters correlating with a slower disease progression are currently poorly understood.

Methodology: A cohort of 117 untreated chronic HIV-1 infected subjects with CD4+ helper cell counts above >500/µl were longitudinally followed at our institution. We analyzed NK cells from 35 untreated, 25 treated HIV-patients and 15 healthy controls with flow cytometry. Analysis of the degranulation marker CD107a and cytokine production (IFN-γ, TNF-α, MIP-1β) were assessed after stimulation with IL-12, IL-15 and K562 cells. Statistical analyses included unpaired t test, One-way ANOVA followed by Tukey post test when comparing more than two groups, Kaplan Meier and Pearson analysis to identify correlations.

Results: High NK cell as well as CD8+/CD3- lymphocyte counts were associated with slower disease progression in a longitudinal analysis of untreated patients. In addition, we found a robust inverse correlation between frequencies of CD8+ NK cells with HIV viral loads and direct correlation with CD4+T cell counts as well as CD4/CD8 ratio. In a cross-sectional analysis we observed substantially reduced numbers of CD8+ NK cells in HIV-1 seropositive patients compared to healthy controls, which were partially restored after initiation of antiretroviral therapy. There were no significant phenotypic differences between CD8+ and CD8- NK cells for a number of markers, except for the CD57, which was higher among CD8+ NK cells. Further analysis of CD8+ NK cells revealed higher frequencies of granzyme B and perforin-expressing cells among CD8+ NK cells compared to CD8- NK cells. Degranulation capacity,

secretion of IFN-γ, TNF-α and MIP-1β were higher amongst CD8+ NK cells. Importantly, the frequency of polyfunctional CD8+ NK cells were higher in HIV-infected individuals with viral loads below 10,000 copies/ml compared to HIV-seronegative individuals. Notably, the lowest frequency of polyfunctional CD8+ NK cells was observed in HIV-infected individuals with viral loads above 10,000-copies/ml suggesting that viremia impacts the functionality of CD8+ NK cells.

Conclusions: We identified the frequency of highly functional CD8+ NK cells as a parameter for delayed disease progression towards AIDS in untreated HIV-1 infected patients. It is thus tempting to speculate that CD8+NK cells can play a prominent protective role in HIV infection.

Session P-C4 Poster Session
Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**
CD8 T-Cell Pathogenesis

279 HLA-B*35:05 Is a Protective Allele With a Unique Structure Amongst CRF01_AE-Infected Thais

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Background: About 1,500 of CTL epitopes including 250 best-defined epitopes and their restricting HLA allele data have accumulated in the Los Alamos database. However, most of these have been derived from subtype B-infected Caucasians, and from subtype C-infected Africans. Studies from south-east Asia, where about 1.5 million patients are living with HIV, and where about 90% of them are infected with subtype CRF01_AE, remain sparse. Although HLA-B*57 is a protective allele amongst Africans and Caucasians, its prevalence amongst Asians is lower than other ethnic groups.

Methodology: 1) 557 HIV-1 CRF01_AE-infected Thais were recruited, and their HLA type and viral load were determined to statistically analyze the association of each allele in viral control. 2) *In silico* molecular dynamics was used to evaluate the effect of HLA structure variants on epitope binding. 3) Recently HLA-B*35-restricted epitope Gag 253-262 NPPIPVGDIY, which D260E escape mutation causing HLA-epitope binding instability and consequent viral load increase, was reported. Sequence mutation at this site was statistically analyzed amongst HLA-B*35:05 positives and HLA-B*35:01 positives.

Results: HLA-B*35:05 was identified as the most protective allele (p=0.003, q=0.17), along with HLA-B*57:01 (p=0.044, q=0.31). Structurally HLA-B*35:05 belongs to PY, which has epitope binding motif of Pro (P) at HLA B pocket and Tyr (Y) at F pocket. However, unlike other HLA-B*35 alleles with Arg (R) at HLA residue 97, HLA-B*35:05 has unique sequences at Thr (T) at 94, Leu (L) at 95, and Ser (S) at 97, located at the peptide-binding groove. Analysis of 3D HLA structure and molecular dynamics showed that S97 in HLA-B*35:05 led to 1) less flexibility in the groove, and 2) shorter distances between the α-helixes compared to the other PY, HLA-B*35:01, suggesting fewer peptide variants will be able to bind to the groove, leading to induction of stronger virus-specific immunity by HLA-B*35:05. In the viral sequence at Gag 253-262 NY10, mutations were significantly identified amongst HLA-B*35:01 positives; p=0.0001 by Fisher's exact test at D260E, p=0.0025 at I261X, and p=0.019 at flanking N252X. However, there was no significant mutations amongst HLA-B*35:05 positives in this site.

Conclusions: Our data indicates the existence of a protective effect of HLA-B*57 across ethnic groups and highlights HLA-B*35:05 as an allele uniquely protective in subtype CRF01_AE-infected Thais, due to its divergence from conventional PY structural sequences at the peptide-binding groove. Identification of unique protective alleles in each endemic area provides the opportunity to better define the nature of HLA-mediated immune control and will be valuable for CTL vaccine development.

280 Eomes and T-Bet Are Differentially Linked To CD8+ T-Cell Exhaustion in HIV Infection

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Background: Loss of CD8+ T cell functionality (exhaustion) represents a major hallmark of chronic HIV infection. T cell exhaustion is generally considered as a consequence of several factors that drive T cells to senescence. However, a mechanistic explanation between the transcriptional regulation of CD8+ T cell differentiation and exhaustion remains elusive. Here we conducted a comprehensive multi-parametric study to elucidate whether two T-box transcription factors governing cytolytic T cell differentiation, T-bet and Eomesodermin (Eomes), were linked to exhaustion of human viral-specific CD8+ T cells.

Methodology: In this prospective study, 52 untreated chronically HIV infected individuals and 20 healthy controls were recruited from the HIV clinics at Karolinska University Hospital Huddinge and Stockholm South General Hospital. A total of 24 patients initiated ART and were followed longitudinally for 6 months. Peripheral blood mononuclear cells were collected and flow cytometry was used to assess immunological markers. The samples were acquired on a LSR Fortessa and data analysis was performed in FlowJo. Non-parametrical tests were performed using GraphPad Prism and SPICE.

Results: We provide evidence that an inverted relationship between T-bet and Eomes is closely linked to exhaustion of human memory and viral-specific CD8+ T cells. Single and co-expression of inhibitory receptors (PD-1, CD160 and 2B4) was thoroughly related to a transcriptional profile of EomeshiT-betdim memory CD8+ T cells. HIV infected subjects showed increased expression levels of PD-1, CD160 and 2B4 compared to healthy controls, which was closely linked to elevated expression of Eomes. Consistently, HIV-specific T cells were trapped within this transcriptional profile (EomeshiT-betdim),

while the anti-CMV CD8+ T cell response displayed a balanced expression pattern between T-bet and Eomes. Highly exhausted cells did not show any features of terminal differentiation, but rather a transitional memory phenotype with poor functional abilities for both HIV- and CMV-specific CD8+ T cells. Interestingly, a decay of the MFI of PD-1 and Eomes was related to each other longitudinally in HIV infected individuals initiating ART. However, in most individuals initiating ART, the HIV-specific CD8+ T cell repertoire still retained elevated frequencies of PD-1, CD160, 2B4 as well as Eomes, and lower T-bet expression.

Conclusions: The current data implicate that CD8+ T cell exhaustion is influenced by differential expression of T-bet and Eomes. This study supports the concept that poor viral-specific T cell functionality is not due to senescence, but rather an intermediate transcriptional profile that impedes the clearance or control of specific human chronic viral infections.

281 Increased Frequencies of HLA-G+ HIV-1-Specific Regulatory CD8 T Cells in HIV-1 Controllers

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Background: Regulatory T cells may influence HIV-1 disease progression by suppressing immune activation or inhibiting antiviral T cell immune responses. Recent data suggest that that the proportion of non-classical regulatory CD4 and CD8 T cells expressing HLA-G was inversely correlated with markers of HIV-1 associated immune activation, as opposed to non-classical regulatory T cells expressing the TGF-b latency-associated peptide (LAP). The role of non-classical regulatory T cell specific for HIV-1 is unknown.

Methodology: 31 HIV-1-specific and 19 CMV/EBV specific CD8 T cell responses were analyzed in 31 HIV-1 infected patients. 17 patients were chronic progressors with median HIV viral load 42500 copies/ml and median CD4 T cells count 456/µl. 14 patients were controllers with viremia below 1000 copies/ml and CD4 T cell counts above 900/µl. HLA-G and LAP expression on HIV-1 specific CD8 T cells was assessed by multimer staining and flow cytometry.

Results: The frequency of HLA-G+ HIV-1 specific ($p=0.015$), 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 ($p=0.05$), while no difference between controllers and chronic progressors was observed when CD8 T cells restricted by non-protective alleles were selectively analyzed. The proportion of HLA-G+ HIV-1-specific CD8 T cells was directly associated with CD4 T cell counts ($p=0.0083$, $r=0.48$), but not with viral loads. In contrast, LAP+ HIV-1-specific CD8 T cells were reduced in frequency in controllers in comparison to chronic progressors and their frequency was directly associated with viral loads ($p=0.0006$, $r=0.61$) and inversely associated with CD4 T cell counts ($p=0.024$, $r=-0.4$).

Conclusions: These data indicate a potentially protective role of HIV-specific HLA-G+ regulatory CD8 T cells on HIV-1 disease progression. Further investigations of functional properties of these antigen-specific, non-classical regulatory CD8 T cells are necessary in order to better elucidate their role in HIV immunopathogenesis.

282 CD8+CD28-CD127^{lo}CD39+ Treg: A New Biomarker for HIV Infection

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Background: The phenotype of non-antigen specific CD8+ T regulatory lymphocytes (Treg) has been recently characterized as CD8+CD28-CD127^{lo}CD39+. In order to study the in vivo compartmentalization of this newly recognized Treg subset, we analyzed its frequency in the peripheral blood of patients (pts) affected by cancer and HIV infection, characterized by an abnormal expansion of regulatory circuits and immunodeficiency, in comparison with healthy subjects (HS).

Methodology: We analyzed these cells with FACSCanto II flow cytometer in HS, in pts affected with cancer and in HIV infected pts subdivided in elite controllers (EC) with CD4+T cells $\geq 400/mm^3$ and persistent HIVRNA ≤ 50 cp/ml without antiretroviral therapy (ART); long term non progressor (LTNP) with CD4+ T cells $\geq 400/mm^3$ and HIVRNA > 50 and < 1000 cp/ml without ART and progressor (HIVRNA ≤ 50 copies/ml treated with at least 2 ART regimens). Statistically significant differences between frequencies were assessed using the Fisher's exact test for binary variables, while statistically significant differences between means were analyzed with the Mann-Whitney test for non-parametric values.

Results: We included 24 HS, 34 pts with cancer subdivided in renal (N=17), bladder (N=16) or colorectal (N=1), 8 EC, 5 LTNP and 20 progressor The CD8+CD28-CD127^{lo}CD39+ T reg were detected in 1/24 (4%) of HS and the frequency was very low (0.1%). The analysis of the frequency of CD8+CD28-CD127^{lo}CD39+ Treg in the surgical tumor specimens showed that these cells were present in 30 out of 34 (88%) total tumors with comparable frequencies between renal and bladder cancers. While these cells were rare in EC and LTNP (2/13 patients [15%]), they were present with high frequency in 95% of progressors ($p= 0.0001$).

Conclusions: These data show the existence of a T cell subpopulation, CD8+CD28-CD127^{lo}CD39+ Treg, that is substantially unrepresented in the circulation of healthy subjects, but that circulates in the peripheral blood of cancer or HIV-infected patients. This finding configures CD8+CD28-CD127^{lo}CD39+ Treg as an optimal biomarker for diagnostic/prognostic or follow-up purposes in diseases characterized by an abnormal predominance of regulatory circuits, as cancer and HIV infection.

Session P-C5 Poster Session
Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Exhaustion Markers

283 Determinants of PD-1 Expression On CD4+ and CD8+ T Cells in Treated and Untreated HIV Disease

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Background: Expression of programmed death 1 (PD-1) is upregulated on CD4+ and CD8+ T cells in untreated HIV infection, resulting in decreased proliferation and function. The impact of antiretroviral treatment (ART) and the determinants of PD-1 expression in CD4+ and CD8+ T cells are not fully understood.

Methodology: We assessed T cell expression of PD-1 longitudinally in a cohort of acutely infected HIV+ individuals who started ART early (6 months) vs. late (2 years after infection) and cross-sectionally in a diverse cohort of chronically HIV-infected adults, including elite controllers and long-term immunologic non-responders (INRs; individuals who failed to achieve a CD4+ T cell count >350 cells/mm3 on long-term ART). PD-1 MFI was measured by flow cytometry on total CD4+ and CD8+ T cells and T cell subsets. Longitudinal mixed effects regression modeling was done to assess the impact of ART and other factors on PD-1 expression.

Results: In the longitudinal cohort (n=121), PD-1 expression increased an average of 6.4% and 7.9% each year without ART on CD4+ and CD8+ T cells, respectively. Early ART initiation resulted in a rapid decline in PD-1 expression on CD8+ T cells (41% after one year of ART, $P < 0.001$); similar results were observed in CD4+ T cells. Delayed ART resulted in a similar decline in PD-1 expression. In the cross-sectional cohort (n=206), PD-1 expression remained high in INRs (median MFI of 218 vs. 130 in responders vs. NRs, $P < 0.001$). This effect was seen in all T cell memory subsets. Compared to HIV-uninfected, elite controllers had similar PD-1 expression on both total CD4+ and CD8+ T cells, while viremic controllers had higher PD-1 on effector memory CD8+ T cells ($P = 0.03$). Amongst all ART suppressed subjects in both cohorts, PD-1 expression on CD4+ T cells was strongly associated with CD4+ T cell activation ($\rho = 0.53$, $P < 0.001$) and inversely with CD4 count ($\rho = -0.50$, $P < 0.001$). In contrast, PD-1 expression on CD8+ T cells was most strongly associated with CD8+ T cell activation and plasma viral load in viremic subjects (CD8+ T cell activation: $\rho = 0.60$, $P < 0.001$; VL: $\rho = 0.30$, $P = 0.01$).

Conclusions: PD-1 expression on CD4+ T cells is strongly associated with peripheral CD4+ T cell count and frequency of activated CD4+ T cells, while PD-1 expression on CD8+ T cells is associated with viremia and CD8+ T cell activation. Effective ART reduces PD-1 on both populations. Multiple mechanisms may account for the CD4+ T cell observations, including a potential role of homeostatic signals such as IL-7 causing proliferation and PD-1 expression. Prospective studies of anti-PD-1 antibody therapy will be needed to define whether PD-1 expression on CD4+ T cells is a cause or consequence of CD4+ T cell lymphopenia. Antigen-driven activation likely accounts for PD-1 expression on CD8+ T cells.

284 CD160 Is the Most Specific Co-Inhibitory Molecule Associated With CD8 T Cell Functional Impairment

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Background: Co-inhibitory molecules are commonly associated with T-cell dysfunction in the context of chronic viral infections such as HIV or HCV, however, their relative contribution in T-cell impairment remains unclear.

Methodology: In the present study, we evaluated the influence of expression of co-inhibitory molecules *i.e.* 2B4, PD-1 and CD160 on CD8 T-cell functions using the prototypic models of cleared (Flu) and persistent (EBV, CMV) virus infections.

Results: We hereby show that $2B4^+CD160^+PD\text{-}1^+$ and $2B4^+CD160^+PD\text{-}1^-$ CD8 T-cell populations are endowed with a reduced capacity to proliferate, produce IL-2 and IFN-γ, associated with a reduced capacity to express perforin, demonstrating that $CD160^+$ CD8 T cells are functionally impaired, independently of PD-1 expression. In addition, the blockade of CD160/CD160-ligand interaction restored CD8 T-cell proliferative capacity and the level of CD8 T-cell proliferative restoration directly correlated with the *ex vivo* proportion of CD160 expression, demonstrating that CD160 signaling negatively regulates TCR-mediated CD8 T-cell signaling. Finally, in contrast to PD-1, CD160 expression was not up-regulated upon T-cell activation or proliferation.

Conclusions: Taken together, this study demonstrates that CD160 is the most specific co-inhibitory molecule associated with CD8 T-cell dysfunctions.

285 Expansion of TIGIT-Expressing CD8+ T Cells Persists in Virally Suppressed HIV-1 Infection

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Background: HIV-1 infection induces a series of phenotypic and functional changes to T cells that eventually results in a state of T cell exhaustion. This immune dysfunction is defined by coordinate upregulation of negative immune checkpoints such as TIM-3 and PD-1. A detailed understanding of immune regulation of effector CD8+ T cells afford novel therapeutic strategies to halt or reverse HIV-1 progression and persistent inflammation. T-cell-Ig-and-ITIM-domain (TIGIT) is a putative checkpoint blocker that upon engagement with its cognate ligand inhibits T cell function. The role of TIGIT in T cell exhaustion during HIV-1 disease progression remains uncharacterized.

Methodology: We assessed gene and surface expression of TIGIT, Tim-3, and PD-1 on CD8 T cells derived from 60 HIV+ subjects [non-controllers (n=20), elite controllers (n=20) antiretroviral (ART) suppressed (n=20)] and 20 demographically matched HIV-1 uninfected adults in the SCOPE cohort study of well-characterized contemporary HIV-1 infected patients in San Francisco. Cryopreserved peripheral blood mononuclear cells (PBMCs) were phenotyped by multiparametric flow cytometry technology for TIGIT, Tim-3, and PD-1 expression, T cell differentiation, and in vitro T cell functional characteristics in response to anti-CD3 and anti-CD28 dynabead stimulation. RNA was isolated from PMBCs and relative gene expression was measured by real-time RT-PCR to determine gene transcription. Nonparametric Mann-Whitney Statistical t-Test were used.

Results: The expression of TIGIT on CD8+ T cells was highest in non-controllers (67.2%), intermediate in controllers (58.9%) and those on ART (49.2%) and lowest in HIV-1 uninfected (33.4%) (p=0.0001, p=0.0002,p=0.0015 for comparisons of non-controllers, controllers and those on ART with HIV-1 uninfected, respectively). In contrast to PD-1 and TIM-3, the majority of TIGIT was highly expressed on effector memory (CD45RA+CD28-) CD8+ T cells. TIGIT mRNA relative expression levels were similarly elevated in non-controllers, controllers, and those on ART, compared to HIV-1 uninfected subjects. In response to polyclonal stimulation, most of the IFN-γ responses were from TIGIT- CD8+ T cells (TIGIT- IFN-γ + 2.06% (0.91,5.8) vs. TIGIT+ IFN-γ + 0.49% (0.16,0.75); p=0.035).

Conclusions: TIGIT is highly expressed on effector CD8 T cells, is actively transcribed and associated with reduced T cell function. These potentially dysfunctional cells persist during ART, suggesting that reversal of this pathway may be necessary during curative interventions.

286 PD-1 Expression Is Associated With Preserved CD4+ T Cell Homeostasis in Viremic Non-Progressors

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Background: Viremic non-progressors (VNPs) are a rare group of ART-naïve, HIV-infected individuals that remain asymptomatic with normal CD4+ T cell counts for >10 years despite high-level viremia, similar to natural hosts of SIV infection. Like natural SIV hosts, VNPs also maintain very low levels of central memory CD4+ T cell (TCM) infection, but the effects of immunologic characteristics of this rare clinical phenotype are unknown.

Methodology: VNPs (n=9) were defined as: ART-naïve, HIV duration >10 years, CD4+ T cell counts stably >500 cells/mm3 (and CD4% >15%), plasma HIV RNA levels (VL) stably > 104 copies/ml, and absence of AIDS-defining illness. We compared them to recently HIV-infected participants (< 2 years post-infection) with similar CD4+ T cell counts and VL who were expected to progress at a typical rate ("putative progressors", n=110), untreated HIV-infected progressors with similar VL, but CD4+ T cell counts <500 cells/mm3 (n=26), and HIV-uninfected controls (n=24). We compared T cell activation (CD38+HLA-DR+), maturation (CCR7, CD45RA), PD-1 expression, and HIV-specific functional responses between groups.

Results: VNPs were known to be HIV infected for a median of at least 22 years, and had higher median CD4+ T cell counts than both putative and chronic progressors (723 vs. 560 and 381, $p \leq 0.004$), but also much higher CD8+ T cell counts (1737 vs. 859 and 986, $p \leq 0.001$). VNPs had higher proportions of activated CD4+ and CD8+ T cells compared with HIV-uninfected controls (14% vs. 2% and 52% vs. 9%, $p \leq 0.001$), comparable to putative and chronic progressors. The proportion of CD4+ T cells expressing PD-1 was higher in VNPs than putative progressors (24% vs. 16%, $p = 0.006$), driven by higher proportions of PD-1 expressing CD4+ TCM (CCR7-CD45RA+, $p = 0.006$) and TEM subsets (CCR7-CD45RA-, $p = 0.01$). Furthermore, in VNPs, the proportion of CD4+ T cells expressing PD-1 was associated with higher CD4+ T cell counts ($r = 0.78$, $p = 0.02$), while the opposite association was observed in chronic progressors ($r = -0.62$, $p = 0.006$). Despite a high proportion of CD4+ T cells expressing PD-1, VNPs had higher Gag-specific CD4+ T cell responses than putative progressors (TNFα+, $p = 0.007$). VNPs had lower proportions of PD-1 expressing CD8+ T cells than chronic progressors ($p \leq 0.05$), and higher Gag-specific CD8+ T cell responses than putative and chronic progressors (TNFα+, $p \leq 0.05$).

Conclusions: Despite maintaining normal CD4+ T cell counts and low levels of CD4+ TCM infection, VNPs have abnormally high T cell activation and CD4+ TCM PD-1 expression. This may suggest that sustained proliferation without productive infection of TCM may contribute to the VNP phenotype. Regardless of the mechanism, the immunology of VNP in humans appears fundamentally distinct from that in natural hosts of SIV.

287 PD-1 Homolog Expression Regulates Spontaneous Cytokine Production in HIV Infection

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Background: Programmed death-1, is upregulated on immune cells in HIV infection and is considered to be a phenotypic marker for functional T cell exhaustion and immune dysfunction. Recently, another related, but distinct ligand PD-1H with a broad hematopoietic lineage distribution has been identified in mice. In this study we sought to examine the expression pattern and functional impact of the human orthologue of PD-1H on hematopoietic cells from normal and HIV infected individuals.

Methodology: PD-1H expression was determined by qPCR analysis of purified monocytes, T cells and B cells from PBMCs isolated from normal donors or HIV infected patients. FACS was done on PBMCs for PD-1H alongwith antibodies to identify monocytes, T cells and B cells. To study functional effects in monocytes, PD-1H-expressing or control plasmids were introduced by nucleofection. Cytokine levels were determined by cytometric bead array or ELISA. qPCR was used to determine the mRNA levels of IL-6, IL-1β and TNF-α. PBMCs from HIV infected subjects were co-stained for PD-1H and T cell activation markers. Effect of PD-1H overexpression or ablation on APC function of monocytes was determined by measuring HIV-gag-specific IFN-gamma response by ELISA.

Results: In normal donor PBMCs, highest expression of PD-1H was seen on monocytes followed by T lymphocytes and then B cells. Upon nucleofection, PD-1H in normal human monocyte/macrophages induced spontaneous secretion of multiple cytokines like IL-6 IL-8, IL-1β and TNF-α. The effect was abrogated with PD-1H silencing using specific siRNA. Signaling was required as deletion of cytoplasmic domain abolished the spontaneous cytokine secretion. In HIV infected patients, PD-1H expression was also found to be highest on monocytes and expression levels were significantly higher than in normal monocytes. Further, activated monocytes expressed higher levels of PD-1H than classic or non-classic subset. PD-1H expression correlated highly with cytokine mRNA expression in monocytes and with expression of immune activation markers CD38 and PD-1 expression on both CD4 and CD8 T cells. Overexpression of PD-1H expression on monocytes enhanced their ability to induce IFN-γ secretion by HIV-specific T cells whereas silencing the molecule abrogated the effect.

Conclusions: PD-1H might play a pathogenic role in HIV-induced immune activation and thus provides a potentially new target for therapeutic intervention.

Session P-C6 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Clades and Pathogenesis

288 HIV Virulence Has Not Increased in the UK Subtype B Epidemic

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Background: The question of whether HIV is evolving and perhaps becoming more virulent has received considerable attention. Two recent meta-analyses have estimated an increase in set-point viral load (spVL), a predictor of disease progression, of 0.044 log10 copies/mL/year and 0.013 log10 copies/mL/year, interpreted by both studies as an increase in virulence that could be caused by viral factors. This would require that the viral genome exerted substantial influence over the spVL, i.e. spVL having high heritability. Previously we estimated this to be only 5% in the UK subtype B epidemic.

Change in spVL over time could be influenced by selection. Transmission and extinction events, on the lineage down which spVL is evolving, exert between-lineage selection, and within-lineage selection occurs at the individual level, as spVL is correlated with probability of transmission. Here we implemented quantitative genetics methods to estimate change in spVL due to between- and within-lineage selection on the viral genome.

Methodology: 8,483 pre-ART subtype B sequences with corresponding spVL were analysed. A phylogenetic tree was reconstructed from the resistance-site stripped sequences in RAxML. The phylogeny and spVL were fitted in a mixed-model with age, sex, ethnicity, time since diagnosis, and year of diagnosis as fixed effects and year of diagnosis and country of origin as random effects.

Within-lineage change can be estimated from longitudinal data by adding sequence sample date as a covariate in the model. Between-lineage selection can be estimated by looking at the difference in predicted genotypic potential ("breeding value") over time. We used Markov chain Monte Carlo methods to obtain a posterior distribution of evolutionary change by averaging over uncertainty in the estimates. To determine whether any change that has occurred is greater than would be expected by chance (drift), we used posterior predictive tests.

Results: We estimated a small change in spVL due to between-lineage selection of 0.002 log10 copies/mL/year, which this was not significantly different from what could be expected due to drift. Our estimate of the change in spVL due to within-lineage selection and environmental effects was small but significant at -0.05 log10 copies/mL/year.

Conclusions: Our estimate of the change in spVL over time, although small, is significant but negative. This is based on the first direct estimate of the viral contribution to spVL across an epidemic and gives no support to the view that virulence in HIV is increasing. However, we previously showed that most of the phenotypic value of spVL in our model is determined by fixed effects (age, sex, time to diagnosis, etc.) which themselves have changed over the epidemic and propose this is a more probable source of the observed change.

289 Subjects Infected With Clade C-Containing HIV Exhibit Higher CD4+ T Cell Activation

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Background: Cellular activation has been implicated in the progressive immunodeficiency and the development of end-organ disease in HIV-1 infection. Recent studies have shown that HIV subtypes may differ in loss of CD4+ T cells and viral load over time. Genetic differences in LTR, Nef, Tat, and Vpu may play important roles in HIV transmission and immunopathogenesis, and may differ in HIV strains from clade C vs. those from other clades. We hypothesized that individuals infected by clade C (or C-containing recombinant strains) would have different cell activation status than non-C containing HIV-infected subjects.

Methodology: Sixty-three Brazilian subjects recently infected by HIV were studied and divided into two groups: a "C" Group (n=20) included those with clade-C-containing virus (subtypes C, BC, CU, CK, CRF_31BC, CRF31-like, CRF40-like, and Complex), and a "non-C" group (n=43) infected by subtypes B, BF, BF1, F1, and CRF02 AG. From each subject, peripheral blood mononuclear cells (PBMC) were analyzed from acute infection (<3-6 months) and after virologic set point (approximately six months later), prior to ART. Samples were analyzed to characterize T cell activation and maturation markers (CD38, HLA-DR, CD27, CD45RA, and CCR7) using multiparametric flow cytometry

Results: HIV viral load, CD4+ T cell count and activation (percentage CD38+ HLA-DR+ expression in total CD4+ T cells) were similar between C and non-C groups during acute infection. In the C group, but not in the non-C group, CD4+ activation increased substantially between acute infection and set point. At the set point (follow-up) visit, CD4+ T cell activation was statistically significantly higher in the C group in T cell subsets including naïve (CD45RA+ CD27+CCR7+) (p=0.005), central memory (CD45RA-CD27+CCR7+) (p=0.003), effector t. (CD45RA+CD27-CCR7-) (p=0.002), and effector memory (CD45RA-CCR7-CD27-) (p=0.005) subsets. In multivariate models, differences in CD4+ CD38+HLA-DR+ expression remained statistically significant after controlling for baseline CD4+ and HIV viral load, gender, and transmission route/risk group

Conclusions: Infection with clade-C-containing HIV-1 strains circulating in Brazil effect was associated with higher levels of T cell activation than infection with non-C containing HIV-1, which emerged shortly following acute infection. This effect was independent of CD4+ T cell counts, HIV viral load, sex and infection route. These finding may have implications for how subtype C causes HIV disease progression, end-organ disease and HIV transmission.

Session P-C7 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Correlative Marker Studies

290 Telomere Length Predicts Immunological Recovery in Older HIV Patients Treated With cART

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Background: Successful cART does not always recover CD4 T-cells despite the effective control of HIV-1 replication. Telomeres are DNA-protein structures essential to chromosomal stability and replication. Telomere length (TL) is probably regulated by oxidative stress. Because little is known about the impact of TL on the immunorecovery we evaluated the relationship between TL and immunorecovery at 48 weeks after cART initiation in patients virologically suppressed.

Methodology: CoRIS is an open, prospective, multi-centre cohort of HIV-positive subjects. We selected those on stable cART who achieved a VL<50 cop/mL after 48 weeks of their first cART. Immunorecovery was defined as an increase in CD4+ counts >100 cells/mL compared to baseline. Leukocyte TL was measured using a quantitative PCR technique and categorized into tertiles (<0.13 for the lowest, 0.13-0.27 for the middle and >0.27 for the highest tertile). Nitric oxide levels were quantified by determining nitrate/nitrite and S-nitroso compounds using an ozone chemiluminescence-based assay. Lipid peroxidation was measured by quantitation of thiobarbituric acid reactive substances. Multivariate logistic regression models were used to estimate odds ratios (OR) and its 95% confidence intervals (CI) for association between TL and the odds of achieving immunorecovery adjusting for sex, age at cART initiation (years) (<50 and ≥50) and CD4+ count at start of cART (cells/ml) (<200, ≥200). Additional adjustment for nitrosative and oxidative stress was also carried out. We assessed whether this association was different in patients aged <50 and ≥50 years at cART initiation by including interaction terms into models.

Results: Of 132 patients included, 86% were male and 81% <50 years at cART initiation. We failed to find an association between TL, and immunorecovery overall (p = 0.47) but found an interaction between TL and age at cART initiation (p = 0.008): while no association was seen in patients <50 years (p = 0.18), in those ≥50 the odds of achieving immunorecovery decreased with decreasing tertiles of TL (OR [95% CI] for middle and lowest tertiles was 0.50 [0.05-4.84] and 0.13 [0.03-0.63], respectively). Additional adjustment for nitrosative and oxidative stress did not change results.

Conclusions: Short TL in HIV-infected patients ≥50 is related to a lower immunorecovery in spite of the successful virological control.

291 The Clinical Impact of Viral Load Copy Years in Antiretroviral-Naïve HIV Seroconverters

Matthias an der Heiden[1], Alexander Zoufaly[2], Caroline Sabin[3], Jan van Lunzen[4], Hans-Jürgen Stellbrink[5], Barbara Gunsenheimer-Bartmeyer[1], Philippe Vanhems[6], Santiago Perez-Hoyos[7], Geneviève Chêne[8], Osamah Hamouda[1], on behalf of CASCADE Collaboration in EuroCoord
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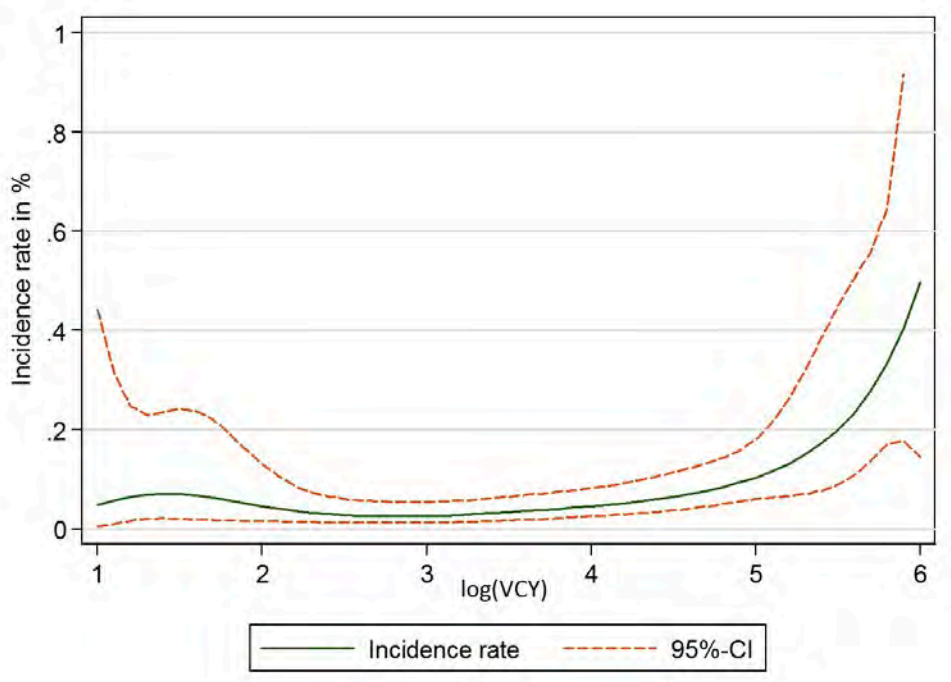
Background: Ongoing viral replication may contribute to immune activation which may have deleterious effects additional to CD4 loss before antiretroviral therapy (ART) is started. A measure of the cumulative exposure to HIV replication (viral load copy years, VCY) may therefore add important prognostic information in chronic HIV infection.

Methodology: Data from CASCADE, a cohort collaboration of HIV-1 seroconverters, were used. All ART-naïve patients >15 years with seroconversion (SC) dates after 1997, who had viral load (VL) and CD4 measured within 4-12 months following SC were included. Patient follow-up began 4 months after SC and was censored at earliest of ART start, CD4 <200 cells/µl, or when there were no VL and CD4 measurements for >12 months. VCY was approximated by the time-updated product of VL and the duration to the next VL measurement. A multivariable Poisson model with outcome clinical AIDS or death was constructed including age at SC as a continuous variable and sex, risk group, current CD4 count and VL, and VCY as categorical variables. To understand the qualitative impact of VCY better, we also used B-splines to model VCY continuously.

Results: Of 5770 patients with 13,330 years of follow-up, 110 (2%) acquired AIDS or died, 2351 (59%) started ART and CD4 count dropped below 200 cell/µl in 160 patients. In the adjusted Poisson model, older age (rate ratio 1.04 per year [95% confidence interval 1.02-1.06]), injection drug use (2.76 [1.25-6.10]) and having a CD4 count of 200-350 cells/µl (rate ratio 1.93 [1.16-3.23]) compared to 500-1000 cells/µl were associated with a higher rate of clinical AIDS or death. Compared to VCY category 20,000-50,000 copies×y/mL, rates of clinical AIDS/death were higher for those with VCY 100,000-200,000 copies×y/mL (2.4 [1.1-5.2]) and >200,000 copies×y/mL (4.9 [2.3-10.1]). Modelling log10(VCY) continuously using B-splines in the otherwise unchanged Poisson model is depicted in Figure 1 for 25 year old males with a CD4 count of 350-500 cells/µl and current VL > 60,000 copies/mL.



Conclusions: VCY appears to provide prognostic information on the risk of clinical AIDS/death additional to current VL and CD4 in naive patients. Choice on when to start ART may also be influenced by the duration and extent of previous HIV replication.

292 Interleukin-32: Expression, Interaction With IFN, and Clinical Significance in HIV-1 Infection

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Background: Given the growing evidence for a role of interleukin-32 (IL-32) in the immune response to HIV-1 infection, and its interplay with type I and III interferons (IFNs), we studied the gene expression of IL-32 isoforms (α and nonα) in untreated chronically HIV-1-infected patients and in gender- and age-matched healthy individuals. To further characterize both the anti-HIV properties of IL-32 and the cytokine's relationship with host antiviral innate immune responses, we evaluated whether IL-32 can induce ex vivo the expression of antiviral IFN-induced genes (ISGs), namely Myxovirus resistance A (MxA), and apolipoprotein B mRNA-editing enzyme-catalytic (APOBEC)3G and APOBEC3F. We also investigated whether in vivo IL-32 isoform levels were correlated with those of MxA and APOBEC3G/3F. Furthermore, since the activity of IL-32 is regulated by microRNA29b, we evaluated the relationship between IL-32 levels and microRNA29b expression.

Methodology: PBMCs from 98 HIV-1 subtype B -infected patients, naïve for antiretroviral treatment, attending the Policlinico Umberto I Hospital in Rome over the seven year period 2005-2012 were included in this study. The CD4+ T cell count was between 83 and 1,300 cells/mm3; the plasma viral load ranged from 300 to 1,805,000 HIV-RNA copies/ml. Blood samples from 36 healthy individuals were also included in this study. Expression of IL-32 subtypes was evaluated using RT-Real Time PCR. Comparison of quantitative values were assessed by Mann Whitney test, and Sperman correlation using SPSS 17 Software.

Results: Results indicated that mRNA levels of both IL-32α and IL-32nonα were significantly higher in chronically HIV-1-infected patients than those measured in the control group. We observed a significant negative correlation between the gene expression of IL-32 isoforms (α and nonα) and HIV-RNA levels measured in plasma but not with the CD4+ T cell count. Our ex vivo studies disclosed that ISGs mRNA levels were significantly increased after IL-32 treatment of PBMCs . Interestingly, our results indicated significant positive correlations between transcript levels of IL-32 subtypes and those of MxA , APOBEC3G and APOBEC3F measured in PBMC collected from HIV-1-infected patients. In contrast we failed to detect any significant association between levels of IL-32 subtypes and microRNA29b expression.

Conclusions: Overall our results demonstrated that IL-32 isoforms are highly expressed during chronic HIV-1 infection and that IL-32 through the induction of IFN stimulated genes and host restriction factors could have a central role in the antiviral immune response against HIV-1.

293 TNFα in Viral Control and Early Disease Progression in Patients With HIV-1 Infection

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Background: Inflammatory biomarkers are associated with increased morbidity/mortality in chronic HIV-1 infection, however, their role in early HIV-1 disease is poorly understood. We hypothesized that inflammatory biomarkers in early infection are associated with the subsequent viral load set point (VLSP) and the time to reach early clinical measures of HIV-1 disease progression.

Methodology: A longitudinal retrospective analysis was conducted of 90 patients with untreated primary HIV-1. VLSP was determined for all study subjects during the first year post-infection and their plasma was tested for TNFα, IL-6, CRP, D-dimer, IL-1β, and IFNγ. Primary endpoints were VLSP and days to $CD4^+$ T cell count <500 cells/mm^3, secondary endpoints were days to $CD4^+$ T cell count <350 cells/mm^3 and days to antiretroviral therapy(ART) start.

Results: Only TNFα was significantly correlated with VLSP (R=0.48, p<0.0001, Spearman-rank) and $CD4^+$ T cell count (p=0.046, Mann-Whitney). Log rank analysis separating the groups by mean TNFα (≥8.5 pg/mL) showed significant difference for days to $CD4^+$ T cell count <500 cells/mm^3 (p=0.006, median days to endpoint of 208 versus 1218 in the high and low TNFα groups, respectively) and for days to ART start (p=0.049, median days to endpoint of 439 versus 1057 in the high and low TNFα groups, respectively). Cox proportional hazard ratios for days to $CD4^+$ T cell count <500 cells/mm^3 in the high versus low TNFα groups were 3.1 in univariate analysis (CI 1.3-7.1, p=0.008), 1.9 (CI 0.8-4.7, p=0.15) when adjusted for concurrent viral load, and 5.1 (CI 1.9-13.5, p=0.001) when adjusted for concurrent $CD4^+$ T cell count.

Conclusions: High plasma levels of TNFα in early HIV-1 infection are associated with poorer viral control as well as decreased time to reach $CD4^+$ T cell count <500 cells/mm^3 and initiation of ART in our cohort. This finding was independent of concurrent $CD4^+$ T cell count and therefore may be relevant for identification of patients at higher risk of early HIV-1 disease progression.

294 Monocyte Activation Markers in HIV Infected Subjects: A Biomarker for HIV Immunotherapy

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Background: Immune activation persists among treated HIV infected individuals and is associated with suboptimal CD4+ T cell recovery and excess morbidity and mortality. Activation of both adaptive (T cells) and innate immune systems are known to be pathogenic in treated HIV disease. This chronic inflammation may also impact outcomes of immune-modulatory and gene-modified cell therapies. In order to better define the optimal host environment for cure-related gene therapy studies, we explored the impact of well-controlled HIV infection on the phenotype and activation of monocytes.

Methodology: Peripheral blood mononuclear cells (PBMCs) collected from fifteen ART controlled aviremic HIV infected subjects (age range = 22-56, CD4 count range = 506-1656) and fifteen HIV negative subjects (age range = 19-54) were evaluated. Markers associated with T-cell activation (HLA-DR, CD40, and CD86) were assessed on three monocyte subsets (CD14hi, CD16-; CD14+, CD16+; and CD14+, CD163+).

Results: Statistically significant greater levels of activation, as defined by expression of HLA-DR, CD40 and CD86 molecules, were observed on monocytes from HIV infected subjects despite long term control of viral load. For the CD14hi, CD16- subset, the mean percent of activated monocytes, as defined by the co-expression of HLA-DR, CD40 and CD86, was 43% (95% CI = 33-54%) and 25% (95% = CI 16-33%) for the HIV infected group and HIV negative group respectively (p = 0.008). Similarly, the level of monocyte activation in the CD14+, CD16+ (Fc γreceptor) monocyte subset was higher in the HIV infected group, 66% (95% CI = 57-75%) versus 39% (95% CI = 30-48%) in the HIV negative group (p = 0.0001). The HIV infected group significantly express a higher level of CD163 (scavenger receptor) (p < 0.0001), another marker of monocyte /macrophage activation. The expression levels of all activation markers (by mean fluorescent intensity) were higher in all monocyte subsets in the HIV infected group.

Conclusions: Even among an optimally treated group of HIV-infected adults (as defined by viral load and high CD4+ T cell counts), HIV infected subjects showed elevated expression level of the immune activation markers in multiple monocyte subsets, as compared to HIV negative individuals. We have previously found that monocyte activation (as defined by co-expression of HLA-DR, CD40, CD86) predicted poor long term CD4 reconstitution (r = -0.75; p = 0.03) in immunologic non-responders after infusion of SB-728-T (autologous ZFN mediated CCR5 gene disrupted CD4+ T cells). These results should provide guidance for identifying HIV infected individuals who may have a more intact immune system and thus more suitable for HIV immunotherapy.

295 Down-Regulation of CD39/CD73 On B Cells of HIV Patients Coincides With a Disturbed Ig Class Switch

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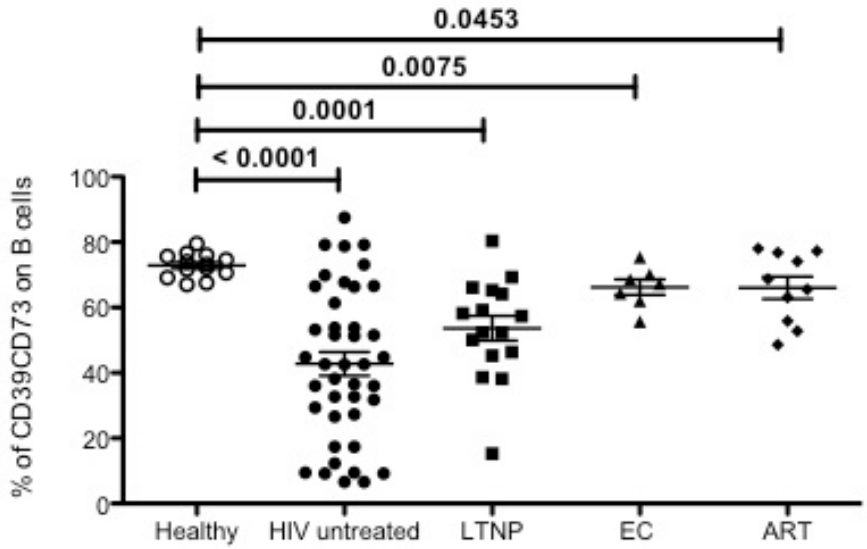
Background: So far, the antibody independent role of B-cells in HIV infection has not sufficiently been characterized. Recently, it has been described that down-regulation of CD73 on B cells in CVID patients correlates with a defective Ig-switch (F. Schena et al Cell Reports 2013). Here, we investigate the surface expression of two ectonucleotidases, CD39 and CD73, of different B cell subpopulations in HIV infection with regards to their class-switch properties.

Methodology: Peripheral (n=52) and lymph nodal B cells (n=10) of HIV infected patients at different stages of disease as well as uninfected controls (n=14) were analyzed via multi-color flow cytometry for their differentiation- (CD19, CD20, CD21, CD27, IgG, IgM, CD39, CD73 and CD26), activation and

exhaustion status (CD38 CD86, PD-1, Ki-67). Furthermore, functional assays were performed with these B cells to assess the cytokine pattern (IL4, IL10, IL13). Then, we compared these data with clinical parameters as well as plasma IgG1-4 and IgM levels.

Results: Overall, we find high expression of CD39 and CD73 on B cells of healthy controls. HIV Elite controller patients display comparable CD39 and CD73 expression on their B cells to healthy controls, while chronic untreated HIV patients show a significant down-regulation of both enzymes (p=<0.0001). Subanalysis of naive and memory B cell subsets revealed, that CD39/CD73 down-regulation can be observed in every naive/memory subset, apart from the IgM memory subset. CD39 and CD73 expression partly recovered after initiation of ART. We find significantly increased IgM expression (untreated p= 0,0001, ART p=0,0231) in both ART and viremic patients compared to healthy controls. However, in ART patients we observed a significantly higher expression of IgG compared to viremic patients as well as healthy controls (p=0,0014) indicating class-switch recovery.



Conclusions: : Untreated, viremic HIV patients with impaired class-switched antibody responses are selectively deficient in the CD73 expression of their B cells, suggesting that lack of CD73-dependent adenosine generation leads to a shift in IgG class switch and contributes to the pathogenesis of this disease.

Session P-C8 Poster Session
Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Elite Controllers

296 Transcriptional Signatures of CD4 T Cell Subsets and Control of HIV Reservoirs in Elite Controllers

Adele de Masson[1], Amos Kirilovsky[1], Rima Zoorob[1], Veronique Avettand-Fenoel[2], Veronique Morin[1], Anne Oudin[1], Benjamin Descours[1], Christine Rouzioux[2], Brigitte Autran[1], the ALT ANRS-Co15 Study Group

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Background: Understanding the molecular mechanisms associated with the exceptional quasi-equilibrium between HIV reservoirs and host cells in the model of functional cure represented by Elite Long-Term Nonprogressors (E-LTNPs) should provide clues for developing strategies to purge the HIV reservoirs but remain to be elucidated.

Methodology: We compared the whole-genome transcriptional profiling of the 4 major resting (CD25-CD69-DR-) CD4 T cell subsets (naïve [TN], central-memory [TCM], transitional-memory [TTM] and effector-memory [TEM]) sorted from PBMCs of 14 HIV-1 infected individuals including 7 E-LTNPs, 7 viremic LTNPs (Vir-LTNPs) and 7 uninfected individuals (UI). Total HIV DNA was quantified in each T cell subset by real time quantitative polymerase chain reaction (qPCR, Biocentric, Bandol, France). The transcriptomes were analyzed using an Illumina Platform. Statistics were performed using the Limma package of R. Differentially expressed genes (DEGs) were considered significant with a false-discovery rate (FDR) below 0.05. Key molecular signatures were quantified by qPCR in each sorted CD4 T cell subset in parallel to the HIV-1 cellular DNA and unspliced RNA levels.

Results: Resting TCM and TTM were the main contributors to the HIV reservoir in LTNPs with a 1-log difference for each subset HIV-DNA content between E-LTNPs and Vir-LTNPs. When comparing each E-LTNP, Vir-LTNP and UI CD4 T-cell subset transcriptome to a single comparator (UI-TN), an increasing gradient of DEGs followed the linear TN to TCM, TTM and TEM differentiation model. Distinct profiles were however observed between groups with the most active and distant transcriptomes in TCM from E-LTNPs but in TEM from Vir-LTNPs. Most DEGs encoded proteins with functions related to intracellular signaling, adherence, cytotoxicity and apoptosis. The E-LTNPs TCM, representing the main CD4 compartment, revealed 2 major specific signatures compared to TCM from Vir-LTNPs and UI: (i) TCR and costimulation signaling genes with 8 overexpressed and 2 down-modulated DEGs, and (ii) type I interferon-related genes with 5 down-modulated and 2 upregulated DEGs. This specific E-LTNPs transcriptome was associated to extremely low levels of HIV-DNA and HIV-RNA transcripts in TCM from E-LTNPs compared to other subsets and to TCM from Vir-LTNPs with significant association between host and HIV genes.

Conclusions: Resting CD4 TCM from E-LTNPs display a unique transcriptional profile with key host genome signatures from the TCR/costimulatory signaling and IFN-I pathways associated to low levels of HIV reservoirs and HIV-RNA transcription. These results allow identification of new molecular targets associated with the control of the HIV reservoirs in models of functional cure.

298 Elite Suppressor CD4+ and CD8+ T Cells Suppress Viral Replication in Monocyte-Derived Macrophages

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Background: Elite suppressors (ES) are HIV-1 infected patients who maintain undetectable viral loads without antiretroviral therapy. The control has previously been associated with a qualitatively superior CD8+ T cell response to infected CD4+ T cells. However, very few studies have examined the effector T cell response to HIV-1 infected macrophages. In the macaque ES model, both CD4+ and CD8+ T cell clones are capable of suppressing infection in macrophages, but in an ex vivo study, SIV-specific primary CD8+ T cells were far less effective at inhibiting viral replication in macrophages than in CD4+ T cells. In this study, we examined the CD4+ and CD8+ effector T cell responses to HIV-1 infected monocyte-derived macrophages (MDM).

Methodology: Monocytes were isolated from 10 uninfected healthy donors (HD) and 7 ES and cultured in macrophage differentiation media (RPMI, 20% human AB serum, 1% HEPES, 50 ng hrM-CSF/mL) for 7 days before infection. On the day of infection, the MDMs were infected with the laboratory isolate Ba-L by spinoculation. Unstimulated primary CD4+ and CD8+ cells isolated from a second blood draw were added to the MDMs at various effector to target ratios immediately after infection. Normalized percent inhibition of viral replication was calculated by comparing culture supernatant p24 levels in the presence and absence of effector CD8+ or CD4+ T cells, and unpaired, two-way Student's T-tests were used to determine statistical significance.

Results: There was no difference in the rate of viral replication in MDMs isolated from ES and HD ($p > .7$). ES effector T cells were capable of suppressing viral production in MDMs. By day 7, CD4+ effector T cells inhibited viral production in MDMs by 56.8 ± 11.2% (mean ± SE; range: 23.0-92.7%), and CD8+ effector T cells inhibited virus production in MDMs by 84.4 ± 9.2% (range: 36.0-99.3%), with the CD8+ effect tending to be stronger ($p < .1$). Conversely, inhibition in HD was significantly lower with an average inhibition of 17.1 ± 8.2% and 12.4 ± 7.7%, respectively (CD4s: $p < .02$, CD8s: $p <$ 10-4). These differences were apparent as early as the third day post infection ($p < .05$). Interestingly, separation of effector cells from target cells with transwells resulted in complete abrogation of the inhibitory response by CD8+ T cells and partial abrogation of the CD4+ T cell response.

Conclusions: Primary unstimulated effector CD4+ and CD8+ T cells from ES are capable of effectively inhibiting viral replication in MDMs in vitro in a cell-cell contact mediated manner. The degree of CD8+ T cell mediated inhibition of viral replication in MDMs was comparable to that seen in target CD4+ T cells. These observations imply that the response of effector cells to macrophages should be considered in rational vaccine design and the continuing goal of eradication.

299 Effective Control of Virus Replication in HIV-1 Elite Controllers by Active SAMHD1

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Background: Elite controllers are a small number of HIV-1 positive individuals who control infection and remain healthy without the need for antiretroviral therapy. The basis of this elite control of infection remains unclear. SAMHD1 has been identified as an HIV-1 restriction factor that controls the intracellular deoxynucleotide pool, limiting HIV-1 reverse transcription. SAMHD1-mediated restriction is counteracted by HIV-2 Vpx and is deactivated by cyclin-dependent kinase (CDK)-mediated phosphorylation.

Methodology: Purified CD4+ T cells from healthy donors (n=11), viremic HIV+ patients (n=10) and elite controllers (n=12) were stimulated and infected with HIV-1 or HIV-2 strains in the presence or absence of coexpressed Vpx. Replication levels were measured by flow cytometry and proviral DNA measured by quantitative PCR (qPCR). Gene and protein expression were measured by mRNA qPCR and Western blot analysis respectively. Cell activation was measured by analysis of CD25 and CD69 expression and proliferation by Ki67 expression and absolute cell count. Unpaired t test was used for statistical analysis.

Results: Despite similar levels of CD4+ T cell activation and proliferation than control cells, anti-CD3 stimulation of CD4+T from elite controllers showed an intrinsic resistance to infection ($p<0.0001$) at the level of unintegrated proviral DNA formation ($p=0.0023$) that was overcome by coexpression of HIV-2 Vpx, indicating that restriction was mediated by SAMHD1. HIV-1 infection of CD4+ T cells from healthy donors correlated with the degree of phosphorylation of SAMHD1 ($r2=0.7437$) measured by Western blot. Moreover, cells from elite controllers showed significantly ($p<0.0001$) lower levels of SAMHD1 phosphorylation compared to healthy donors or cells from viremic HIV+ individuals. RNA interference or pharmacological intervention showed that CDK2 and CDK6 control SAMHD1 phosphorylation in primary hematopoietic cells. Moreover, CD4+ T cells from elite controllers showed lower mRNA expression of CDK2 ($p<0.0001$) and CDK6 ($p=0.0085$) concomitant to reduced activation of CDK2 as measured by CDK2 Thr160 phosphorylation.

Conclusions: These results provide a mechanism of viral control common to HIV-1 elite controllers linking virus replication and cell cycle regulation, and suggest that SAMHD1-mediated restriction may be relevant in vivo as a determinant of HIV-1 disease progression and control.

Session P-C9 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Pathogenesis: Insights From Clinical Trials

300 Effect of Raltegravir Intensification in the Cytokine Profile of Treated HIV+ Individuals

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Background: Inflammatory markers are increased in untreated HIV infected individuals and, as immune activation, are not normalized by combination antiretroviral therapy (cART). Long term (48 weeks) intensification of cART with Raltegravir reduced CD8 T-cell activation in the Discorral and IntegRal studies. Therefore, we have evaluated the effect of Raltegravir intensification in several soluble plasma markers in these studies.

Methodology: Longitudinal plasma samples (0-48 weeks) from the Integral (67 individuals with high CD4 T-cell counts, 22 control and 45 intensified individuals) and the DiscorRal studies (44 individuals with CD4 T-cell counts >350 cells/µl, 14 control and 30 intensified individuals) were analyzed using a BioRad Multiplexed cytokine array covering 22 markers. Mann-Whitney, Wilcoxon and Spearman tests were used for analysis.

Results: Before intensification, individuals enrolled in the Discorral Study (median CD4 T-cell counts 248 cells/µL) showed a significant higher level of most inflammatory cytokines when compared with individuals enrolled in the IntegRal study, which had a median CD4 T-cell counts of 520 cells/µL. Main differences were observed in pro-inflammatory cytokines IP10 ($p=0.001$), IL-1b ($p=0.0006$), IL-12 ($p=0.006$), IL-13 ($p=0.0001$), IL-17 ($p=0.0084$) and TNFa ($p=0.0024$), apoptosis mediators such as TRAIL ($p=0.0024$) or homeostatic cytokines as IL-7 ($p=0.0009$). Consistently, significant negative correlations between most of these markers and CD4 T-cell counts were found: IP10 ($r^2=0.074$), TRAIL ($r^2=0.074$), IL-17 ($r^2=0.064$), IL-1b ($r^2=0.06$) and IL-13 ($r^2=0.06$), $p<0.02$ in all cases. Moreover, a marker of endothelial function, sVCAM-1, was negatively correlated with CD4 T-cell counts ($r^2=0.06$, $p=0.009$). Longitudinal analysis showed that 48-week raltegravir intensification failed to induce significant changes in cytokine levels in individuals with high CD4 T-cells (IntegRal study) although significantly reduced some of the cytokines increased in individuals with low CD4 T-cell counts (Discorral study) at week 48, especially IP10 ($p=0.03$) and a trend was observed with TNFa ($p=0.09$).

Conclusions: Inflammatory profile is strongly associated with the level of CD4 T-cells in long term cART treated HIV infected individuals. Raltegravir intensification has little effect on these markers, although a positive impact could be observed in individuals with poor CD4 T-cell recovery.

301 Analyses of HIV-1 Viral Dynamics During Treatment With a Regimen Including an Integrase Inhibitor

Jeremie Guedj[1], Ruy Ribeiro[2], Adriana Andrade[3], Susan L. Rosenkranz[4], Darlene Lu[5], Douglas Richman[6], Mathew Strain[6], John Mellors[7], Daniel R. Kuritzkes[8], **Alan S. Perelson[2]**

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Background: Viral dynamics analyses have improved our understanding of HIV infection, revealing the timing and rates of important processes in the viral replication cycle. Here we analyzed the early kinetics observed with raltegravir-based treatment to gain new insights into the kinetic of viral decline.

Methodology: We analyzed data from 11 HIV-1 infected subjects enrolled in an intensive viral dynamics substudy (A5249s) of ACTG trial A5248 in treatment-naïve subjects initiating treatment with raltegravir (RAL 400mg BID) and emtricitabine (FTC 200mg QD)/tenofovir disoproxil fumarate (TDF 300mg QD). After initiating treatment, subjects had plasma HIV-1 RNA measured at 0, 2, 4, 6, 12, 18, 24, 30, 36, 42, 48h and then on (or about) days 3, 4, 7, 10, and 14. To fit these data, we used a mathematical model of viral dynamics that distinguishes between infected cells with unintegrated HIV DNA and productively infected cells. Parameters were estimated using non-linear least square fitting.

Results: : Whereas HIV RNA is usually described as declining linearly during the first two weeks of treatment (phase 1), our analysis revealed that RAL/FTC/TDF led to a biphasic decline of viral load, with a rapid first phase lasting for about 5 days, followed by a second slower phase of viral decline. The new model attributes the first phase (phase 1a) to the rapid elimination of productively infected cells. The second phase (1b) had a slower slope of decline and reflects the loss of infected cells with non-integrated provirus due to both cell loss and integration of HIV DNA. The model describes the data well and we estimate the half-life of productively infected cells was ~17 h, in good agreement with previous estimates; and the half-life of infected cells that had completed reverse transcription but had not yet integrated HIV DNA was >4.3 days, and quite variable. Additional parameters could not be estimated precisely, but the data is consistent with the time for half of activated cells to transition between pre-integration to post-integration being between 2 h and 16 h and the efficacy of RAL in preventing HIV-1 integration being ~96%. Lastly, our model predicts that the higher the efficacy of the integrase inhibitor the larger the phase 1a viral decline.

Conclusions: : Using viral kinetic analyses we characterized the determinants of HIV RNA decline in a RAL containing regimen and estimated the effectiveness of RAL (~96%). We found, as previously suggested for RAL monotherapy, that the first phase was composed of two subphases corresponding to the half-lives of infected cells with integrated proviruses (17 hours) and unintegrated HIV-1 DNA (>4.3 days).

302 Characterization of Functional Profile of HIV-Specific CD4+ T Cells in VISCONTI Group of Patients

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Background: The mechanisms underlying the exceptional control of HIV replication and reservoirs observed in Post Treatment Controllers (PTC) remain unknown. To further understand such control we evaluated the functional profile of HIV-specific CD4+ T cells of PTCs from the prospective VISCONTI study (Virological and Immunological Sustained CONtrol after Treatment Interruption).

Methodology: Ten VISCONTI patients# defined as controlling HIV (<400cp/mL) for a median 89 [IQR:73-103] months long interruption of a median 3 [IQR:1.7-5.9] years long HAART initiated within 10 weeks post-infection. Multiparametric flow cytometry assessed HIV-specific CD4 T cells producing IFNγ, IL2, TNFα,MIP1β or expressing CD40L after stimulation by HIV-p24 peptides pool or p24 recombinant protein. Results were compared to those from 10 control fully-suppressed treated patients (pts) under at least 5 years long HAART initiated within 10 weeks post-infection. Statisticswere done using Mann-Whitney tests.

Results: Relatively high frequencies of CD4+ T cells against the HIV-p24 peptide pool and recombinant protein were found and did not significantly differ between both groups with median values of: 0.125% [0.03-0.49] and 0.12% [0.02-0.68], respectively in VISCONTI pts, and 0.195% [0.01-1.16] and 0.44% [0.1-1.44] in control treated pts, though lower in the VISCONTI pts. In both groups, CD4+ T cells specific for HIV-p24 peptides produced more IL2 and MIP1β than IFN-γ while CD4+ T cells specific for the p24 recombinant protein were more polyfunctional, producing IL2, IFNγ and MIP1β and expressed CD40L. Polyfunctional CD4 T cells directed against HIV p24 pool and p24 recombinant protein can be detected in both groups. Nevertheless in both groups specific CD4+ T cells expressed 1 to 4 functions with 29%, 37% 20% and 6% vs 55%, 17%, 15% and 1% producing 1, 2, 3 or 4 functions against HIV p24 peptide pools and 51%, 26%, 12% and 3% vs 62%, 13%, 14% and 1% against the p24 recombinant protein in Visconti vs controls pts . VISCONTI pts CD4 T cells against HIV p24 peptides produced significantly at leat 2 functions than control treated pts (p=0.029).

Conclusions: The major virus control observed in PTC from the VISCONTI study is associated with relatively high frequencies of multi-functional HIV-specific CD4+ T cells. The 3 years long HAART regimen introduced early after infection might have preserved those HIV-specific cells which might participate in the post-treatment control of HIV.

Asier

Saez-Cirion et al. Post-Treatment HIV-1 Controllers with a Long-Term Virological Remission after the Interruption of Early Initiated Antiretroviral Therapy ANRS VISCONTI Study. 2013, PLoS Pathog Mar;9(3).

303 Immune Activation and Defective pTFHs Are Associated With Impaired Immunity in Aging HIV+ Persons

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Background: With improved antiretroviral treatment (ART) and increasing survival, the aging HIV infected population is rising. HIV infection and aging are independently associated with waning immunity including poor vaccine induced antibody responses, but the combination of HIV and aging needs further investigation.

Methodology: This study represents initial observations from a larger ongoing study in young (Y) and old (O) people in the presence (+) or absence (-) of HIV infection. Four groups n=12 each, O+ median age (Δ) 63yr; O- Δ 65yr; Y+ Δ 37yr, and Y- Δ 33yr were investigated. HIV+ were well controlled on ART with<48 HIV RNA copies/ml and mean±SD CD4 counts (cells/mm^3) of 602.7±273.6 (O+) and 654.3±313.8 (Y+). Investigations included Hemagglutination inhibition (HAI) titers at pre- (T0) and 4 weeks post (T2) seasonal 2011-2012 influenza vaccination, immune activation (IA), and Immunologic analysis of peripheral T follicular helper cells (pTfh) and B cells. Differences between groups were analyzed by Student *t*-test and correlation between variables was determined by Pearson correlation and linear regression analysis.

Results: At T0, seroprotection [HAI titers ≥1:40] was less frequent in Old (O+ 33%,O- 25%), compared to Young (Y+ 75% and Y- 91.6%). At T2, a 4-fold increase in HAI titers was noted in 75% of Y- [peak mean±SD titer, 246±337] but only in 50% of each of the other groups, with O+ exhibiting lowest peak titer (81±61). At T0, the O groups compared to Y had higher CD4 IA (CD38+HLADR+) and lower frequencies of pTfh (CD4+CD45RO+CXCR5+), with highest and lowest values respectively noted in O+. Following vaccination,

HAI titers at T2 correlated with pTfh changes (expansion, upregulation of ICOS expression and intracellular IL21) and memory B cell changes (expansion, upregulation of IL21R and increases in H1N1 specific Ab responses in Elispot assay). The magnitude of these responses was in the order Y->Y+>O->O+. CD4 T cell IA at T0 was negatively correlated with HAI titers at T2. In 5 day PBMC cultures, addition of exogenous IL-21 augmented expansion of pTfh and ICOS expression in all four groups, and H1N1 specific Ab responses in ELIspot assay were augmented in all except the O+ group.

Conclusions: Aging and HIV infection were independently associated with lower pTfh defects that contribute to B cell impairment, but the presence of HIV infection and aging together exhibited the worst immune profile, with highest underlying IA and poorest serologic response following influenza vaccination. Supplementation of IL-21 ex-vivo was partially restorative of the observed immune defects with better effects noted in HIV+ young than in HIV+ old, indicating the need for additional investigations and measures e.g. targeting immune activation in the HIV+ aging population.

304 Fresh Cohort: Acute HIV-1 Infection in Cohort of High Risk HIV Negative Women in KZN, South Africa

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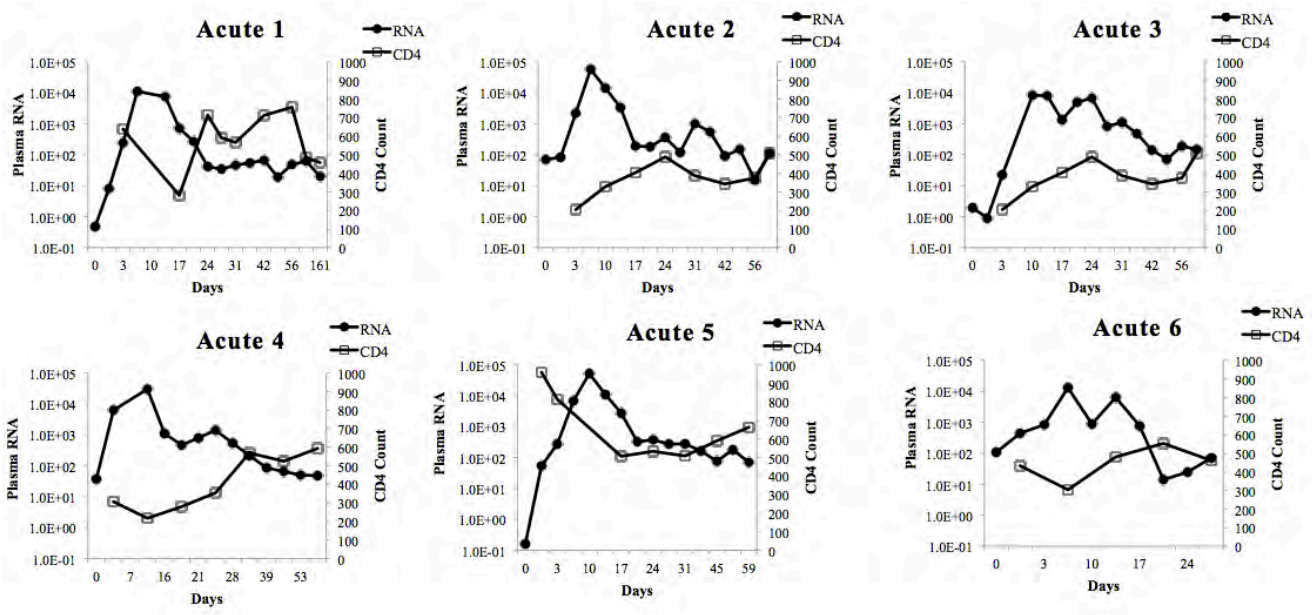
Background: The HIV epidemic in KZN South Africa continues unabated amongst young at risk women. Seroprevalence data collected in 2009 at an antenatal clinic in the Umlazi KZN showed that 2 of 3 women become HIV-infected by 22 years of age. While ART availability in SA has increased steadily since launch of treatment in 2004 the magnitude of the epidemic underscore the need for a vaccine. Key to vaccine development is understanding factors that influence HIV disease progression. Characterization of immune responses in both the peripheral circulation and the female genital tract, the site of most common exposure, just prior to and in the earliest stages of acute infection may offer valuable insights.

Methodology: The study launched in December 2013, enrolling 30 women per month to create a cohort of 300 HIV-negatives aged 18 to 23 years to be followed for 24mo. Monitoring occurs twice weekly to check HIV-1 RNA PCR by finger prick during year 1, then 3-monthly during year 2. Blood collection and pelvic examination are performed every 3mo for 24mo for collection of PBMCs and mucosal tissue via cervical and vaginal swab, cervical cytobrush and cervicovaginal lavage . To support study retention participants are concurrently enrolled in 1-year life-skills poverty alleviation program, which meets on the same days as scheduled study follow-up.

Results: In September 2013 at 9mo after launch, 410 women have been screened and 288 found eligible. 205 are enrolled and in active follow-up; 6 identified with acute HIV-1 infection. 5 of 6 experienced flu-like symptoms consistent with acute viral syndrome around the time of infection. First +RNA PCR occurred after 16w of monitoring (4.5 to 44w) with initial VL of 34,616 copies/mL (160 - 120,000). Peak viremia was 28.5mil copies/mL (11-57) occurring at 7.6 days (7-11) after initial +RNA PCR. CD4 nadir of 299 mm-3 (217 - 506) occurred at 13d (3-24). Seroconversion by HIV rapid occurred at 16.8 days (14 - 21d) after +RNA PCR. 4 of 4 screened were found to have an STI at the time of acute infection. Seroconversion rate was estimated to be 7.71 (95% CI: 2.50-18.0) per 100 person-years.

Conclusions: Frequent monitoring of a cohort of high-risk women in KZN, SA enables identification of acute HIV-1 infection. Peak viremia is rapid, occurring within 7 days of initial +PCR. CD4 drops below 350 within 2w of +PCR, but rebounds. Combining a life-skills/empowerment intervention may increase study retention and compliance of high risk individuals expected to comply with frequent study visits.



305 Vitamin D Significantly Changes the Immune Transcriptome and Augments CD4 Recall Responses in HIV

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Background: In vitro studies, including our laboratory, highlight the active metabolite of Vitamin D, Calcitriol, to have pleiotropic effects on innate and adaptive immunity. More recently, *in vivo* Vitamin D supplementation showed beneficial effects by promoting resolution of inflammation. HIV progression, which is associated with excessive immune activation and impaired T-cell immunity, is also associated with low serum vitamin D level although biological plausibility and causality have yet to be established. This study was therefore designed to assess the impact of Vitamin D supplementation on T-cell function in both HAART treated and treatment naïve HIV+ subjects.

Methodology: This prospective controlled study enrolled 28 subjects with low plasma vitamin D (Vit D) (<20ng/l, 50micromol/l) comprising 17 HIV+ patients (11 on HAART, 6 treatment naive) and 11 healthy controls. A single dose of 200,000 IU oral cholecalciferol was administered. Blood samples were

analysed at baseline and one month. Advanced multi-colour flow cytometry was used to assess T-cell signalling, T cell effector responses, and markers of T-cell activation and homeostasis. In addition the whole blood transcriptome was analysed along with the primary Vitamin D receptor, VDR.

Results: Plasma Vit D levels were restored to normal at one month. The following statistically significant results were found: CD4 T-cell responses to CMV and SEB were markedly augmented in HAART+ subjects and similarly HIV-specific responses in HAART Naïve subjects. Specifically MIP1β+ CD4 T-cell frequency increased in HAART+ subjects, concomittant with an increase in plasma MIP1β+, which correlated with plasma Vit D levels. An associated increase in promimal T-cell pERK mobilisation following PMA stimulation was noted. T-cell CD38 expression was downregulated only in HAART+ subjects; however no significant changes to T-cell CD39 or Treg and IL-17 numbers were noted. These specific changes to the T cell compartment were associated with changes to some 250 genes at the whole blood level in HAART naive and healthy controls. However, 10-fold fewer genes were altered in HAART+ subjects associated with significantly lower basal VDR expression. Pathways impacting T-cell function were altered in all three groups but a common gene signature spanning all three groups was not identified.

Conclusions: Vit D therapy may be a useful adjunct to HAART therapy in HIV infection by improving the quality of the T-cell response. The potential therapeutic benefit of this cheap, safe, easily administered therapy on slowing progression and reducing mortality in HIV merits testing in adequately powered clinical trials.

306 Impact of Methamphetamine Use On Immunologic and Virologic Markers During Suppressive ART

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Background: Methamphetamine (meth) is a widely used recreational drug in North America, especially among HIV-infected men who have sex with men (MSM), and is associated with worse health outcomes in HIV infected persons.

Methodology: Fifty HIV-infected MSM on long-term antiretroviral therapy (ART) (median 3.8 years) with plasma HIV RNA <50 copies/ml and who were enrolled in a prospective clinical trial to reduce sexually transmitted infections were studied. Meth and other drug use in the past month were assessed at baseline with a self-administered internet-based survey along with other risk behaviors. Levels of immune activation (CD45RA-CD38+) and proliferation (Ki67+) of CD4+ and CD8+ T-cells subsets were determined from frozen peripheral blood mononuclear cells (PBMC) by multicolor flow-cytometry. Total HIV DNA (pol), 2-long terminal repeat (2-LTR), and cellular HIV RNA (unspliced and multiply-spliced encoding for tat/rev) were measured in PBMC by droplet digital PCR. Using non-parametric statistics, we investigated associations between recent use of meth with immune activation and proliferation of subsets of CD4+ and CD8+ T-cells in blood, CD4 count, time on ART, and with levels of HIV DNA and cellular HIV RNA.

Results: Twelve of 50 (24%) MSM reported meth use in the past month. Meth use was significantly associated with higher levels of immune activation (CD45RA-CD38+) and proliferation (Ki67+) of total CD4+ T-cells (both $P<0.05$), and with higher levels of proliferating CD8+ T-cells ($P<0.01$), in each analyzed subset (i.e. naïve, central memory, transitional memory, effector memory CD8+ T-cells). Recent meth use was also associated with a trend towards higher levels of proviral HIV DNA reservoir (median of 2.09 vs. 1.83 log10 copies/million CD4+ T-cells, $P=0.09$) and higher levels of multiply-spliced cellular HIV RNA transcripts compared to those not using meth ($P=0.06$). Use of other drugs (cannabis, cocaine, other 'club' drugs, alcohol), CD4 counts and time on ART were not associated with any differences in immunologic or virologic markers. Self-reported adherence to ART was not significantly different between meth users and non-meth users ($P=1.0$).

Conclusions: Self-reported meth use by HIV-infected MSM on long-term ART with fully suppressed plasma HIV RNA levels was uniquely associated with increased T-cell immune activation and proliferation, both of which could explain meth-related co-morbidities. Meth users might also have a greater HIV DNA reservoir and residual HIV RNA replication than non-meth users, but this observation and the underlying immunomodulatory mechanisms of meth in HIV-suppressed individuals need to be confirmed in a longitudinal study including a larger population.

307 Vitamin D-Receptor Gene Polymorphisms: Association With Virologic Failure and Mortality

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Background: Host genetic factors play an important role in disease. Due to its extensive role in the immune system, vitamin D may have a potential role in altering HIV disease progression. Vitamin D actions are mediated by the vitamin D receptor (VDR). Polymorphic variations exist in the VDR gene, each of which may have different significance in disease susceptibility and progression. We set out to examine if VDR gene variations, corresponding to Apa1, Bsm1, Fok1 and Taq1 polymorphisms were associated with HIV disease progression.

Methodology: We analyzed cohort data for 142 HIV-infected patients initiating ART in South Africa between November 2008-March 2009. We defined disease progression as: 1) failure to achieve viral suppression (viral load <50copies/ml) within the first 12-months of ART and; 2) mortality during follow-up. Genomic DNA was extracted from whole blood using standard methods and analysed for polymorphisms in the VDR gene. Cox proportional hazards models were used to estimate the association of genotype status (Hazard Ratios (HR) and 95%CI) with disease progression. Models were adjusted for age, gender, BMI, WHO stage, CD4 count, haemoglobin level, employment status and ART regimen.

Results: The genotype frequencies were as follows: Apa1: AA=42.3%, Aa=50% and aa=7.8%; Bsm1: BB=3.5%, Bb=32.4% and bb=64.1%; Fok1: FF=69.7%, Ff=29.6% and ff=0.7%; and Taq1 genotype, TT=60.6%, Tt=33.8% and tt=5.6%. The genotype distributions were in Hardy-Weinberg equilibrium ($p > 0.05$). By 12 months post-ART initiation, 22.2% failed to achieve viral suppression and over a median follow-up of 40.4 months (IQR 13.3-41.7) and 12.7% died. Patients with non-bb Bsm1 genotypes (BB+Bb) had 3.1-fold increased risk of failure to achieve viral suppression, adjusted HR (aHR) 3.05, 95%CI 1.18-7.90, p=0.02 and 3.4-fold increased risk of mortality during follow-up, aHR 3.37, 95%CI 1.28-8.86, p=0.01, vs. the bb Bsm1 genotype. A similar trend was observed for the non-FF Fok1 (Ff+ff) vs. FF Fok1 genotype but estimates were not statistically significant: risk of failure to achieve viral suppression, aHR 2.25, 95%CI 0.83-6.07, p= 0.11 and of mortality, aHR 2.11, 95%CI 0.75-5.87, p=0.16. No association with risk of disease progression was observed with Apa1 and Taq1 genotypes.

Conclusions: Some VDR gene polymorphisms seem to contribute to differential rates of disease progression among HIV infected patients initiating ART. Patients carrying non-bb genotypes (BB+Bb) of the Bsm1 polymorphism demonstrated 3.1-fold increased risk of failure to achieve viral suppression and also 3.4-fold increased risk of mortality during follow-up. Understanding this role of VDR genotypes among HIV-infected patients may offer new insights for developing therapeutic strategies to alter disease progression.

308 Statins Use Is Associated With Greater CD4 Gains in HIV-Infected US Veterans

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Background: Incomplete immune reconstitution (IR) on HAART is possibly mediated by persistent inflammation and is associated with increased all-cause mortality and incidence of AIDS and HIV-associated non-AIDS complications. We explored if statin use was associated with faster IR and greater CD4 gains on HAART.

Methodology: We used the US Veterans' Cohort (1995-2011) to identify patients with ≥1 viral load (VL) and CD4 measurement before and after HAART initiation within the VA system. HAART use and cumulative statin use rate (SUR) were computed from pharmacy refill data and defined as the % of time during the follow-up (f/u) period in which patients were exposed to HAART or any statin, respectively.

To examine the association of SUR and time to IR we carried out 3 Cox proportional hazards analyses in subgroups of patients defined by baseline (BL) and threshold CD4 to achieve IR: a) <350 to ≥500; b) <200 to ≥500; and c) <200 to ≥700 cells/μL. We controlled for baseline CD4 and VL, age, race, gender, hepatitis C co-infection, clinical AIDS before HAART, and year of HAART initiation as baseline covariates as well as virologic suppression status and HAART adherence as time-updated covariates. Controlling for the same covariates we then used generalized estimating equations to characterize the contribution of statin use to quarterly average CD4 gains after HAART initiation.

Results: A total of 21,132 patients were eligible for analysis. Median f/u time was 7.6 years, median BL CD4 count was 249 cells/μL. 6,957 patients (33%) were exposed to statins after HAART initiation. HAART use rate and SUR were not directly correlated. The table below outlines the proportion of patients achieving IR, the median time to IR and the hazard ratios (HR) for IR for the 3 multivariate Cox models.

The contribution of 100% SUR to CD4 gains by generalized estimating equations was + 97 cells/μL (95% CI 89-106, p<0.0001) while 100% HAART use contributed +175 cells/μL (95% CI 169-181, p<0.0001).

The following covariates were associated with faster IR or greater CD4 gains in all multivariate models: time-updated virologic suppression status, baseline CD4 count and baseline VL, younger age, female gender, black race, and year of HAART initiation.

Conclusions: In our cohort, statin use was associated with substantially greater CD4 gains and faster IR. This effect may be mediated by reductions in persistent inflammation and immune activation and warrants further study.

Multivariate Cox models						
BL CD4 → Threshold CD4	Achieving IR / Total n (%)	Median years to IR (IQR)	Median years of follow-up (IQR)	HR (95% CI) for immune reconstitution for 100% HAART and statin use		p-value
BL CD4 <350 IR: CD4 ≥500	6,454 / 14,332 (45%)	2.5 (1.0-5.1)	7.1 (3.7-11.3)	HAART	4.45 (3.97-4.98)	< 0.0001
				Statins	1.27 (1.14-1.41)	< 0.0001
BL CD4 <200 IR: CD4 ≥500	2,883 / 8,678 (33%)	4.0 (2.1-6.5)	6.9 (3.3-10.9)	HAART	5.07 (4.24-6.06)	< 0.0001
				Statins	1.19 (1.02-1.40	0.032
BL CD4 <200 IR: CD4 ≥700	1,394 / 8,672 (16%)	5.6 (3.4-8.7)	6.9 (3.3-10.9)	HAART	5.48 (4.20-7.14)	< 0.0001
				Statins	1.43 (1.17-1.76)	0.001

309 Maraviroc Intensification in HIV-Infected Patients Induces Increased CCR5 Expression On T Cells

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Background: Our group showed that Maraviroc (MVC) intensification over 24 weeks (W) in immunological non responders over the last two years (CD4<350 cells/mm^3, CD4 slope <50 cells/mm^3/year and HIV-RNA<50 copies/ml) enhanced CD4 cell slopes and significantly decreased CD8+ T cell activation#. We analyzed whether these effects were associated with modulation of CCR5 expression on various T cell subsets, frequencies of virus-specific T cells and levels of CCR5 ligands.

Methodology: 31 patients were monitored at baseline, after 24W of MVC intensification and at W28 (4W post-intensification). We evaluated CCR5 modulation on different T-cell subsets (Naïve (N), Central-Memory (CM), Effector-Memory (EM), Effector (E) and on CD4 T cells expressing CXCR3, CCR4 or CCR6, as well as on activated CD4+ and CD8+ T cells in parallel to plasma CCR5 ligands (MIP-1A, MIP-1B and RANTES) levels. T cells specific for HIV-1 gag and CMV antigens were quantified using IFN-G ELISpot assay.

Results: During MVC intensification, a decrease in activated CD8+DR+CD38+ T cells is observed (-26%; p=0.001). We also observe to a significant increase of CCR5 on CD4+ (+6%; <0.001) and CD8+ T cells (+15%; p<0.001), mainly on CD8+ TEM (+14%; p=0.003) and on activated CD8+DR+38+ T cells (+10%; p=0.00014). MVC intensification also resulted in significant increase in CCR5 expression on CD4+CXCR3-CCR4+CCR6+ T cells defining Th17 cells (+4%; p=0.003). This increased CCR5 expression paralleled an increase in MIP-1B plasma levels (+57pg/ml; p=<0.001). At W28, 4 weeks after stopping MVC both CCR5 expression and MIP-1B levels were reversed. No significant changes were observed in frequencies of CMV- or HIV-specific T cells.

Conclusions: The blockade of CCR5 receptor-ligand interaction by MVC not only reduced CD8+ T-cell activation but also increased CCR5 expression mainly on effector-memory and activated T cells, paralleling the increase in plasma levels of MIP-1B the CCR5 ligand. These changes during MVC intensification might reflect a preferential decrease of activated T cells that do not display CCR5 and the redistribution of CCR5+ activated differentiated T cells in association with the positive effect on CD4 counts in immunological non responders.

Cuzin L. et al. Maraviroc Intensification of Stable Antiviral Therapy in HIV-1-Infected Patients With Poor Immune Restoration: MARIMUNO-ANRS 145 Study. J Acquir Immune Defic Syndr. 2013 Apr 1;62(4).

Session P-C10 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Innate Immunity and Pathogenesis

237 CD161+Vα7.2+IL18R+ MAIT Cells Are Reduced in HIV Infection Regardless of the Disease Status

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Background: Mucosal-associated invariant T (MAIT) cells are characterized by the combined expression of the semi-invariant TCR Vα7.2, the lectin receptor CD161 and the IL18 receptor. They play an important role in the antibacterial host defense of the gut. CD161+ MAIT cells vanish almost completely from the bloodstream in HIV-infected patients and cannot be restored by antiretroviral therapy. To date, the mechanisms causing this HIV-associated reduction of MAIT cells are not well understood and it is not known whether the magnitude of the reduction depends on the disease status. Thus, we aimed to comprehensively characterize a large cohort of HIV patients including patients with slow disease progression and elite controllers and to explore the mechanisms that lead to the loss of MAIT cells in HIV infected patients.

Methodology: PBMC and lymph node samples from 60 patients with different disease status, including patients with a high viral load (high VL), patients under antiretroviral therapy (ART), elite controllers (EC) and long term non-progressors (LTNP), were analyzed by multicolor flow cytometry. MAIT cells were analyzed for their activation level and migration pattern ex vivo and after in vitro stimulation with different cytokines (IL-7, IL-18, IL-12) and fixed bacteria (E.coli). Furthermore, their capacity to produce cytokines (IL-17, IL-22, IFN-γ) was determined by intracellular cytokine staining. Plasma IL18-, sCD14- and sCD163-levels were determined by ELISA, to reveal further associations with disease progression.

Results: We demonstrate an irreversible reduction of MAIT cells during HIV infection regardless of the patients disease status in the blood (p< 0.05 for all patient groups vs. healthy controls) as well as in lymph nodal tissue. Elevated levels of IL18 and soluble CD14/CD163 are detectable in the plasma of HIV patients, which was paralleled by a loss of CD161+ MAIT cells and increased activation and exhaustion status as well as upregulation of the gut-homing markers CCR9 and beta7 integrin. Analysis of the expression of CD161 and IL18R on TCR Vα7.2+ T cells revealed a phenotypic shift with a loss of these markers accompanied by a functional disturbance involving a reduced capacity to produce IL17. This phenotypic shift can be replicated by in vitro stimulation of MAIT cells with IL18 and IL12 and fixed E.coli.

Conclusions: MAIT cells are drastically reduced in the peripheral blood of all HIV infected patient groups regardless of the disease status. We propose a multifactorial model to explain loss of MAIT cells during HIV infection that involves activation induced cell death, a phenotypic shift and an increased tissue migration.

238 HIV-1 Alters Plasmacytoid Dendritic Cell Phenotype and Function by Modulating ILT Receptors

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Background: Dendritic cells (DC), the antigen presenting cells that initiate or shut down adaptive immune responses, exist as two main subsets in peripheral blood namely: myeloid (m)DC, the precursors of tissue DC; and plasmacytoid (p)DC, the main producers of IFN-alpha. Both populations are reduced in HIV-1 infection and their dysfunction has been implicated in HIV-1 immunopathogenesis. The aim of this study was to characterise the impact of HIV-1 on the immunoregulatory functions of peripheral DC, in particular the IFN-alpha blocking immunoglobulin like transcript (ILT)-7 and the T-regulatory (T-reg) inducing receptors, ILT-3 and ILT-4.

Methodology: Peripheral blood was collected from three cohorts of patients: healthy controls (n=11), therapy naïve patients (n=11), and treated patients (n=11). Cell surface expression of ILT-3, -4, and -7 by pDC and mDC was determined by flow cytometry. For functional studies, pDC and mDC were isolated from healthy donors using magnetically-labelled beads and treated with live HIV-1 IIIB, HIV-1 BAL, or Influenza virus with or without toll like receptor-7 ligand (R848). The ability of DC to stimulate T-reg was determined using co-culture assays followed by intracellular staining for FoxP3. Statistical analysis was performed using the non-parametric Mann-Whitney U test or the Wilcoxon matched pairs test. Significance was defined as $p<0.05$.

Results: Myeloid DC from HIV-1+ patients exhibited normal levels of ILT-3, -4, and -7 regardless of therapy status, whilst pDC from viremic patients expressed significantly higher levels of ILT-3 and lower levels of ILT-7 in comparison to healthy donors and treated patients. Activation of purified pDC with R848 in vitro resulted in a significant reduction in ILT-3 and ILT-4 expression compared to unstimulated pDC. Whilst, treatment of pDC with HIV-1 IIIB failed to reduce ILT-3 levels and resulted in moderate down-modulation of ILT-4, which remained statistically higher than that observed with R848. Co-treatment of pDC with R848 and HIV-1 IIIB, or HIV-1 BAL resulted in reversal of R848-mediated reduction of ILT-3 expression. Functionality of ILT-3 was further confirmed by its cross-linking on pDC that resulted in increased levels of FoxP3+ T-regs.

Conclusions: Elevated proportions of circulating pDC displaying higher levels of T-reg inducing molecules with a predisposition to chronically secrete IFN-alpha through down-regulation of ILT-7 characterise untreated HIV-1 infection. HIV-1 may subvert adaptive immunity through its ability to inhibit full maturation of pDC by blocking activation-induced down-regulation of ILT-3 and ILT-4, potentially leading to raised T-reg activity.

239 Innate Immune Reconstitution With Viral Suppression in HIV-1 Infection

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Background: HIV-1 infection leads to both marked immunodeficiency and to dysregulated immune activation and inflammation. Given the broad nature of immune dysfunction and pathogen susceptibility, we hypothesized that HIV-1 viremia would alter innate immune responses, the fundamental mediators of pathogen recognition. Using longitudinal samples collected before and after initiation of antiretroviral therapy (ART), we tested the capacity of myeloid dendritic cells (mDCs) and monocytes to respond to a panel of innate stimuli. We combined these direct measures of ex vivo cellular responses with measures of T cell activation and plasma inflammatory markers to elucidate the inflammatory environment and viral parameters associated with impaired innate immune function.

Methodology: Pre and multiple post-ART peripheral blood mononuclear cell (PBMC) samples were selected for 8 subjects identified in early HIV-1 infection. Cells were stimulated with heat killed Listeria monocytogenes (HKLM, TLR2 agonist), lipopolysaccharide (LPS, TLR4 agonist), or N-muramyl glycopeptide (NOD agonist), and stained for intracellular cytokine production (TNF-alpha, IL-1beta, IL-23) after 20 hours of culture. Matched plasma samples were tested for levels of LPS, soluble CD163 and CD14, and a panel of inflammatory cytokines.

Results: Declining viral load was correlated with increasing magnitude of monocyte and mDC response to LPS stimulation (% TNF alpha+; repeated measures analysis: $p<0.01$ for both cell types, rank correlations = -0.57 and -0.54). Responses also negatively correlated with CD8 T cell activation level ($p<0.01$) but were not related to CD4 count. Exploratory analyses indicate similar associations of declining viral load with increasing TNF alpha and IL-1beta responses to TLR2 agonists, and IL-1beta responses to NOD stimulation. Suppression of HIV-1 was associated with an increase in polyfunctional responses by monocytes and mDCs to LPS, NOD, and HKLM. Plasma viral load had the strongest association to innate cell function, although paired analysis of plasma samples revealed trends towards association between increasing magnitude of innate response and declining sCD163, sCD14 and LPS.

Conclusions: Suppression of HIV-1 viral load with ART was associated with increased innate immune cell responsiveness in longitudinal samples. Depressed innate immune function was most strongly tied to high viral load and T cell activation, possibly suggesting an innate exhaustion in HIV-1 viremia parallel to that seen in adaptive immunity. Identifying the drivers of innate immune dysfunction offers important insights into the determinants of HIV-1-associated immune deficiency and may help to identify patients at risk for immune reconstitution inflammatory syndrome following ART.

Session P-C11 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

CD4/CD8, Aging, and Immune Senescence

240 CD4:CD8 Ratio Remains Significantly Depressed Despite Viral Suppression With Effective ART

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Background: Inverted CD4:CD8 ratio is known to be indicative of advanced, untreated HIV infection. In the HIV-uninfected population, a low CD4:CD8 ratio has also been associated with near-term mortality in the elderly. This study aimed to characterize the CD4:CD8 ratio in untreated and treated HIV-infection, and to determine the relative dynamics of changes in each population over time during effective ART.CD4:CD8 ratio in HIV-infected individuals on effective antiretroviral (ARV) regimens.

Methodology: CD4:CD8 ratio was evaluated in HIV-infected subjects with viral loads >10,000 copies/µl ("non-controllers", n=42), those with undetectable viral loads on ART ("ART-suppressed", n=53), and HIV-uninfected subjects (n=22) from a longitudinal cohort study in San Francisco (SCOPE). In addition, CD4:CD8 ratio, and T cell phenotypes were evaluated in 25 non-controllers, 18 ART-suppressed, and 7 HIV-uninfected subjects.

Results: CD4:CD8 ratio in non-controllers, ART suppressed, and HIV-uninfected subjects was 0.25, 0.48, and 1.95 respectively (P<0.0001 for all comparisons). The increased ratio in ART-suppressed compared to non-controllers was driven by an increase of CD4+ T cells, with limited differences in the expanded CD8+ T cell population. We also studied longitudinal changes in ratio in a a subset of 15 individuals who had been on effective therapy for for a median of 3.7 years (1.0 - 6.9) and who had a median CD4+ T cell count of 482 (range 300-1079) and a ratio of 0.44 (range 0.21-1.52). With additional time on ARV (median of 3.1yrs, range 1.3-4.2 yrs), total CD4+ T cell counts increased by 101 cells/mcl (p=0.02) while CD8+ T cells generally remained stable (p=0.22), resulting in an overall increase in CD4:CD8 ratio from 0.44 to 0.60 (p=0.02). However, the overall gains in CD4:CD8 ratio was driven by only a few individuals (five of fifteen), with the majority of individuals showing minimal change in the ratio during this time.

Conclusions: Untreated HIV infection is associated with a low CD4:CD8 ratio. Effective therapy improves the ratio, but this improvement is primarily caused by increases in CD4+ T cell counts. Increases in the ratio are largely due to increased CD4+ T cells, with a persistently expanded CD8+ T cells limiting further normalization of the ratio. Only a minority of individuals demonstrated any further gains in CD4:CD8 ratio with prolonged ARV therapy. A low CD4:CD8 ratio is a biomarker of poor clinical outcomes in the elderly non-HIV infected population, but requires further studies of clinical correlation in HIV-infected individuals.

241 CMV Reactivation and Immune Aging in HIV-Infected Individuals Virologically Suppressed On ART

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Background: Immune abnormalities including T cell and macrophage/monocyte activation and immune senescence have been associated with age-associated co-morbidities in HIV. We hypothesize that reactivation of chronic herpes viruses (specifically CMV) may drive the persistent immune changes in HIV infection- despite good control with ART. We aim to define the occurrence of CMV reactivation and its relationship to age in HIV/CMV co-infected individuals compared to CMV monoinfected individuals and to define the contribution of CMV to a CD8 dominant pro-inflammatory phenotype of aging.

Methodology: We used stored samples from 20 virologically-suppressed HIV-infected and 9 sociodemographically-matched HIV-uninfected individuals enrolled in the Stanford HIV Aging Cohort (SHAC). Plasma CMV IgG antibody titer was measured, restricting our analysis to 19 of 20 HIV-infected and 8 of 9 HIV-uninfected participants who were documented to be CMV-infected. Flow cytometric analysis on peripheral blood mononuclear cells allowed phenotyping of both total immune subsets (bulk) and CMV-responsive T cells, identified by IFNγ production following CMV peptide pool stimulation (pp65 and IE-1 pools, JPT Peptide Technologies). We used Mann-Whitney tests and nonparametric Spearman correlations to evaluate p and r values.

Results: HIV-infected participants (median age 54.5, median nadir and current CD4 135 and 653 cells/µL, respectively) had significantly higher CMV IgG titer than similarly aged HIV-uninfected participants (p=0.002), suggesting higher rates of CMV reactivation. Higher CMV IgG titers were also correlated with increasing age in both HIV-infected individuals (r = 0.57; p = 0.010) and in the overall study population (r = 0.44; p = 0.021). Bulk T-cell phenotyping revealed a higher percentage of terminally-differentiated effector memory CD8+ T cells (CD27- CD28- CD45RA+) in HIV-infected individuals compared to similarly aged HIV-uninfected individuals (Median 18.7% vs. 4.9%, p=0.018). HIV-infected individuals exhibited increased presence of late-stage differentiated cells staining for the pro-inflammatory cytokine, IFNγ, compared to HIV-uninfected individuals (median IFNγ+ cells/ml: 4810 vs. 333; p=0.001), which correlated positively with a higher CMV IgG response (r = 0.43, p = 0.045). IFNγ+ late-stage differentiated cells correlated positively with duration of HIV infection (r = 0.6265, p = 0.0110), while showing no significant relationship with age.

Conclusions: More frequent reactivation of CMV in HIV may contribute to immune aging in HIV patients. The immune-senescent CD8+ T cells appear to be CMV specific and related to duration of HIV infection rather than age.

242 A Low CD4/CD8 Ratio During Effective ART Predicts Immunosenescence and Morbidity/Mortality

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Background: A low CD4/CD8 ratio in elderly HIV-uninfected adults is associated with increased morbidity and mortality. A subset of HIV-infected adults receiving ART fails to normalize this ratio, even after a normal peripheral CD4 count is obtained. The immunologic and clinical characteristics of this clinical phenotype remain undefined.

Methodology: We evaluated the associations of the CD4/CD8 ratio with 1) maturational subsets and markers of T-cell activation (%HLADR+CD38+) and senescence (%CD28- and %CD28-CD57+) of CD8+ T-cells in 67 treated HIV+ subjects with CD4≥500 cells/mm3 and VL<50 copies/mL and 15 HIV-CMV+ healthy controls; 2) inflammatory markers in 192 treated HIV+ adults; 3) the CD4/CD8 ratio in gut mucosa and lymph nodes in 32 and 10 treated HIV+ subjects, respectively; 4) early (≤6 months after estimated HIV infection) vs. later (≥2 years) ART initiation in 68 HIV+ adults; 5) the risk of serious non-AIDS events in two nested case-control studies of in 66 and 192 ART-suppressed HIV+ adults.

Results: Among individuals with an apparently normal CD4+ T cell count, the CD4/CD8 ratio significantly correlated with the %naïve (rho +0.34, P=0.005), %TEMRA (rho -0.37, P=0.003), and %CD28- (rho -0.43, P<0.001) CD8+ T-cells. Compared to HIV-CMV+ controls, ART-suppressed individuals with a low CD4/CD8 ratio (≤1st Qrt, 0.4) showed a markedly skewed CD8+ T-cell phenotype from naïve to TEMRA, and higher %HLA-DR+CD38, %CD57+CD28- and %CD28- CD8+ T-cells (all P<0.05), while those with a normal CD4/CD8 ratio (≥4th Qrt, 1.0) had normal levels. The CD4/CD8 ratio correlated substantially with sCD14, hs-CRP, IL-6 and the KT ratio-a marker of indoleamine-dioxygenase-1 induction-with only the KT ratio significantly correlated in the subgroup with CD4≥500 cells/mm3 (Rho -0.29, P=0.041). The peripheral CD4/CD8 ratio was similar to the ratio in gut mucosa (Rho=0.68, P<0.001) but not in lymph nodes. In a longitudinal study, early ART initiators had a faster CD4/CD8 ratio increase than later ART initiators (+0.44 vs. +0.25, respectively, P<0.001). After a median of 3 years of ART, early ART initiators had more CD4/CD8 ratio normalization (OR, 3.6; 95% CI, 1.2, 10.8). After controlling for age, gender, ART duration, nadir and CD4 count, each 10% decrease in the CD4/CD8 ratio was associated with 48% higher odds of serious non-AIDS events (P=0.045) and 13% higher odds of mortality (P=0.01).

Conclusions: A persistently low CD4/CD8 ratio during otherwise effective ART is associated with increased innate and adaptive immune activation, an immunosenescent phenotype, and higher risk of morbidity/mortality. This ratio may prove useful in monitoring response to ART and could identify a unique subset of individuals needed of novel therapeutic interventions.

243 CMV and HIV: A Double Hit On the CD4/CD8 Ratio

Talia Sainz[1], Sergio Serrano-Villar[2], Sulggi A. Lee[3], Peter W. Hunt[3], Elizabeth Sinclair[3], Jeffrey N. Martin[3], Joseph M. McCune[3], Steven G. Deeks[3]
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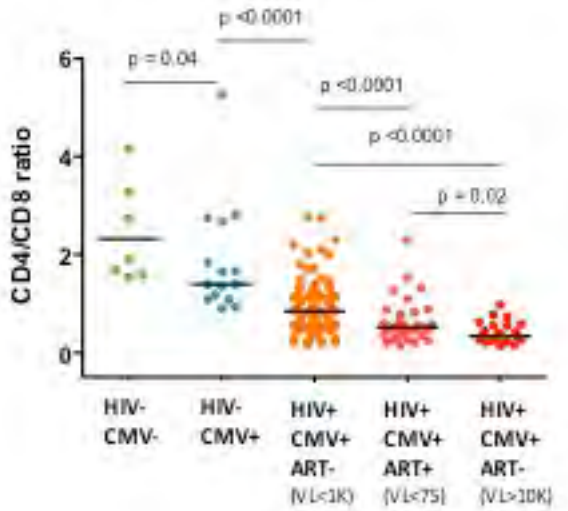
Background: Advanced age is associated with a number of immunologic abnormalities, including a low CD4/CD8 ratio and increased frequency of terminally-differentiated CD8+ T cells ("immunosenescence"). CMV infection significantly contributes to this immunosenescent phenotype. Although HIV infection is associated with high levels of CMV-related inflammatory responses and many of the classic markers of immunosenescence, the relative contribution of CMV and HIV to the development of T cell abnormalities during HIV disease is not known. We examined the impact of CMV and HIV on the CD4/CD8 ratio, which is one of the most validated markers of T-cell senescence.

Methodology: We analyzed 228 subjects, including 8 HIV-CMV-, 15 HIV-CMV+ and 205 HIV+CMV+ individuals [91 controllers (<1000 HIV RNA copies/mL), 91 ART-suppressed and 23 untreated]. We analyzed correlations between the CD4/CD8 ratio and CMV- and HIV-specific T cell responses [proportion of T cells expressing high levels of IFN-gamma, CD107-alpha, TNF-alpha and IL-2 after stimulation by CMV and HIV proteins (IE and pp65, and gag, respectively)].

Results: The CD4/CD8 ratio significantly changed across all subgroups, according to the different immunological background determined by HIV and CMV, as shown in the figure.

Among 228 individuals, high CMV-specific IFN-gamma production of CD8 T cells was associated with low CD4/CD8 ratio (Rho -0.30, P<0.01). Similar associations were observed for CMV-specific CD107-alpha, IL-2, TNF-alpha and CD8 T-cell response (all P<0.05). The effect of CMV-specific T cell response on ratio was more consistent than the association with either absolute CD4 or CD8 T cell counts, and was consistent within both the HIV- and the HIV+ ART-suppressed groups (in ART-suppressed, for IFN-gamma CD8 T cell response, Rho=-0.24, P=0.01). The CD4/CD8 ratio was also lower across all groups in subjects with higher HIV-specific CD4 T-cell responses, being the strongest correlations with IFN-gamma (Rho -0.25, P<0.001), IL-2 (Rho -0.23, P=0.001) and TNF-alpha (Rho -0.29, P<0.001) CD4 T-cell responses.

Conclusions: The specific inflammatory responses elicited by CMV and HIV are likely major drivers of a low CD4/CD8 ratio across the whole spectrum of HIV



disease. The CD4/CD8 ratio parallels well the progressive decline in immune competence determined by CMV and HIV, and might be considered in clinical settings as a surrogate marker of immunosenescence.

Session P-C12 Poster Session
Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**
Mucosal CD4 and TH17 Cells

244 Severe Depletion of Lung CD4 T Cells During HIV Infection Impairs Alveolar Macrophage Function

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Background: HIV establishes a widespread reservoir of infected cells, particularly within mucosal tissues, which house over 90% of the body's lymphocytes. In the lung HIV infects resident CD4+ T cells and macrophages, leading to virus-specific local responses. In 70% of all HIV patients this results in lung complications and increased susceptibility towards deadly diseases such as tuberculosis (TB). The risk of active TB rises from 5-10 % in a lifetime to 10% annually for those who are HIV-positive. However, the characterization of the effects of HIV infection on the lung immune system has been surprisingly incomplete.

Methodology: To study HIV infection in the lung, we made use of a humanized mouse model. 7 weeks after HIV-1 challenge, bronchoalveolar lavage fluid (BALF) and lung tissue were harvested. Alterations in the frequency, phenotypes and gene transcription of human macrophages and T cells in the alveolar space and lung tissue of HIV infected animals were analyzed using FACS, luminex and immunohistochemistry. Results were confirmed in BALF samples obtained from HIV-infected and uninfected individuals and surgical excess lung tissue. Further, alveolar macrophages from HIV infected and uninfected subjects were isolated and changes in the transcriptional profile determined using RNAseq.

Results: Prior to HIV infection, the majority of human CD4 and CD8 T cells in the lung and alveolar space were of an effector memory phenotype whereas the majority of blood T cells were naïve. Percentage of activated and CCR5+ CD4 T cells was significantly higher in the lung compared to PBMCs. HIV infection resulted in 3 fold higher depletion of CD4 T cells in lung tissue compared to blood whereas CD4 T cells in the alveolar space were almost completely depleted. Lung macrophage cell numbers were not altered after HIV infection however, CD40 expression was significantly reduced, which correlated with CD4 T cell depletion and decrease of soluble CD40L in BALF. Whole RNA sequencing analysis of human alveolar macrophages revealed over 160 genes differently expressed in macrophages isolated from HIV+ individuals compared to HIV negative control donors. Pathway analyses revealed significant down-regulation of pathways involved in pro-inflammatory cytokine responses and intracellular bacterial killing in the HIV+ individuals.

Conclusions: Prior to HIV infection, CD4 T cells in the lung have a memory phenotype, are activated and express CCR5. Upon HIV infection CD4 T cell depletion in the lung is much more severe relative to blood leading to impairment of T cell help for alveolar macrophages and down-regulation of important intracellular macrophage defense mechanism against bacterial infections such as tuberculosis.

245 Impaired IL-23 Signalling and Th17 Dysfunction in HIV Infection

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Background: Th17 cells maintain gut homeostasis by co-ordinating a variety of innate and adaptive immune responses. HIV infection causes a profound depletion of gut Th17 cells, contributing to loss of mucosal barrier function and microbial translocation, thus driving systemic immune activation. Despite normalization of circulating CD4+ T cell counts with highly active antiretroviral therapy (HAART), Th17 frequency and function often remain impaired. The IL-12 family cytokine member IL-23 plays a crucial role in maintaining normal Th17 cell function. We hypothesize that HIV inhibits IL-23 signalling in Th17 cells, resulting in Th17 dysfunction.

Methodology: Th17 cells were isolated from peripheral blood of HIV-seronegative donors by magnetic selection and infected with HIVCS204, a dual-tropic clinical isolate for 24 hours. Expression of IL-17 was examined by ELISA and flow cytometry. Levels of Th17-associated transcription factors STAT3 and retinoic acid orphan receptor C (RORC) mRNA expressed in response to IL-23 stimulation were quantified by qRT-PCR. Phosphorylation of STAT3, the primary transducer of IL-23 signalling, in response to IL-23 stimulation was assessed by flow cytometry. Th17 cells were then isolated from untreated and HAART-treated HIV-infected individuals, and STAT3 phosphorylation (pSTAT3) in response to IL-23 was examined. Expression of the IL-23 receptor protein IL23R on Th17 cells was examined by flow cytometry.

Results: *In vitro* HIV infection significantly inhibited IL-17 production in response to TCR and mitogenic stimulation. *In vitro* HIV infection also significantly reduced IL-23-induced pSTAT3 and expression of STAT3 and RORC mRNA. Th17 cells isolated from untreated and HAART-treated HIV-infected individuals showed complete loss of IL-23 responsiveness. IL-6 induced pSTAT3 was unaffected by *in vitro* and *in vivo* infection, suggesting that HIV infection results in specific inhibition of IL-23 signalling. Expression of the IL-23 receptor protein IL23R was comparable between HIV-seronegative controls, untreated, and HAART-treated HIV-infected individuals.

Conclusions: These results demonstrate that *in vitro* and *in vivo* HIV infection results in impaired IL-23 signalling which is not reversed by HAART and is not a result from reduced receptor expression, demonstrating that HIV interferes with IL-23-activated signalling pathways. These findings may explain the inability of HAART to restore Th17 frequency and function and the resulting persistent chronic immune activation observed in HIV-infected individuals.

246 Th17 and Tregs at Early HIV Infection Influence Disease Progression and HIV Specific CD8+ Responses

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Background: Th17 and Treg subsets have been related to HIV/SIV disease progression. Their role and direct relation with specific HIV-adaptive T cell responses during primary HIV infection (PHI) are unexplored topics. Aim: To analyze the frequency and balance of Th17 and Treg subsets and the correlation with clinical parameters, immune activation and HIV-specific responses during early infection.

Methodology: PBMCs were obtained from 6 healthy donors (HDs) and 28 HIV infected subjects: 6 elite controllers (ECs), 5 chronics (Chs) and 17 PHIs (within 6 months post-infection (mpi)). Th17 and Treg cells (baseline and 12 mpi samples) were identified as CD3+/CD4+ IL-17+ or CD25+/FoxP3+ (respectively). Data was compared inter/intragroups and correlated to clinical parameters (viral load (VL), CD4 counts), CD4+ or CD8+ CD38+/HLA-DR+ activated T cells and HIV-specific CD8+ responses (specifically a viral inhibitory activity (VIA) assay and intracellular cytokine staining (ICS) for IFN-gamma production and CD107a/b cytotoxicity markers) measured at baseline, 6 and 12 mpi, using parametric and nonparametric statistics.

Results: Chs had lower % of Th17 cells compared to HDs and ECs ($p=0.006$ and 0.021 respectively), among which frequencies were similar (median 0.14 vs 0.11 respectively). In PHI group, CD4 counts at 6 mpi directly correlated with baseline Th17 counts ($p=0.048$, $r=0.5$). Moreover, VL at 12 mpi inversely correlated with baseline % of Th17 ($p=0.041$, $r=-0.596$). Th17/Tregs ratio was higher for HDs compared to any HIV+ group ($p<0.01$), and within PHIs Th17/Tregs was directly associated with CD4 counts at 12 mpi ($p=0.017$, $r=0.793$). Significantly, Th17 and quality of HIV-specific CD8+ responses, previously observed to be protective, were directly associated: higher basal % of Th17 correlated with higher CD8+-mediated VIA at 12 mpi ($p=0.004$, $r=0.829$) and Th17 counts at 12 mpi also related with % of HIV CD8+/CD107a/b+/IFN-gamma+ cells ($p=0.024$, $r=0.847$). Regarding immune activation, as expected HDs had the lowest and Chs the highest % of activated T cells compared to the other groups ($p<0,05$). Of note, in PHIs activation occurs rapidly after infection and normalizes at 12 mpi ($p=0,004$). Importantly, Th17/Tregs ratio of groups altogether, negatively correlated with activated CD8+ and CD4+ T cells ($p<0.05$), suggesting a proper balance is associated with a lower level of immune activation.

Conclusions: Results indicate that higher counts and frequency of Th17 and higher Th17/Tregs ratio at early stages of HIV infection associate with slower disease progression in terms of clinical parameters and immune activation. Importantly, preservation of Th17 subset associates with the capacity to exert protective HIV-specific CD8+ responses at later times post-infection.

247 Profound Lung CD4+ T-Cell Depletion in HIV-Associated Chronic Obstructive Pulmonary Disease

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Background: As overall survival improves, individuals with chronic HIV infection become susceptible to other chronic diseases. In this regard, select HIV-infected individuals develop accelerated chronic obstructive pulmonary disease (COPD). We hypothesized patients with HIV-associated COPD develop dysregulation of lung mucosal immunity compared to HIV-infected individuals without COPD.

Methodology: To test our hypothesis, we evaluated the clinical characteristics in 11 HIV+COPD+ versus 10 HIV+COPD- individuals from a prospectively followed inner city cohort, and performed phenotypic/functional T cell analysis using multi-parameter flow cytomteric analysis. Consented subjects underwent bronchoalveolar lavage (BAL) to obtain lung mononuclear cells (LMNC) and same day blood draw for isolation of peripheral blood mononuclear cells (PBMC).

Results: HIV+COPD+ individuals had profound CD4+ T cell depletion with reduced CD4+:CD8+ T cell ratios and absolute CD4+ numbers in LMNC ($p<0.002$), not observed in PBMC. In addition, HIV+COPD+ individuals had significantly decreased HIV-specific CD4+IFN-γ+ T cell responses to the antigens Gag ($p<0.05$) and Pol ($p<0.02$) and HIV-specific CD4+ T cell multi-functional responses (IFN-γ, TNF-α, IL-2, MIP-1β and CD107a) in LMNC from HIV+COPD+ patients compared to HIV+COPD- controls ($p=0.01$), but not in the PBMC ($p=0.6$). In contrast, HIV-specific CD8+ T cell responses were preserved in HIV+COPD+ individuals similar to controls. Lung mucosal CD4+ T cells from HIV+COPD+ individuals expressed increased levels of surface Fas death receptor (CD95) and programmed death-1 (PD-1) ($p\leq0.02$). HIV RNA levels from BAL supernatants were increased in HIV+COPD+ patients not on anti-retroviral therapy (ART) ($p<0.01$). To investigate the mechanism for CD4+ T cell depletion, we measured expression of the early apoptosis marker, annexin V. Baseline annexin V expression was increased in LMNC CD4+ T cells ($p\leq0.05$) from HIV+COPD+ patients and re-stimulation with HIV antigen markedly increased expression of annexin V and this was significantly attenuated with Fas blockade ($p\leq0.0002$). Lastly, LMNC, but not PBMC, CD4+:CD8+ ratios were significantly correlated with forced expiratory volumes in one second (FEV1), a physiologic marker of COPD ($p=0.027$, $R=0.48$).

Conclusions: Together, our findings reveal profound lung mucosal CD4+ T cell depletion and dysregulation of HIV-specific CD4+ T cell immunity in HIV-associated COPD. Our results also indicate increased BAL HIV-RNA, and activation-induced cell death of lung CD4+ T cells via a Fas-dependent mechanism in HIV-associated COPD. Finally, our data suggests lung mucosal CD4+ T cell depletion plays a role in the pathogenesis of HIV-associated COPD.

248 Site Specific HIV-Infection of Th17 Cells in the Human Female Reproductive Tract

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Background: Successful prevention of sexual transmission of HIV in women requires a substantial increase in our knowledge regarding HIV-target cell availability and regulation in the female reproductive tract (FRT). In this study we analyzed CD4+ T cell phenotype and susceptibility to HIV-infection in three different FRT compartments likely involved in HIV-acquisition: endometrium (EM), endocervix (CX) and ectocervix (ECX).

Methodology: Tissues from EM, CX and ECX from pre- and post-menopausal women were enzymatically digested and CD4+ T cells isolated with magnetic beads. CD4+ T cell phenotype was analyzed by flow cytometry and mRNA analysis used to determine transcription factor and cytokine expression. CD4+ T cells were also infected with HIV (BaL) in vitro and p24+ cells analyzed by flow cytometry 6 days after viral challenge.

Results: We found that Th17 cells represent a major subset in FRT tissues with differential distribution among sites. In pre-menopausal women, CD4+ T cells in general, and also Th17 cells in particular, were significantly lower in the EM relative to the CX and ECX. Differences in T cell subsets were found between pre- and post-menopausal women in the EM, but not in the CX and ECX. Th17 cells were the main CD4+ T cell population expressing CCR5 and were more susceptible to infection than the other CD4+ T cell subsets. Susceptibility to HIV infection was different between tissues, with CD4+ T cells from the EM being the least susceptible.

Conclusions: Unlike the EM, Th17 cells in the CX and ECX are a major population that has increased susceptibility to HIV infection. Differences in Th17 cell distribution may account for differences in HIV-susceptibility between EM, CX and ECX. Our results provide valuable information for designing preventive strategies directed at targeting highly susceptible target cells in the FRT. Supported by NIH contract HHSN272201000001C and NIH grants AI102838 and AI071761 (CRW).

249 Transcriptional Profiling Identifies New Mechanisms of HIV Permissiveness in Primary Th17 Cells

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Background: Th17 cells are major players in mucosal immunity. Th17 cells are highly permissive to HIV infection, while Th1 cells are relatively resistant. As a consequence, Th17 but not Th1 cells are depleted in HIV-infected subjects and their frequency is not restored under antiretroviral therapy. Thus, there is a need for new therapeutic strategies to prevent Th17 cell infection and depletion. We hypothesized that Th17 *vs.* Th1 cells express a distinctive transcriptional profile compatible with HIV permissiveness.

Methodology: Leukapheresis were collected from uninfected subjects (n=10). Th17 (CXCR3-CCR4+CCR6+) and Th1 (CXCR3+CCR4-CCR6-) subsets were sorted by flow cytometry and stimulated *via* CD3/CD28. Total RNA was extracted (Qiagen). The expression of 47,000 probe-sets was tested using the Illumina technology. Genes were classified by biological function using GO and GSEA. Cytokine production and proliferation was measured by intracellular straining, CFSE dilution assay and flow cytometry. Levels of HIV-p24 and integrated HIV-DNA were measured by ELISA and real-time PCR, respectively. The Amaxa RNA interference technology was used to evaluate the functional role of top-modulated genes.

Results: Among 2,533 "present calls", 1,335 and 1,198 probe-sets were upregulated and downregulated, respectively, in Th17 *vs* Th1 cells (p-value<0.05; 1.3-fold change cutoff). Genes associated with T-cell differentiation (RORC), TCR signaling (ZAP-70, Lck, MAP3K4), activation/apoptosis (PTPN13), and HIV replication (PPARG) were upregulated in Th17 *vs.* Th1 cells. Differential expression of these transcripts was validated by RT-PCR and/or fluorescence microscopy. HIV permissiveness was associated with high sensitivity to TCR triggering, increased proliferation potential, and superior NF-κB DNA-binding activity in Th17 *vs.* Th1 cells. RORC and MAP3K4 RNA interference decreased HIV replication, while PPARG silencing induced opposite effects. Genes down regulated in Th17 *vs.* Th1 cells and previously linked to HIV resistance included CCR5 binding chemokines and IFN-induced molecules. By using HIV-VSVG-GFP pseudotyped virions, we demonstrate that HIV permissiveness in Th17 *vs.* Th1 is regulated by both entry and post-entry mechanisms.

Conclusions: Our study reveals the transcriptome of HIV permissive Th17 and resistant Th1 cells; identifies RORC, kinases associated with TCR signaling and NF-κB as key regulators of HIV replication in Th17 cells; and demonstrates that HIV permissiveness in Th17 cells is regulated by mechanisms acting at both entry and post-entry levels. Novel therapeutic strategies aimed at interfering with Th17-specific transcripts may limit HIV replication, while preserving the beneficial role of Th17 cells in mucosal immunity.

Session P-C13 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

In Vitro Studies

250 Elevated Soluble CD40 Ligand During HIV Infection Suppresses Dendritic Cell Function

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Background: Soluble CD40 ligand (sCD40L) levels are increased in various inflammatory states, including human immunodeficiency virus (HIV) infection. sCD40L exists in both monomeric and multimeric forms, however, the majority of circulating sCD40L is monomeric. sCD40L is predominantly released

by activated platelets, which we have previously shown are increased during antiretroviral-treated HIV disease. In this study we tested the hypothesis that monomeric sCD40L suppresses dendritic cell (DC) function, thus contributing to immune suppression during HIV infection.

Methodology: We compared the effects of monomeric versus multimeric sCD40L on monocyte-derived DC maturation after overnight stimulation and cytokine expression following subsequent overnight Toll-like receptor (TLR) stimulation via FACS analysis and cytokine bead arrays. We also evaluated T cell proliferation and Th1-skewing capacity of DCs exposed to monomeric versus multimeric sCD40L following co-culture with carboxyfluorescein succinimidyl ester (CFSE) labeled naïve CD4+ T cells.

Results: We found that only sCD40L multimer, but not monomer, matures DCs after overnight incubation, as measured by CD86 surface expression. Furthermore, DCs incubated with sCD40L multimer, but not monomer, enhance T cell proliferation. However, both monomeric and multimeric forms of sCD40L suppress the production of the Th-1 skewing cytokine, IL-12, by DCs in the setting of subsequent TLR stimulation with Poly ICLC (fold change decrease by 3 and 5 respectively). DCs incubated with either sCD40L monomer or multimer suppress Th-1 skewing of naïve CD4+ T cells in the setting of subsequent TLR stimulation with Poly ICLC, as measured by interferon-gamma production.

Conclusions: In summary, multimeric sCD40L activates DCs to become potent antigen presenting cells and appropriately downmodulates the ability of DCs to be subsequently stimulated with TLR ligands after initial activation, whereas the predominant monomeric form of sCD40L plays a solely immunosuppressive role on DC function. Thus, elevated levels of monomeric sCD40L during HIV infection may hinder the ability of DCs to stimulate adaptive responses during the course of disease. Future mechanistic studies will define differential signaling pathways induced by monomeric versus multimeric sCD40L in DCs. Future clinical trials will test whether anti-platelet therapy may reduce circulating sCD40L and improve DC function.

251 Chronic Exposure To Type-I IFN Under Lymphopenic Conditions Alters CD4 T Cell Homeostasis

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Background: HIV infection and the associated chronic immune activation alter T cell homeostasis leading to CD4 T cell depletion and CD8 T cell expansion. While the acute CD4 depletion observed in the initial phase of HIV infection is likely due to direct cytopatic effects of the virus, the mechanism/s underlying the steady decline of the CD4 T cell pool during the chronic phase of infection are not totally understood. We hypothesized that the homeostatic response to HIV-induced CD4 T cell depletion occurs in an inflammatory environment rich in Type-I IFNs and driven by HIV replication and that combination of these two distinct forces: lead to a form of immune T cell activation that results in a decline in the CD4 T cell pool and an increase in the CD8 T cells.

Methodology: We analyzed the in vitro effects of IL-7 and IFN-α to increase the total expression levels of the Signal Transducer and Activator of Transcription (t-STATs) in CD4 and CD8 T cells from healthy controls (n=12). We also analyzed the relationships between CD4 T cell counts and tota levels of STAT-1 (t-STAT-1) in HIV infected patients (n=53). To examine the combine effects of lymphopenia and IFN-α in vivo we developed an animal model in which lymphocytes were adoptively transferred into lymphopenic mice that were receiving chronically administered IFN-α.

Results: IL-7 in vitro upregulated the expression levels of t-STAT-1, -2, -3 and enhanced T cell responsiveness to IFN-α as measured by phosphorylation of STAT-1. In patients with HIV infection and suppressed viremia <50 copies/ml, levels t-STAT1 were inversely correlated with the degree of lymphopenia ($R= -0.52$, $p< 0.01$ and $R= -0.34$, $p< 0.01$) in CD4 and CD8 T cells respectively. In addition, a positive correlation between STAT-1 and IL-7 serum levels was observed in CD4 ($R= 0.38$, $p= 0.01$) but not in CD8 T cells. In a murine model, lymphopenia and chronic treatment with IFN-α led to diminished survival of CD4 T cells and an expansion of CD8 T cells, thus recapitulating the alterations of the homeostasis of these pools observed in patients with HIV infection.

Conclusions: IL-7 in vitro and lymphopenia in vivo can modulate T cell responsiveness to Type I IFNs, suggesting a synergistic interaction of these cytokines. Therefore, the persistent stimulation of this pathway in the setting of a lymhopenic host, such as chronic untreated HIV infected patients could be deleterious for CD4 T cell homeostasis and may contribute to the aberrant immune activation and eventual depletion of the CD4 T cells. The analysis of these pathways may contribute to the development of new strategies to reverse the dysregulation of the T cell pools seen in patients with HIV infection.

252 IL-15 Induces Id2 To Drive Effector Differentiation of CD8 TM and EM Cells While Maintaining CM Pools

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Background: During HIV infection the majority of CD8+ T cells are arrested in their differentiation potential at the TM stage and lack effector function. Our transcriptional profile of HIV-specific CD8+ T cells from chronic HIV infected patients showed downregulation of the regulator of differentiation, Id2. The common gamma chain cytokines (IL-2, IL-7, IL-15, IL-21) are necessary for the generation and maintenance of virus-specific effector CD8+ T cells. A better understanding of signal transduction pathways involved in the regulation of CD8+ T cells is critical for the development of effective HIV immunotherapies aimed at restoring effector and cytotoxic ability of antigen-specific CD8+ T cells. In this study we have focused on defining the role of IL-15 in promoting CD8+ T cell differentiation and effector function mediated by upregulation of Id2.

Methodology: CD8+ T cell subsets were sorted from total PBMCs obtained from healthy volunteers for naïve, CM, TM, EM and EMRA subsets. Gene expression profiles were assessed ex vivo by gene array and after IL-15 or TCR stimulation by multiplex PCR. Shut-down of Id2 was performed by siRNA assay on total memory CD8+ T cells and functional analysis was assessed by flow cytometry. PBMCs from chronic HIV infected patients were stimulated with IL-15 with an optimum HLA class I restricted HIV peptide. At day five we measured activation (Ki67, GrzB) and differentiation of tetramer positive cells

(Id2 levels and CCR7,CD27,CD45RA). Cytolytic activity was measured by a cell-based assay that measures the capacity of HIV-specific CD8+ T cells to kill CD4+ T cells loaded with their cognate peptide.

Results: We show that Id2 and its target genes are mostly expressed in human EM and EMRA while being poorly expressed in CM. Silencing of Id2 impacts on T cell survival, proliferation and differentiation. Id2 expression was regulated by TCR but also by IL-15 which was the most effective among common γ-chain cytokines in upregulating Id2 expression and inducing proliferation, and survival of CD8+ EM cells. IL-15 induced proliferation of all memory subsets from healthy subjects while inducing differentiation, GzmB production, and cytotoxic effector function of CD8+ TM and EM cells while maintaining CM pool. Stimulation of CD8+ cells from HIV infected subjects with peptide plus IL-15 induced Id2 expression and differentiation of tetramer+ TM cells, and restored their HIV-specific cytotoxic activity.

Conclusions: Immunotherapy with agents such as IL-15 treatment that increase Id2 expression levels, in combination with antiretroviral therapy and blocking PD-1 signaling may provide a novel way to restore and enhance the immune response that triggers the functional re-activation of HIV-specific CD8+ T cells and the killing of latently HIV infected CD4+ T cells.

253 Double Stranded RNA Stimulates IL-1β Secretion in Cervical Epithelial Cells via the Inflammasome

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Background: The female genital tract (FGT) is a critical mucosal site for HIV transmission, and inflammation in the FGT prior to HIV exposure is thought to facilitate HIV infection. IL-1β has been identified as one of the key pro-inflammatory cytokines associated with HIV acquisition risk in women when detected at high levels in cervicovaginal (CV) lavages. Little is known about the mucosal factors that induce CV IL-1β secretion, but identification of the stimuli and inflammatory pathways could lead to anti-inflammatory interventions that may reduce HIV acquisition risk. We hypothesize that pathogen-associated molecular patterns (PAMPs) lead to activation of the inflammasome in the FGT, resulting in IL-1β secretion.

Methodology: To determine whether PAMPs induce inflammasome activation in the female genital tract, primary human immortalized endocervical (End1) and ectocervical (Ect1) epithelial cell lines were treated with TLR 2/6, 3, 4, 7/8, and 9 ligands followed by ATP. Activated caspase-1 was measured with a FAM-YVAD-FMK fluorescent probe and detected by flow cytometry, with exclusion of necrotic cells using propidium iodide. IL-1β secretion was assessed independently by ELISA (R&D) or in conjunction with other human cytokines by Luminex (Millipore). Quantitative PCR was performed using validated primers and normalized to human GAPDH. Humanized BLT mice received repeated intravaginal poly(I:C) treatments, and inflammatory responses were measured in CV lavages by Luminex.

Results: The TLR3 and RIG-I agonist poly(I:C) induced a two-fold increase in activated caspase-1 in End1 cells ($p<0.05$), and ODN2006 induced a three-fold increase in End1 and Ect1 cells ($p<0.05$) relative to no treatment. Poly(I:C) treatment also caused a significant and dose-dependent increase in IL-1β secretion from both End1 and Ect1 cells ($p<0.01$), while other TLR ligands did not. TLR3, RIG-I, and NLRP3 were expressed at baseline in both End1 and Ect1 cells and upregulated by poly(I:C) treatment. In response to poly(I:C) but not LPS and FSL1, End1 and Ect1 cells strongly upregulated expression of human beta defensin 2 and IFN-β. In vivo, repeated intravaginal treatment of poly(I:C) in humanized mice induced secretion of pro-inflammatory cytokines like human IL-1β and IFN-α2, as well as T cell chemoattractants such as RANTES and MIP-1β.

Conclusions: Poly(I:C) induces IL-1β secretion when applied to human cervical epithelial cells in vitro and humanized mice in vivo. The mechanism of IL-1β secretion appears to be inflammasome mediated, as measured by caspase-1 activation, and NLRP3 and RIG-I are potential triggers. Future work will determine which bacteria and viruses are associated with genital IL-1β secretion and the potential role in mediating risk of HIV acquisition in women.

254 Alpha-Defensins Modulate HIV Transcytosis: Role of STI-Mediated Enhancement of HIV Transmission

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Background: Sexually transmitted infections (STIs) increase the likelihood of HIV transmission. Defensins are antimicrobial peptides important for innate immunity at the mucosa. Alpha-defensins, including human neutrophil defensins 1-3 (HNPs1-3) and human defensin 5 (HD5), are elevated at the genital mucosa in individuals with STIs, suggesting their role in early events of HIV infection. HD5 and HD6 promote HIV infectivity and contribute to enhanced HIV infection of conditioned media from Neisseria gonorrhoeae-exposed female genital epithelial cells. In contrast to HD5 and HD6, HNPs exhibit anti-HIV activity in vitro; however, increased levels of HNPs have been associated with enhanced HIV acquisition. HIV can cross the mucosal epithelium by transcytosis. In this study, we examined the effect of alpha-defensins on tight junction formation, permeability, and HIV transcytosis in polarized epithelial cells.

Methodology: Endocervical (A2EN) or intestinal (Caco) epithelial cells were grown and polarized in 24-well transwell inserts for 7 days. Defensins were added to the apical side of polarized cells and incubated for 24 and 48h. Tight junction was assessed by immunostaining with antibodies against ZO-1 or occludin. Transepithelial resistance was measured by an EVOM voltmeter or by cellZscope to monitor the physical barrier function. HIV transcytosis was determined by addition of HIV-1BAL at the apical side of epithelial cells followed by monitoring HIV at the basolteral side using HIV p24 ELISA.

Results: Alpha-defensins caused discontinuation of tight junctions and nuclear localization of occludin in polarized epithelial cells. HNP-1 significantly increased the epithelial permeability. The levels of transcytosed HIV were increased in defensin-treated polarized epithelial cells compared to untreated control.

Conclusions: Our results show that defensins can affect the integrity of the mucosal epithelium, leading to an increase in HIV transcytosis. Our study offers a new role of defensins in enhancement of HIV transmission in the setting of sexually transmitted infections.

255 Exposure To IFNα Leads To Generation of IL-10-Producing Tr1 Cells

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Background: In HIV-1 infection elevated serum levels of interferon alpha (IFNα) and Interleukin-10 (IL-10) are associated with immune hyperactivation and disease progression. Recently, coexpression of CD49b and LAG-3 was shown to identify Type 1 regulatory cells, which secrete large amounts of the immunesuppressive cytokine IL-10. This study aimed at assessing whether IFNα production during HIV infection might directly cause immune activation and increased expression of Tr1 cells.

Methodology: Plasmocytoid dendritic cells (pDC) (BDCA2+CD123+) and Tr1 (CD3+CD4+CD49b+LAG-3+) cells in peripheral blood of seronegative controls (n = 10) and HIV-1+ subjects (viremic: n = 15; elite controllers n = 5) were quantified by flow cytometry. Spontaneous IFNα and IL-10 expression was assessed by cytokine secretion assays. In an in vitro model of primary antigen-driven immune response, CD4+ T cells from uninfected donors were activated and expanded for 7 days with monocyte-derived dendritic cells (MDDC) in the presence (or absence) of 10 ng/ml IFNα supplied every second day. We used cytokine expression to profile CD4+ T cell subsets (IFN-γ and IL-2 for Th1; IL-4 for Th2; IL-10 for Tr1; IL-17 for Th17 generated in the presence or absence of IFNα. Data (expressed as mean and standard error of the mean, SEM) were analyzed using Mann Whitney tests.

Results: We found higher frequency of circulating Tr1 cells in viremic HIV-1+ patients (1.2% ± 0.5) vs. elite controllers (0.5% ± 0.2; $p<0.05$). In contrast, lower frequency of circulating pDC was observed in viremic (0.2% ± 0.02) vs. elite controllers (0.5% ± 0.07; $p<0.01$) vs. controls (0.8% ± 0.08; $p<0.0001$). Elevated IFNα secretion (geometric mean fluorescence intensity, GMFI) was found in viremic patients (12.4 ± 1.28) vs. elite controllers (4.4 ± 1.2; $p=0.02$) and controls (Mean 8.9 ± 2.9; $p=0.012$). CD4+ T cells activated and expanded in vitro in the presence of IFNα expressed lower levels of Th1, Th2 and Th17 cytokines, and higher levels of the Tr1 cytokine IL-10.

Conclusions: Our results suggest that over-expression of IFNα during HIV-1 infection drives the generation of Tr1 cells that produce the immunosuppressive cytokine IL-10.

256 TNF Drives Foam Cell Formation by Monocytes From HIV+ Donors in an **In Vitro** Atherosclerosis Model

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Background: HIV+ individuals have an increased risk of cardiovascular disease (CVD) which is independent of traditional risk factors, but the mechanisms driving this are unknown. We have recently shown that monocytes are activated in HIV+ patients despite combination antiretroviral therapy, and that this is associated with chronic inflammation. The migration of monocytes across endothelial blood vessel walls into developing plaques is a critical early event in atherosclerosis. We hypothesize that inflammation increases the proatherogenic properties of monocytes and drives CVD in HIV+ individuals.

Methodology: We have developed an in vitro model of atherosclerotic plaque formation, which enables monocyte transendothelial migration to be studied using purified donor monocytes and primary endothelial cells. We measured the rates of forward and reverse transendothelial migration, and also the propensity of monocytes to ingest lipids and become inflammatory foam cells (associated with plaque progression) using a combination of phase contrast- and fluorescent live cell microscopy and flow cytometry.

Results: Monocytes from HIV+ individuals showed increased foam cell formation and an impaired ability to migrate out of our atherosclerotic plaque model ($p<0.05$ for all, n=16 HIV+ donors and 7 controls). Serum from virologically suppressed HIV+ individuals contained higher concentrations of TNF (median 5.7 vs 3.5 pg/ml for controls, $p=0.016$) and increased foam cell formation in autologous HIV+ as well as uninfected control monocytes. As expected, TNF increased monocyte migration but we additionally found that blocking TNF receptor ligation post migration inhibited foam cell formation (38.9% vs 7.5% for istotype vs anti-TNF treated control monocytes, $p=0.002$, and 59.1% vs 10.8%, $p<0.0001$ for HIV+ monocytes). Live cell imaging confirmed monocytes from HIV+ individuals showed reduced post-migration speed, consistent with increased foam cell formation. Flow cytometric analysis of foam cells showed greater intracellular TNF than non-foamy migrated macrophages, revealing their pro-inflammatory nature.

Conclusions: Monocytes in HIV+ individuals are primed for foam cell formation following transendothelial migration. In addition to established effects on endothelial cells to promote leukocyte migration, TNF also increases the propensity for monocytes to develop into inflammatory foam cells and thus become retained in subendothelial plaques. Elevated TNF levels persist in HIV+ individuals despite virological suppression and may contribute to increased risk of atherosclerosis. These data provide a critical mechanistic link between chronic inflammation, monocyte activation and increased CVD risk in HIV+ individuals.

257 HIV-Altered mRNA Expressions of Type 1 IFN Pathway Related To Activation/Exhaustion in CD4+ T Cells

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Background: Recently, the LCMV model study suggests a mechanism whereby persistent viruses modulate Type I Interferon (IFN)-signaling during chronic infection leading to hyperactivation and immune exhaustion in mice. HIV+ patients treated with peg-IFN-α had sustained virologic suppression and

decreased levels of integrated HIV DNA. These findings suggest that type-1 IFN may play a key role in supporting both protective and pathogenic effects in HIV infection. Here we identified 18 host genes that are involved in Type-1 IFN response: IFNs & Receptors, IFN-signaling, and IFN-stimulated genes (ISGs)/cytokines in HIV+ patients and healthy controls. Association between immune activation/exhaustion and expression levels of selected genes was analyzed in this study.

Methodology: CD4+ cells were purified from PBMCs from 49 subjects (33 HIV+ and 16 Healthy controls) by using anti-CD4 microbeads (Miltenyi Biotec). mRNA was isolated and reverse transcribed to cDNA by iScriptTMcDNA Synthesis Kit (Bio-Rad) and expression levels were evaluated by RT-PCR array (Applied Biosystems). β-actin and GAPDH were used as housekeeping genes to normalize gene expression results. All statistical analyses were conducted using STATA 11.2 and R statistical softwares. The fold changes were obtained from the 2-ΔΔCt method and the p-values were obtained from Wilcoxon rank-sum test. To account for the multiple testing issues, adjusted p-values were obtained using the Benjamini and Hochberg method to control for false discovery rate (FDR).

Results: Compared to CD4+ T cells from healthy controls, gene expression levels of IFNAR1, JAK1, and TRIM5 were significantly decreased ($p = 0.0002$, 0.02, and 0.046, respectively) and CD80, CXCL10, IL15, and MX1 ($p = 0.03$, 0.03, 0.003, and 0.03, respectively) were increased in CD4+ T cells from HIV infected patients. Expression levels of IFNAR1, JAK1, and CXCL10 were also significantly associated with HIV viremia in this study. Moreover, levels of CD4+ T cell activation (CD38+HLA-DR+) and CD4+ T cell exhaustion (PD-1+) were significantly inversely correlated with IFNAR1 and JAK1 levels and directly correlated with OSA1, MX1, ISG15, IL15, CXCL10, and IRF7 mRNA expression levels.

Conclusions: Our results demonstrate that during HIV infection there is a complex, defective type-1 IFN response, including decreased HIV restriction factor and IFN-α receptors/signaling genes and increased ISGs at the same time. HIV-1 replication can also modify type-1 interferon responsiveness and alters the expression of ISGs. These results suggest that HIV could perpetuate interferon-related immune dysfunction and activation that underlies HIV pathogenesis, and thus reveals possible molecular mechanisms contributing to T cell exhaustion.

258 Dysfunctional High Density Lipoprotein Directly Upregulates T Cell Activation in HIV-1 Infection

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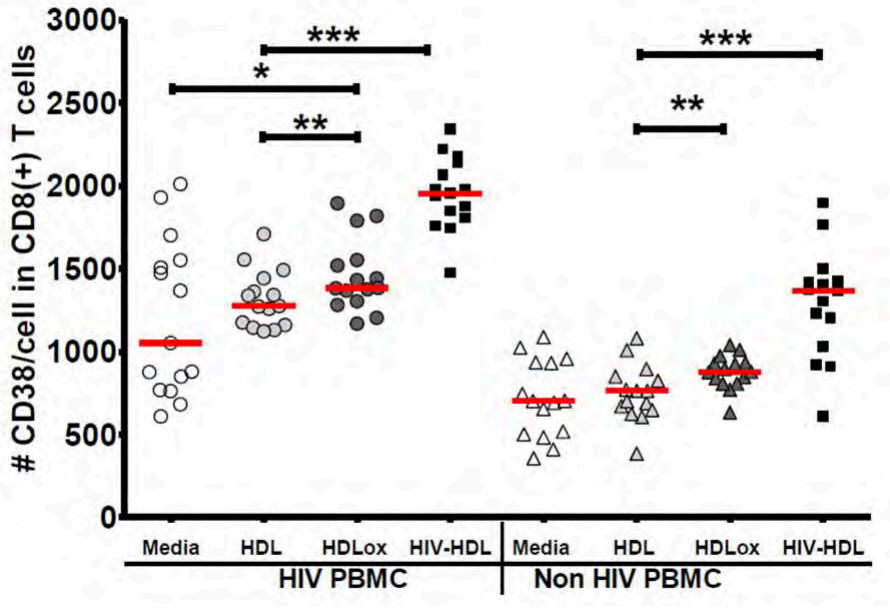
Background: The mechanisms that drive immune activation in HIV-1-infection remain unclear. We have recently shown that HIV-1-infected subjects have dysfunctional (oxidized) HDL that is associated with biomarkers of T cell activation. Herein, we investigated whether in vivo modified native dysfunctional HDL from HIV-1 infected subjects (HIV-HDL) and in vitro oxidized HDL (HDLox) directly upregulate T cell proliferation and activation in vitro.

Methodology: HIV-HDL was isolated from HIV-1 infected subjects (n=8) with suppressed viremia (HIV-1 RNA <50 copies/mL) on antiretroviral therapy (ART) known to have dysfunctional HDL based on a validated biochemical assay. Pooled HDL from healthy subjects was oxidized in vitro using an in vivo generated potent lipid oxidant (Drug Metab Lett. 2010; 4:139-48)(HDLox). Peripheral blood mononuclear cells (PBMCs) from HIV-1 infected (n=15) subjects with suppressed viremia on ART and uninfected (n=15) subjects were incubated with serum free media, anti-CD3 antibody and IL-2 for 72 hours with or without HIV-HDL, HDLox (6.25 ug/ml). Immune activation and proliferation index (PI) was assessed on T cells (#CD38/cell, % CD38+DR+ cells) of HIV-1 infected and uninfected subjects using flow cytometry and the Quantibrite method. Paired T-test was used for comparison of values between pairs.

Results: All HIV infected subjects were male, 65.2% were white with a median age 41 (range 18-58), median CD4+ T cells 510 cells/mm3 (IQR: 401-620). Addition of HDLox, HIV-HDL significantly ($p<0.01$) increased #CD38 on CD8+ T cells (Figure, Medians are shown), % CD38+DR+ CD8+ T-cells (not shown) compared to addition of normal HDL. Similar results were found in CD4+ T cells (not shown). Compared to HDL, HDLox directly increased PI of T cells (median 1.45 vs 1.31, $p<0.001$), T cell expression of INF-γ (median 12.3% vs 8.7% INF-γ+ T cells, $p<0.01$) and IL-2 (median 7.13% vs 5.37% IL-2+ T cells, $p<0.01$) and expression of both CXCR4 (median fluorescence intensity [MFI] 757 vs 679, $p<0.001$) and CCR5 (MFI 200 vs 164, $p<0.01$) on CD4+ T cells in HIV-1 infected but not in uninfected subjects.



Conclusions: Our results suggest a costimulatory effect of dysfunctional HDL on T cells of HIV-1-infected subjects with suppressed viremia on ART. Since HIV-1 infected subjects have dysfunctional HDL compared to uninfected subjects, further studies are warranted to evaluate whether modified lipoproteins may contribute to T cell activation in HIV-1 infection despite successful virologic therapy.

259 Dysfunctional High Density Lipoprotein Directly Reduces HIV-1-Specific Antiviral Responses

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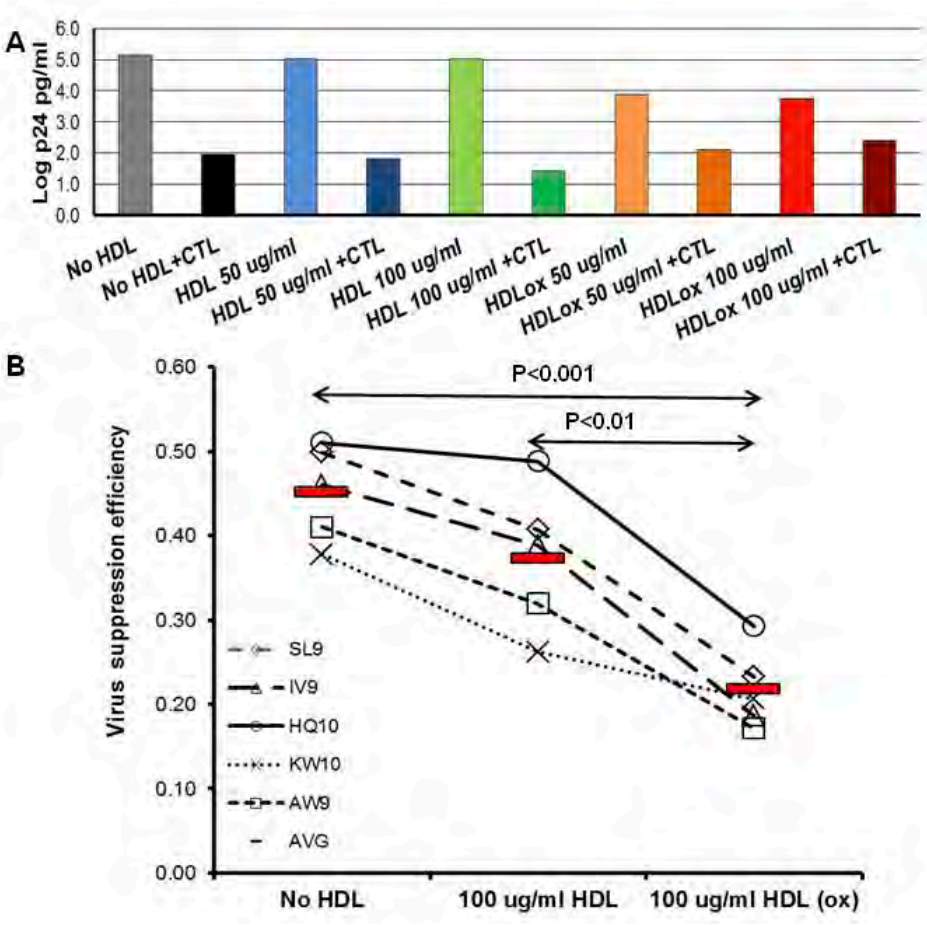
Background: Oxidized lipids play key roles in both viral replication and T cell biology and oxidized lipoproteins may directly affect adaptive immunity. High density lipoprotein (HDL) has many functions including the disposal of oxidized lipids. However, in systemic inflammatory states, it can become oxidized (HDLox) and dysfunctional. To examine effects of oxidized HDL that may potentiate HIV-1 replication and further drive immune activation we evaluated the in vitro effects of HDLox on the antiviral activity of HIV-1-specific CD8+ T-cells (CTLs).

Methodology: Pooled HDL from healthy subjects was oxidized in vitro using 13(S)-hydroperoxy-9Z, 11E-octadecadienoic acid (13(S)-HPODE), an in vivo generated potent lipid oxidant that has previously been shown to modify HDL in vivo and make it dysfunctional. T1 cells were infected with HIV-1 NL4-3.1 at low multiplicity and cultured with or without HIV-1 specific CTLs (Figure) in the presence of normal HDL or HDLox (50-100 ug/ml). Viral replication was assessed by p24 ELISA. At six days after infection virus suppression was quantified by using a virus suppression assay and was calculated as: "Suppression" = (Log10 pg/ml p24 antigen without CTL) - (Log10 pg/ml p24 antigen with CTL) and Virus Suppression Efficiency as: "Suppression Efficiency"= "Suppression" ÷ (Log10 pg/ml p24 antigen without CTL). Paired T-test was used for comparison of values between pairs.

Results: A representative experiment from a Gag-specific CTL clone is shown in Figure 1A. HIV-1-specific CTLs reduced Log10 pg/ml p24 antigen and suppressed virus replication but HDLox reduced the suppression efficiency of HIV-1-specific CTLs in a dose-dependent way (Figure).

Conclusions: Dysfunctional (oxidized) HDL but not normal HDL reduced the ability of HIV-1-specific CTLs to suppress viral replication. Thus, oxidized HDL may contribute to viral persistence in vivo through dysfunction of cellular antiviral immunity. Since HIV-1 infected subjects have dysfunctional HDL compared to uninfected subjects, further studies are warranted to evaluate whether modified lipoproteins may contribute to immune activation in HIV-1 infection.



Session P-C14 Poster Session
Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**
Genomics and Endogenous Retroviruses

260 HLA Gene Loci Associated With HIV Load in CSF and Blood Plasma in the CHARTER Cohort

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Background: Polymorphic gene loci in the major histocompatibility complex (HLA) are associated with better control of HIV in plasma of patients with European but not African ancestries. To determine whether HLA alleles influence HIV replication in the CNS, we compared cerebrospinal fluid (CSF) HIV with HLA genotypes.

Methodology: HLA-C*-35 (rs9264942) and HLA-B*5701 (rs2395029) were identified using PCR in 564 blood DNA isolates from HIV-infected patients in the CHARTER cohort. HIV RNA log10 copy per ml was determined in plasma and CSF and differences in patients with versus without the two HLA polymorphisms were assessed using Fisher's exact test, T test, or Wilcoxon rank sum test.

Results: In 48 treatment naïve European subjects the C allele of HLA-C*-35 was associated with lower HIV concentration in plasma (TT = 4.45 log c/ml, CT = 4.30 log c/ml, CC = 3.60 log c/ml, p = 0.034) but not in CSF (p = 0.61). In 205 Europeans on combination antiretroviral therapy (cART), HLA-C*-35 was not associated significantly with plasma or CSF HIV RNA concentration. In treatment naïve Europeans the HLA-B*5701 analysis resembled the HLA-C*-35 results for plasma (+ = 4.49 log c/ml, - = 3.19 log c/ml, p = 0.032) and CSF HIV (p = 0.20). Unexpectedly, in the 164 treated patients of African descent, those with the C allele of HLA-C*-35 had greater detection of HIV (worse HIV control) (plasma, 73% versus 38%, p = 0.012; CSF, 45% versus 19%, p = 0.017). The number of treated Africans that possessed an HLA-B*5701 allele was too small to yield a meaningful result. No association between HLA-C*-35 or HLA-B*5701 type and HIV RNA concentration in plasma or CSF was observed in 33 treatment naïve patients of African ancestry.

Conclusions: Plasma but not CSF HIV RNA concentration was lower in HLA-C*-35/C and HLA-B*5701/+ treatment naïve patients of European descent. This effect was not seen in treated individuals, likely because the treatment effect overshadows the genetic effect. In contrast, treated patients of African descent with HLA-C*-35 C alleles had higher plasma and CSF HIV RNA concentrations. This association was not seen in the patients not on cART and suggests that those subjects are less likely to attain virologic suppression in plasma or CSF.

261 GUAVAh: A Compendium of Host Genetic Data in HIV Biology and Disease

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Background: There are increasing amounts of data on host genes that are modulated during HIV infection, influence disease susceptibility and that carry genetic variants that impact HIV infection. We created GUAVAh (Genome Updates of Associations and Viral Analyses in HIV) a public resource that supports multipurpose analysis of genome-wide genetic variation and transcriptome profile across multiple data sets and phenotypes in HIV biology.

Methodology: We included original data from 11 genome and transcriptome studies addressing viral and host responses in *in vivo* and *ex vivo* settings, including diverse phenotypes such as HIV acquisition, viral load, disease progression, viral life cycle, latency and viral host genome interaction. This represents genome-wide association data from more than 14,000 individuals, exome sequencing data from 400 individuals, *in vivo* transcriptome data from 250 patients/conditions, and 135 sets of RNA-seq data.

Results: The publicly available GUAVAh framework supports queries on (i) unique single nucleotide polymorphism across different study phenotypes, including viral escape sites, (ii) gene structure and variation with possible relevance to HIV biology, (iii) gene expression in the setting of human infection (CD4 and CD8 T cells), and (iv) RNA-seq data in the setting of *in vitro* models of permissive infection and in primary cell latency and reactivation.

Conclusions: The complexity of the analysis of host gene influences on HIV biology and pathogenesis calls for comprehensive motors of research on curated data. The tool developed here allows queries and supports validation of the rapidly growing body of host genetic information pertinent to HIV research.

262 HIV-1 Infection Leads To Increased Expression of HML-2 Proviruses In Vivo But Not Virion Production

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Background: Human endogenous retrovirus (HERV) sequences make up ~8% of our genome. One group of HERVs, HERV-K (HML-2), includes the most recently integrated proviruses, present as both fixed and polymorphic loci in the population. Some HML-2 proviruses have retained ORFs for the retroviral genes gag, pro, pol and env. Interestingly, increased HML-2 expression is found in a variety of human disease states, particularly cancers. In particular, HML-2 viral particles have been detected in the plasma of HIV-1 infected individuals. It is unknown how expression is activated or whether it affects HIV-1 pathogenesis.

Methodology: To further investigate HML-2 expression, a specific quantitative PCR was designed based on a comprehensive alignment of all known HML-2 proviruses. This assay is capable of detecting 51 out of the 91 known HML-2 proviruses in the human genome, is highly reproducible and provides a solid basis for expression analysis in HIV-1 infected individuals.

Results: HML-2 RNA expression was assessed in plasma previously collected from HIV-infected individuals (n=9) and from subjects recruited in an ongoing clinical study (n=6). Contrary to previous studies, HML-2 RNA was not detected in the plasma of infected individuals. A robust signal for HML-2 was detected only when the extracted nucleic acid was not DNase-treated prior to reverse transcription. While this condition led to high levels of signal as seen in published reports, such signal could be attributed entirely to the presence of cellular DNA. HML-2 RNA expression was increased in PBMCs from HIV-1 infected individuals (n=19) as compared to uninfected controls (n=13; 2.1 fold increase, $p < 0.0001$). The level of HML-2 expression in PBMCs was not related to patient use of antiretrovirals or HIV-1 plasma RNA, cellular RNA or cellular DNA levels. In order to investigate the source of HML-2 RNA expression, HIV-1 infected and uninfected patient PBMCs were sorted into CD3+ CD4+, CD3+CD8+, CD3-CD14+ and CD3-CD20+ cell subsets and then analyzed for HML-2 RNA levels. No single cell subset was enriched for HML-2 RNA expression in HIV-1 patients, but there appears to be substantial variability in the level of HML-2 expression dependent on the cell type.

Conclusions: Our study shows that expression of HML-2 as virus in HIV-1 infected individuals is not universal in that HML-2 virions may not be produced; however, HML-2 viral RNA appears to be upregulated in PBMCs from HIV-infected individuals. Cell sorting and expression analysis did not identify a specific cellular source of HML-2 RNA in HIV-1 infected patients. In fact, HML-2 RNA expression was detected in all cell subsets. This study reveals the complexity of HML-2 RNA expression during HIV-1 infection and the need for additional studies to clarify its effects on HIV-1 pathogenesis.

263 Exome Sequencing To Evaluate the Impact of Rare Coding Variation On HIV-1 Control

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Background: Common variants (>5% frequency) in the MHC and CCR5 regions are known to influence set point HIV-1 viral load (spVL) yet explain only a portion of the total trait variance. The impact of rare coding variation on HIV-1 disease progression has not been as thoroughly investigated. Here we utilize exome sequencing in 392 HIV-1 infected individuals with stable spVL to look for rare and functional variants that mediate control of HIV-1 infection.

Methodology: Set point HIV-1 viral load was calculated as the average of at least 3 measurements obtained during the chronic phase of infection. We captured and sequenced all coding exons in 392 HIV-1 infected individuals of the Swiss HIV Cohort Study using the Illumina Truseq 65Mb enrichment kit and the Illumina HiSeq2000. Quality control and variant calling were performed using the GATK and variant functional annotation was performed using snpEff version 3.3. Individual variants were tested for association using linear regression. Testing of the combined effects of multiple low frequency variants across each of > 18,000 genes was performed using SCORE-Seq and SKAT.

Results: Consistent with previous results, single marker variant tests showed a strong signal of association in the MHC. The top association was observed between spVL and rs1131446 (p=2.3x10-11) in exon 3 of HLA-B. Conditioning on this SNP, residual association was observed at rs2308622 (conditional p=2.2x10-6) in HLA-C. Accounting for these two SNPs, no other variants showed evidence for association. Analyses aimed at detecting the combined effect of multiple low frequency variants within a gene showed no significant associations. Restricting this analysis to only those variants that result in a change in protein sequence did not reveal further signals.

Conclusions: Outside of the MHC, no significant impact of rare variation on spVL was detected by exome sequencing in 392 individuals. Larger samples are likely required to fully explore the role of rare coding variation on this phenotype. Additional classes of variation not detected by GWAS or current sequencing technologies may also contribute to host HIV-1 control.

Session P-D1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

It's All About the Gut

310 Increased Immune Activation After Gut Permeabilization in SIV-Infected African Green Monkeys

Jan Kristoff[1], Thaidra Gaufin[2], Rajeev Gautam[3], Dongzhu Ma[1], Jacob Estes[4], Russell Tracy[5], Cristian Apetrei[1], Steve Nelson[6], Gregory Bagby[6], Ivona Pandrea[1]

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Background: Microbial translocation (MT) has been proposed as a major cause of increased immune activation in HIV/SIV infection and subsequent cardiovascular comorbidities, including hypercoagulability. Our hypothesis was that alcohol administration to African green monkeys, that maintain a healthy intestinal barrier despite high levels of viral replication during chronic SIV infection, will result in increased gut permeability and consequent levels of immune activation and hypercoagulability.

Methodology: Six AGMs were administered ethanol by indwelling gastric catheters for 3 months, and then intravenously infected with SIVsab92018. Alcohol administration continued for up to 6 months postinfection. We compared levels of viral replication, T cell changes, immune activation (HLA-DR CD38 and Ki-67), MT (LPS, sCD14), coagulation (D-Dimer) and plasma cytokines in alcohol-treated infected AGMs and infected AGM controls. Microbial products and fibrosis were assessed in the liver by immunohistochemistry.

Results: Alcohol administration to AGMs altered the mucosal barrier and resulted in increased MT, as illustrated by the significantly higher levels of LPS and sCD14 in alcohol receiving AGMs, and increased levels of microbial products in the liver. In addition, alcohol administration induced increased levels of T cell activation and proliferation and higher levels of proinflammatory cytokines (IL-1b, IL-6, IL-17) in the treated animals compared to controls. Furthermore, alcohol administration resulted in a slight increase of plasma viral loads in acutely SIVagm-infected AGMs and a delayed $CD4^+$ T cell restoration in the gut and periphery. Numerous inflammatory infiltrates and increased fibrosis were observed in the liver in the alcohol treated AGMs. Finally, induction of MT in alcohol-treated AGMs infected with SIVagm resulted in significantly higher levels of the coagulation biomarker D-dimer.

Conclusions: Our study confirmed that alcohol plays a role in permeabilizing the gut and is increasing MT in African green monkeys, a nonhuman primate model that maintains gut integrity during SIV infection despite high viral replication. Alcohol treatment of SIVagm-infected AGMs resulted in increased systemic immune activation and inflammation, delayed immune restoration, and activation of coagulation. Our results bring direct proof that MT is one of the important mechanisms of excessive immune activation/inflammation and a major cause of cardiovascular comorbidites in HIV infected patients.

311 Breaches in Colonic Claudin-4 Expression Correlate With T-Cell Activation in HIV-1 Infection

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Background: Disruption of the mucosal barrier leading to microbial translocation has been suggested as a cause of systemic immune activation in HIV-1 infection. Dysregulation of the tight junction protein network, which contribute to maintaining barrier function, has previously been described in HIV-1 infected patients. We sought to determine if HIV-1 infection is associated with changes in the immunohistochemical staining pattern of the tight junction proteins claudin-4, previously not investigated in HIV infection, and claudin-1. We also measured T cell activation and levels of bacterial 16s ribosomal DNA in the blood of HIV-1 infected patients to determine if tight junction abnormalities correlate with levels of microbial translocation and systemic immune activation.

Methodology: Paired blood and colonic samples were collected from 19 healthy controls and 35 HIV-1 infected patients (25 on suppressive ART and 10 untreated). Claudin-1 and 4 staining was performed on tissue sections by indirect immunohistochemistry. Quantitative image analysis was performed using high-resolution scans of whole tissue sections. Microbial translocation was assessed using quantitative real time PCR and HLA DR and CD38 was measured on memory T cells by flow cytometry to assess immune activation. Differences between groups were identified using Kruskal-Wallis test with Dunn's Multiple Correction and correlations were performed using Spearman's Rho. Median values are reported in the results.

Results: HIV-1 infection was associated with disruption of claudin-1 and claudin-4 staining at the apical surface of colonic epithelial cells (breach/intact ratios: claudin-1: control=0.23, viraemic=7.32, aviraemic=1.15; claudin-4: control=0.60, viraemic=4.22, aviraemic=1.96, all $p<0.001$). The magnitude of claudin-4 disruption was positively correlated with levels of 16s ribosomal DNA in plasma ($p=0.005$, $rs=0.505$) and CD4 and CD8 T cell activation ($p=0.030$, $rs=0.367$ and $p=0.002$, $rs=0.499$ respectively) in the grouped HIV cohort. Levels of viraemia in untreated infection were also positively correlated to claudin-4 disruption ($p=0.026$, $rs=0.750$).

Conclusions: Alterations in the distribution of expression of the epithelial gap junction proteins may contribute to the pathogenesis of HIV-1 infection. The magnitude of claudin-4 disruption is directly correlated to the level of HIV viraemia, which supports in vitro studies showing HIV viral components may directly impair the integrity of the mucosal barrier. The significant association of 16s rDNA and systemic T cell activation with claudin-4 breaches supports the hypothesis that disruption to the mucosal barrier leads to increased microbial translocation and systemic T cell activation.

312 Rapid Gut-Homing of Plasmacytoid Dendritic Cells During Acute SIV Infection

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Background: Lentivirus infections are characterized by a rapid loss of mucosal CD4+ T cells and breakdown of the gut mucosa. In addition, multiple studies have shown that IFN-α-producing plasmacytoid dendritic cells (pDC) are activated early after lentivirus infection, but despite the importance of the gut mucosae in HIV/SIV pathogenesis, little is known about pDCs in these tissues during acute infection.

Methodology: This planned sacrifice study included a total of 21 rhesus macaques - six naïve and six infected with SIVmac239 sacrificed at 14 days post-infection, and nine infected with SIVmac239 sacrificed in chronic stage disease. Animals had colorectal and lymph node biopsies prior to infection, were followed longitudinally by blood collection and full tissue collections were performed at necropsy. Phenotypic and functional analyses were performed using polychromatic flow cytometry.

Results: During acute SIV infection the frequency of pDCs in blood declined rapidly, as early as day 3 post-infection, with an ~5-fold loss by day 14, inversely correlating with viral load ($R = -0.55$, $p < 0.001$). Furthermore, when compared to naïve controls, pDC frequencies in animals sacrificed at day 14 post-infection were reduced 5- to 10-fold in lymphoid organs including liver and spleen, but were generally unchanged in lymph nodes. This overall loss in blood and vascular organs coincided with 2- to 8-fold increases in pDCs in colon and jejunum. Of note, when comparing individual animals pDC frequencies in colorectal tissue at day 14 sacrifice were between 6- and 12-fold greater than pre-infection colorectal biopsies. Also, as early as day 6 the gut-homing receptor, $\alpha4\beta7$, increased significantly over baseline on circulating pDCs, peaking at ~day 10 post-infection and suggesting a likely mechanism for increased gut-homing. Interestingly, in all chronically infected animals, pDC numbers remained significantly elevated in the mucosa, regardless of viral load. Clinically, re-distribution of pDCs was significantly associated with markers of activation and correlated with loss of CD4+ T cells in the gastrointestinal tract ($R = -0.603$, $p < 0.001$), indicating a potential mechanism of pDC-induced depletion.

Conclusions: Herein we demonstrate evidence for acute and permanent accumulation of pDCs in the gastrointestinal tract during SIV infection. While pDC accumulation in the mucosa could aid in virus control, over-production of IFN-α derived from these cells could also contribute to increase the immune activation, inflammation, and CD4+ T cell death in the gut mucosa commonly associated with progressive lentivirus infections.

313 CCR6+ and CD161+ CD4 T Cell Loss Contributes To the Pathogenesis of SIV Infection in Rhesus Macaques

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Background: Determining which subsets of CD4+ T cells are lost during HIV and SIV infections in humans and rhesus macaques (RMs) is a critical component to understanding the pathogenesis of infection. Recent studies have shown that CD4+ T cells expressing CCR6, a chemokine receptor that distinguishes Th17 lineage polarization, and those expressing CD161, found on human Th17 precursors, are depleted from blood during chronic HIV

infection. However, little is known about the kinetics of the depletion of these CD4+ T cell subsets, their levels in lymphoid tissues, and the mechanism behind their loss from peripheral blood during HIV/SIV infection.

Methodology: To answer these questions, we used multicolor flow cytometry to compare the levels of CCR6+ and CD161+ CD4+ T cells in the blood of 46 SIV-uninfected and 20 SIV-infected RMs, as well as in 27 SIV-uninfected and 35 SIV-infected sooty mangabeys (SMs), a natural host for SIV in which infection is nonpathogenic. Furthermore, the blood and tissue levels of these CD4+ T cell subsets were longitudinally analyzed in six RMs experimentally infected in vivo with SIVmac239 (i.v.). Memory CD4+ T cells expressing either CCR6 or CD161 (or neither) were then sorted from the blood and LN and the level of SIV gag RNA quantified in each cell subset by digital droplet PCR.

Results: CCR6+ ($p<0.0001$), CD161+ ($p<0.0001$) and CCR6+CD161+ ($p<0.0005$) CD4+ T cells were all significantly depleted from the blood of SIV-infected RMs compared to uninfected animals. Differently from RMs, these CD4+ T cell subsets were maintained at healthy levels in SIV-infected SMs. Surprisingly, only CD4+CD161+, and not CD4+CCR6+ T cells, coexpressed the HIV/SIV coreceptor CCR5. Longitudinal data in SIV-infected RMs showed that the loss of CD4+CD161+ T cells is progressive and occurs across all compartments sampled, including blood, LN and rectal mucosa. However, CD4+CCR6+ T cells were lost rapidly from the blood and LN but accumulated in the rectal mucosa. Consistent with the hypothesis of redistribution, we found a negative association between the frequencies of CD4+CCR6+ T cells in blood and those at mucosal sites ($p=0.0147$). While neither CD4+CCR6+ nor CD4+CD161+ T cells were preferentially infected by SIV in the blood compared to CCR6-CD161- T cells (DN), CD4+CD161+ T cells harbored significantly higher levels of SIV gag RNA compared to DN cells in the LN ($p=0.0055$).

Conclusions: This study provides evidence that a profound depletion of CD161+ and CCR6+ CD4+ T cells contributes to the pathogenesis of SIV infection in RMs. Furthermore, our results suggest a heightened susceptibility of CD4+CD161+ T cells to SIV infection and a redistribution of CD4+CCR6+ T cells to mucosal sites as central mechanisms for the dysregulation of these critical CD4+ T cell subsets during HIV infection.

314 SIV Vaccine Controllers Prevent Aberrant Accumulation of Follicular CD4 T Cells in Rectal Mucosa

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Background: Chronic SIV/HIV infection promotes an accumulation of virus-infected T follicular helper cells (T-FH cells, PD-1hi, CXCR5+, Bcl6+) in the lymph nodes, an important site of viral replication. However, the fate of these cells and their contribution to viral persistence in the rectal mucosa (rectum), another preferential site of virus replication, is not known. Here we studied the fate of PD-1hi CD4 T cells in the rectum following intrarectal SIV251 infection in a cohort of unvaccinated and DNA/MVA vaccinated rhesus macaques (RM).

Methodology: Lymphocytes isolated from the rectum of SIV naïve and SIV infected rhesus macaques (RM) were separated and characterized by multi-color flow cytometry. Sorted cells were used for measuring cell associated viral RNA by qRT-PCR. Cellular localization was determined by immunofluorescense staining.

Results: In the SIV-naïve RM, a small fraction of CD4 T cells in the rectum expressed high levels of PD-1 (PD-1hi cells), the majority co-expressed CXCR5 and Bcl-6 (T-FH), and localized to germinal centers (GC) of lymphoid follicles. Following a pathogenic SIV infection, despite a global depletion of CD4 T cells, T-FH cells increased dramatically in animals that failed to control SIV infection below 104 viral RNA copies/ml of plasma at set-point. Similar to uninfected animals, the PD-1hi cells in the non-controller RM expressed CXCR5 and Bcl-6 (T-FH), did not express CCR5, and localized to GC of B cell follicles. Moreover, these PD-1hi CD4 T cells were enriched in viral RNA, indicating that these cells exist as an active site of viral production. In contrast, in vaccine-controllers that maintained viral loads below 104 viral RNA copies/ml of plasma at set-point, the frequency of T-FH cells did not increase, and lower frequencies of CXCR5+ PD-1hi CD4 T cells and higher frequencies of CCR5+ CD4 T cells were observed. This CXCR5lo CCR5+ phenotype suggests a possible altered distribution of these cells away from the GC region of B cell zones towards the T cell zone where anti-viral CD8 T cells predominantly reside. Interestingly, higher frequencies of functional SIV specific CD8 T cells (Granzyme B+ CXCR5+ Gag CM9+ CD8 T cells) were observed in the LN follicles of vaccine-controllers compared to non-controllers.

Conclusions: These data demonstrate that SIV-infected T-FH cells accumulate in B cell follicles of the rectum during uncontrolled chronic SIV infection and thus may evade killing by anti-viral CD8 T cells. They also demonstrate that vaccine-mediated SIV control is associated with lack of T-FH cell accumulation. These data warrant the exploration of therapeutic interventions that limit aberrant T-FH accumulation as a means to enhance control of chronic SIV/HIV replication.

315 Decreased Diversity of Gut Microbiota Is Associated With Immune Status During HIV-1 Infection

Piotr Nowak[1], **Babilonia Barqasho[2]**, Ekatarina Avershina[3], Kajsa Noyan[2], Jan Vesterbacka[1], Marius Trosseid[4], Knut Rudi[3], Anders Sönnerborg[1]

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Background: Progressive HIV-1 infection is characterized by dysregulation of the intestinal barrier and chronic systemic inflammation. Translocation of immunostimulatory microbial products is proposed as key mechanism behind this inflammation associated with clinical complications during chronic HIV-1 infection. In this study, we wanted to explore the alterations of the gut microflora in HIV-1 infected patients and if gut microbiota is influenced by antiretroviral treatment (ART).

Methodology: In total, 32 patients and 9 controls were included (median CD4 T cell count: 355 cells/ul (120-1040). Faeces and plasma samples were collected at baseline and for 19 patients at follow up (median 7 months [5-15]) after ART introduction. The samples from three elite controllers (EC) were included at baseline. The patients who were prescribed antibiotics or probiotics for the preceding 2 months, or had infectious diarrhea were excluded. The microbiota composition was evaluated by deep sequencing of 16S rRNA gene with 150 bp Illumina chemistry. Additionally, ''classical' ' markers of microbial translocation (MT) were analysed (LPS and sCD14).

Results: The number of observed bacterial species (richness) was lower in HIV-1 infected patients as compared to controls. The alpha diversity (Simpson index) of bacterial species was decreased at baseline and did not change significantly during ART. At baseline, alpha diversity significantly correlated with CD4 T cell % ($r=0.42$, $p=0.01$) and CD8 T cell % ($r=-0.37$, $p=0.03$) but not with soluble markers of MT. Moreover, the bacterial composition varied in HIV-1 infected patients with significant decrease of bacteria within the *Prevotella* and *Cyanobacteria* group. Gut flora after ART introduction contained more *Pseudomonas* as compared to baseline and healthy controls samples. Notably, EC had high alpha diversity and microbiota composition that resembled status of uninfected controls.

Conclusions: Collectively, the data show that gut microbiota is altered during HIV-1 infection and correlates with immune status. ART influences its composition. The higher similarity of gut microbiota between EC and healthy controls implicate that a healthy state of gut microbiota may be associated with delayed disease progression.

316 Dysregulated miR-34a-SIRT1-Acetyl-p65 Axis Induces Immune Activation in Chronic SIV-Infection

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Background: Chronic gastrointestinal (GI) inflammation, a hallmark of progressive HIV/SIV infection is associated with disruption of the gastrointestinal epithelial barrier leading to microbial translocation and contributing to localized and systemic immune activation/inflammation, which drives AIDS disease progression. While most of our knowledge regarding regulation of inflammation has come from protein regulators such as proinflammatory cytokines, transcription factors, etc. recent evidence also suggests critical roles for small non-coding RNA molecules called microRNAs (miRNAs) in controlling and managing certain aspects of the inflammatory process.

Methodology: Using TLDA arrays, qRT-PCR, luciferase assays and ISH/Immunofluorescence methods we profiled changes in miRNA expression and characterized specific differentially expressed miRNAs in colon samples from 10 chronically SIV-infected and 4 control macaques.

Results: After applying multiple comparisons correction 10 miRNAs showed differential expression (3-up and 7-down). Among the 3 upregulated miRNAs was miR-34a, previously linked to inflammation, cell cycle arrest, apoptosis and cellular senescence. Further, miR-34a showed statistically significant upregulation in both epithelial and lamina propria leukocyte (LPL) compartments. Interestingly, the intensity of the DNA damage response marker γH2AX was markedly elevated in colonic epithelium and LPL of chronically SIV-infected macaques and confirmed the reported role of oxidative stress in driving miR-34a upregulation. Luciferase reporter assays validated rhesus macaque SIRT1 (histone deacetylase) and Notch2 (epithelial proliferation and differentiation) genes as direct miR-34a targets.

In contrast to miR-34a, expression of SIRT1 and Notch2 mRNA significantly decreased in both colonic epithelium and LPL. Reduced SIRT1 expression resulted in constitutively enhanced protein expression of the transcriptionally active form of the p65 (acetylated on lysine 310) subunit of NFκB exclusively in the LPL. The intensity and number of acetylated p65 positive cells was markedly elevated in the LPL of chronically SIV-infected macaques compared to uninfected controls and localized to increased numbers of IgA and IgG secreting plasma cells.

Conclusions: These findings provide new insights into the potential role of miR-34a in causing hyperactivation of mucosal plasma cells resulting in their dysfunction and, possibly, hypergammaglobulinemia. Our results point to a mechanism where the normal function of SIRT1 as an inhibitor of inflammation and immune activation in the colon is suppressed by elevated miR-34a expression resulting in constitutive expression of the proinflammatory acetylated p65 (lysine 310) subunit of NFκB.

317 Dysbiotic Bacteria Translocate in Progressive SIV Infection

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Background: HIV/SIV infection of GI tract-resident CD4+ memory T-cells during acute infection leads to rapid loss of these cells with subsequent damage to the epithelial layer and microbial translocation. Immune activation, in part, caused by microbial products leads to progression to AIDS. Although microbial translocation has been demonstrated in SIV infected non-human primates, the identity of translocating bacteria has not been determined. In this study we examine the community makeup of bacteria both within the GI tract and distal tissues of healthy, experimentally SIV-infected, and SIV-infected and probiotic-treated Asian macaques.

Methodology: Bacterial DNA was isolated from colon, mesenteric lymph nodes (MLN) and liver taken from sacrificed Asian macaques. The identity of bacteria populating these was determined by 454 pyro-sequencing of 16s ribosomal DNA or quantitative PCR directed against particular phyla of 16s DNA. DNA and RNA were isolated from the stool of SIV-infected Asian macaques both before and during treatment with a HAART or HAART with probiotic (VSL#3). RNA was reverse transcribed using 16s specific primers and levels of particular phyla of 16S rRNA or DNA were used to determine stool associated microbial structure using 454 pyro-sequencing or qPCR.

Results: Analysis of bacterial DNA found in the tissues of infected animals revealed a preference for members of the phylum Proteobacteria. No bacterial dysbiosis was observed in the colon itself during infection, suggesting that the increased prevalence of Proteobacteria in the tissues was due to preferential translocation of these particular bacterial species. Indeed, 454 analysis revealed a further preference for specific members of this phylum (with motile species frequently observed). Analysis of stool during infection and treatment of animals revealed changes in the metabolic activity of bacteria within the GI tract. The biggest change being observed after the administration of anti-retroviral medication with increased metabolic activity of Proteobacteria. Probiotic treatment seemed to decrease the metabolic activity of these proteobacteria.

Conclusions: Proteobacteria preferentially translocate from the GI tract during SIV infection of Asian macaques. Translocating species involved motile flagellated species, some of which can cause disease. suggesting these potentially pathogenic species cause systemic immune activation. Interestingly, metabolic activity of proteobacteria is highest during acute infection (when translocation begins) and increases drastically during HAART treatment. Probiotic administration may potentially counteract this and ameliorate systemic immune activation which could improve the prognosis of ARV-treated, HIV-infected individuals.

Session P-D2 Poster Session
Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**
New SIV Models

318LB Viral Suppression Was Induced by Anti-PD-L1 Following ARV-Interruption in SIV-Infected Monkeys

Stephen W. Mason[1], Srisowmya Sanisetty[2], Christa Osuna-Gutierrez[3], So-Yon Lim[3], Susan Chaniewski[1], Shalyn Campellone[1], Daniel Tenney[1], Scott Balsitis[1], James B. Whitney[3]
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Background: BMS-936559, a fully human antibody against huPD-L1, was tested in antiretroviral-suppressed SIVmac251-infected rhesus macaques. The primary endpoints for this study were to assess safety during repeated i.v. administration of BMS-936559, to determine any improvement in the function of SIV-specific T cells and to monitor for effects on viral recrudescence after cessation of ARV therapy.

Methodology: 13 MHC-defined rhesus macaques were confirmed to be SIVmac251 positive and ARV treatment was initiated, using a 3-4 drug ARV regimen, for an average of 6 months prior to the administration of BMS-936559. Animals received either BMS-936559 (N=8) or iso-type control antibody (N=5). Multiple immunologic and virologic analyses were used to evaluate ARV regimen efficacy, safety and occupancy of PD-L1 by BMS-936559.

Results: Durable virologic suppression of SIVmac251 at ≤50 RNA copies/ml was achieved in all animals with the administration of a well-tolerated ARV treatment regimen. Significant reductions in inflammatory markers were observed during ARV treatment. Repeat dosing of BMS-936559 was well tolerated in all animals with no noted untoward effects based on physical examination and laboratory assessments. Occupancy of PD-L1 by BMS-936559 was observed throughout the dosing period and pharmacokinetic analyses verified exposure of antibody. Perturbations in SIV viral RNA levels were observed after ARV treatment interruption, such that 4 of 8 animals in the BMS-936559 treatment group had a delay in viral load rebound and a significantly lower viral load set point, with 2 animal having undetectable VL for 3-4 weeks after an initial rebound. Changes in proviral DNA levels and T cell functional assays have been assessed.

Conclusions: These data provide proof of concept for the safety of repeated high-level dosing of BMS-936559 in vivo. The effects on viral suppression observed in this study may reflect a restoration of immune function by anti-PD-L1 in SIV-infected rhesus monkeys.

319 A Novel HIV-1mt Encoding CCR5-Tropic Env Established Persistent Infection in Cynomolgus Macaques

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Background: With the aim of developing a monkey model of HIV-1 infection, we have been utilizing a combination of macaque-tropic HIV-1 (HIV-1mt) and cynomolgus macaques (CM). While we previously reported that CXCR4-tropic HIV-1mt (X4 virus) replicated efficiently in CM homozygous for *TRIMCyp*, none of infected animals had persistent viremia. Since most HIV-1 in human population use CCR5 as a co-receptor (R5 virus) during transmission, the co-receptor usage may be important for establishment of persistent infection in monkeys. Based on this hypothesis, we here constructed an R5-tropic HIV-1mt and analyzed viral replication in monkeys.

Methodology: The 5' region (from 5' LTR to *vpu*) and 3' region (from *env* to 3' LTR) of viral genome were PCR amplified from X4-tropic HIV-1mt plasmid with high fidelity DNA polymerase. By overlapping with these fragments, a fragment covering *env* gene was PCR amplified from an R5-SHIV MK38 strain that shows pathogenicity in infected rhesus macaques. These amplified fragments were subjected to co-transfection of stably CCR5 expressing T cell line, C8166-CCR5 cells. Several days after co-transfection, an R5-tropic HIV-1mt named MN38 strain was collected. We analyzed the co-receptor usage of MN38 and monitored its replication capability in CM PBMCs. We further analyzed the replication property of MN38 in monkeys having *TRIMCyp*.

Results: MN38 virus showed CCR5-tropism and replicated well in CM PBMCs. In monkeys, MN38 induced viremia, with plasma viral loads reaching a peak at 2-3 weeks post infection and ranging from $1.5x10^4$ to $1.0x10^5$ copies/ml. While the viremia became undetectable at 8 weeks post infection, administration of anti-CD8 monoclonal antibody into animals led to reappearance of viremia. In order to obtain monkey-adapted virus, we then inoculated plasma and whole blood of MN38-infected animals into one naïve monkey. The inoculated virus stock was named MN38P1. MN38P1 replicated well in the

recipient monkey and established persistent viremia. We further performed the 2nd round of adaptation. The virus stock named MN38P2 was inoculated into two naïve CM. We observed an increase in levels of acute viremia, reaching 10^6 copies/ml in these animals.

Conclusions: We successfully obtained a monkey-adapted R5-HIV-1mt strain. This virus was found to induce persistent viremia in CM for at least 20 weeks. This combination of MN38-ralated strains and CM will encourage us to develop pre-clinical animal model of HIV-1 infection. We are still following up on the possibility of establishment of long-term persist infection. Moreover, it will be of great interest to elucidate which viral mutations are responsible for adaptation in monkeys. To this end, we are now analyzing whole viral genome by using next generation sequencing method.

320 New SIVsmm Strains To Achieve Control of Virus Replication With Conventional ART in Rhesus Macaques

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Background: There is a renewed enthusiasm for a "cure research" aimed at understanding the mechanisms of HIV-1 persistence and developing therapeutic strategies to reduce and ultimately eliminate viral reservoirs. Limitations of human clinical studies make it imperative to develop analogous and tractable animal models for cure research. However, a major limitation of animal use is that SIV infection in rhesus macaques (RMs) is more virulent than HIV-1 and very difficult to control with antiretroviral therapy (ART). We have identified new SIVsmm strains that are less virulent in RMs and more closely reproduce the pathogenesis of HIV-1. Our hypothesis was that these new strains can be more readily controlled with ART. Our goal was therefore to achieve control of SIV replication in RMs by employing conventional ART regimens.

Methodology: Nine RMs (MaMu A*01, B*08, B17 neg and Trim5a matched) were iv infected with a newly derived transmitted-founder infectious molecular clone of the SIVsmmFTq strain that was never adapted *in vitro*. At 65 days postinfection (dpi), ART was initiated in four RMs (PMPA, 20 mg/kg/day; FTC, 40 mg/kg/day; integrase inhibitor L870812, 20 mg/kg bid). ART impact on viral replication was assessed by measuring plasma viral load (VL), as well as monitoring the memory $CD4^+$ T cells in the intestine, the levels of T cell immune activation and proliferation, and biomarkers associated with disease progression in RMs: C-reactive protein, D-dimer, IL-6 and sCD14.

Results: All RMs become persistently infected with SIVsmmFTq. VL peaked at 10 dpi at 7-8 logs/ml and reached a set-point of 4.2-5.4 logs/ml by 42 dpi. After initiation of ART, VL decreased by 1.5-2 logs in 48 hours, followed by a slower decline to undetectable levels (<30 copies/ml) that were reached by 30 days post-treatment initiation. Over the next four months, VLs remained undetectable, without blips $\geq$30 copies/ml. Restoration of mucosal memory $CD4^+$ T cells and reduction in immune activation wasobserved in RMs receiving ART but not in untreated controls. ART also normalized biomarkers associated with disease progression and mortality in RMs.

Conclusions: We established a robust macaque model of ART suppression with a three drug antiretroviral regimen that is analogous to current ART employed for HIV-1 infection. This simplified animal model of ART will permit evaluation of interventions targeting persistent viral reservoirs that are obstacles to a cure.

Session P-D3 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

SCID Mice

321 Immune-Pathogenesis/-Therapy of Persistent HIV-1 Infection in Humanized Mice

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Background: The role of FoxP3+CD4+ Treg cells in HIV-1 diseases (aberrant immune activation) is poorly understood due to lack of a robust model. We have demonstrated that functional CD4+FoxP3+ natural Treg cells are developed in all lymphoid organs in humanized rag2-/-γC-/- DKO-hu HSC mice. These FoxP3+ Treg cells are preferentially infected and depleted by HIV-1. We discover that, while inhibiting IL-2 gene expression, FoxP3 enhances HIV-1 LTR expression in an NFkB-dependent fashion. FoxP3 silences the chromatin at the IL2 locus but activates it at the HIV-1 LTR.

Methodology: My laboratory studies development and function of the human immune system, as well as chronic human viral infection and immuno-pathogenesis. Treg cells are depleted during different stages of HIV-1 infection and during HAART treatment. HIV-1 replication, pathogenesis and HAART-reservoirs are investigated.

Results: When CD4+CD25+/hi Treg cells are depleted in vivo, acute HIV-1 infection is impaired, associated with enhanced immunity. However, when Treg cells are depleted during chronic infection, HIV-1 replication is enhanced with accelerated disease progression. When Treg was depleted during HAART, HIV-1 gene expression was induced from the HAART-resistant HIV-1 reservoir cells in various lymphoid organs. Therefore, FoxP3+ Treg cells can promote acute HIV-1 infection by suppressing anti-HIV immunity and by serving as target cells. During chronic HIV infection, however, Treg cells play an important role in suppressing immune activation and HIV-1 replication, contributing HIV-1 reservoirs during HAART.

Conclusions: Therefore, FoxP3+ Treg cells can promote acute HIV-1 infection by suppressing anti-HIV immunity and by serving as target cells. During chronic HIV infection, however, Treg cells play an important role in suppressing immune activation and HIV-1 replication, contributing HIV-1 reservoirs during HAART.

322 Dual Roles of Plasmacytoid Dendritic Cells in HIV-1 Infection and Pathogenesis

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Background: Plasmacytoid dendritic cells are potent type I interferon producing cells and crucial for controlling various viral infection. However, the contribution of pDC in HIV-1 infection and pathogenesis remains controversial. On one hand, pDC have been shown to inhibit HIV-1 replication through their IFN-I production. The numerical and functional decline of pDC in HIV-1 infected patients correlates with opportunistic infection independent of CD4+ T-cell counts. On the other hand, pDC may contribute to HIV immunopathogenesis. The sustained pDC activation and IFN-I production in HIV-1 infected patients does not correlate with viral control but is predictive of disease progression. Additionally, pDC activation is rapidly controlled in the nonpathogenic SIV infection, whereas its activation and IFN-I production sustain during pathogenic infection in Asian monkeys. These reports highlight the importance of studying the interaction between HIV and pDCs.

Methodology: A monoclonal antibody specific to blood dendritic cell antigen-2, 15B, was used to deplete pDCs from humanized mice model through intraperitoneal injection. For acute HIV-1 infection, humanized mice were injected three times with 15B on -5, -3 and -1 days before infection, and mice were terminated at 8 days post-infection. For chronic HIV-1 infection, 15B was applied to mice at 11 weeks post-infection by injecting twice every week for 10 weeks. Mice were killed at 21 weeks post-infection.

Results: The expression of type I interferons and interferon stimulated genes are severely impaired by pDC ablation either before or during chronic HIV-1 infection. HIV-1 replication was significantly upregulated in pDC-depleted mice. However, HIV-1 induced depletion of human immune cells including T cells and total human leukocytes was reduced in spite of the increased viral replication.

Conclusions: pDC play a role not only in suppressing HIV-1 infection but also in promoting HIV-1 induced pathogenesis. These findings suggest that pDC depletion or suppression will provide a novel approach for HIV-1 therapy.

323 Characterizing the Acute Spread of Cell-Associated HIV in Humanized Mice

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Background: The direct spread of HIV from one cell to another has been shown to be a prominent mode of infection in vitro. The extent which cell-to-cell infection operates in vivo, where the spatial organization and dynamic of cell-cell contacts is likely to be drastically different, has yet to be examined. This led us to investigate the mechanisms of HIV dissemination in vivo comparing cell-free viral inoculums with the injection of HIV-infected cells and following the initial round of infection in humanized mouse models that support HIV replication.

Methodology: We performed bioluminescence whole body imaging allowing us to visualize the trafficking patterns of adoptively transferred CD4+ T cells that were infected with infectious gaussia luciferase-expressing (NL-GlucI) HIV. To examine the efficiency with which cells become co-infected in vivo, we utilized a dual virus infection strategy whereby two infectious fluorescent HIV R5 tropic variants (NL-GI or NL-CI) are simultaneously introduced into mice and the numbers of singly infected and doubly infected cells were detected by flow cytometry and two photon imaging. We measured how efficiently the two viruses are co-transmitted by cell-to-cell transmission in vivo, when CD4+ T cells coinfected with NL-GI (green) and NL-CI (red), are used as donors that are intravenously injected into humanized mice.

Results: The lung of hu-mice is the first site where adoptively transferred NL-GlucI-infected CD4+ T cells traffic to, prior to localization into the spleen a few hours later. Administration of pertussis toxin, which prevents the migration of T cells, confirms these results. The increase in bioluminescence signal or appearance of target cells that are GFP positive suggest that HIV is replicating in vivo and spreading to endogenous CD4+ T cells. Mice injected with donor cells infected with both red and green viruses gave rise to a high frequency of doubly infected target cells. Control mice that were injected with donor cells that were either red or green gave rise to similar levels of infection with fewer target cells that coexpressed two fluorescent proteins.

Conclusions: Using two humanized mouse models, we observed that spread of cell-associated HIV is efficient in vivo after intravenous exposure. We find that infected cells traffic initially to the lung where replication occurs. In addition, inheritance of multiple copies of HIV indirectly shows that infection of target cells may occur through VS. The frequent coinheritance of two fluorescent virus species in vivo, may be explained by a high frequency of cotransmission through VS. The results suggest that HIV dissemination in vivo can be driven by lymphocyte migration of cell associated virus.

Session P-D4 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Non-Pathogenic vs Pathogenic Hosts

324 Differential TCR Activation and TRAIL Regulation in Sooty Mangabeys and Rhesus Macaques

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Background: We have previously shown that SIV infection resulted in increased CD4+ T lymphocyte apoptosis and elevated plasma tumor necrosis-receptor associated apoptosis-inducing ligand (TRAIL) in rhesus macaques (RM) but not sooty mangabeys (SM). We therefore investigated the relationship between T cell activation and TRAIL upregulation in SM and RM in vitro.

Methodology: PBMC from SIV-negative SM (n=15), SIV-negative RM (n=18), naturally SIV-infected SM (n=20), and SIVmac239-infected RM (n=7) were cultured for up to 24 hours with plate-bound anti-CD3 and anti-CD28 and monitored for direct and indirect effects of T cell receptor (TCR) signaling. T and non-T lymphocyte subsets were evaluated for activation, apoptosis and TRAIL upregulation by flow cytometry and cell supernatant for cytokines by multiplex luminex assays. Anti-TRAIL antibody and recombinant macaque soluble death receptor 5 were used for in vitro TRAIL-blocking experiments.

Results: TCR cross-linking resulted in rapid T cell activation and a significant increase in surface TRAIL expression on T and NK cells of both RM and SM. However, the magnitude of TRAIL increase was significantly higher in SM compared to RM and was not associated with increased apoptosis. Of interest, while T cell upregulation of CD69 expression was comparable in SM and RM, the production of T-derived cytokines IFNγ, IL-2, TNFα, IL-17, MIP-1α, and IL-5 was significantly higher in SM compared to RM. Exogenous addition of IL-2, IL-7, IL-15 and IL-21 induced a dose-dependent increase in TCR activation-induced NK TRAIL in RM, but the levels did not reach the magnitude seen in SM. Furthermore, in vitro inhibition of TRAIL decreased SM T cell activation suggesting that T cell-associated TRAIL may have co-stimulatory function. Following SIV infection, RM CD8+ T cells showed a significant decrease in TCR activation-induced TRAIL expression, while TRAIL upregulation was significantly increased in CD8+ T cells from SIV-infected SM. In contrast to TRAIL expression on T cells, SIV-infected RM but not SIV-infected SM showed a significant increase in TRAIL induction on pDC and mDC.

Conclusions: While mDC-associated TRAIL has been implicated in apoptosis, our data indicate a co-stimulatory function of T cell-associated TRAIL in SM. Disparities in induction of TRAIL on CD8+ T lymphocytes, NK cells and DCs in SM and RM, suggest that the dominance of non-apoptotic functions of TRAIL in SM may protect natural hosts against immunodeficiency and aberrant apoptosis.

325 Divergent CD4+ T Memory Stem Cell Dynamics in Pathogenic and Nonpathogenic SIV Infections

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Background: Pathogenic SIV infection of rhesus macaques (RM) results in infection and progressive depletion of central memory CD4+ T cells (TCM) which predicts the overall loss of CD4+ T cell homeostasis. In contrast, nonpathogenic SIV infection of sooty mangabeys (SM) is characterized by limited infection and preservation of CD4+ TCM. Recent studies have identified a novel subset of memory T cells with stem cell-like properties (TSCM) that include increased longevity and multipotency when compared to other T cell memory subsets. We sought to characterize, for the first time, the pathophysiology of CD4+ TSCM during SIV infection in RM and SM and their potential contribution to CD4+ T cell homeostasis.

Methodology: We used multi-parametric flow cytometry to identify and phenotypically define CD4+ TSCM in the blood of both healthy and SIV-infected RM and SM. Plasma viral load and quantification of cell-associated SIVmac gag or SIVsmm utr DNA were determined by real-time PCR.

Results: We monitored the level of CD4+ TSCM during acute (day 7-14), early chronic (d. 65-84), and late chronic (d. 128-365) phases of SIV infection in RM and determined that, despite decreases in all other CD4+ T cell subsets, there was no change in either frequency or absolute number of CD4+ TSCM. However, CCR5+CD4+ TSCM were significantly depleted in SIV-infected RM. We also found increased levels of proliferating CD4+Ki-67+ TSCM in SIV-infected RM, which inversely correlated with the frequency of TCM during chronic infection. In contrast, when healthy and SIV-infected SM were compared, CD4+ TSCM remained stable in terms of frequency, absolute number, CCR5 expression, and proliferation. Of note, the percentage of CCR5-expressing CD4+ TSCM was greater in RM compared to SM. Interestingly, we readily detected SIV DNA in CD4+ TSCM from 9/9 RM and at levels comparable to other memory CD4+ T cell subsets, while only 2/10 SM had detectable SIV DNA in CD4+ TSCM.

Conclusions: Although CD4+ TSCM are numerically preserved during both pathogenic and nonpathogenic SIV infections, CD4+ TSCM homeostasis is significantly disrupted only in SIV-infected RM, with increased CD4+ TSCM proliferation and robust levels of virus infection of these cells. In contrast, CD4+ TSCM homeostasis is unperturbed in SIV-infected SM, with the majority of animals lacking SIV DNA within CD4+ TSCM, possibly as a result of low levels of CCR5 expression on the surface of these cells. We propose that increased proliferation and infection of CD4+ TSCM may contribute to SIV pathogenesis in RM.

326 Double-Negative T Cells Are Functionally Distinct and Maintained in SIV-Infected Sooty Mangabeys

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Background: Recent studies have shown that CD4/CD8 double-negative (DN) T cells possess CD4 T-like functional properties and have been implicated in the lack of AIDS in natural hosts of SIV, including sooty mangabeys (SM). However, there are limited data in non-natural hosts of SIV like rhesus macaques (RM). This study aimed to compare DN T cells in SM and RM and to analyze the impact of chronic SIV infection on DN T cell function in both species.

Methodology: Peripheral blood DN T cells were evaluated in a cohort of SIV-negative and SIV-infected SM and RM. Functional analysis was performed using polychromatic flow cytometry and 28-plex luminex assay of TCR-stimulated (anti-CD3/anti-CD28 crosslinking) unfractionated and FACS-sorted purified T cell subsets respectively. Additionally, transcriptional profiling of 91 genes associated with T cell differentiation and function were evaluated in ex vivo and TCR-stimulated pure T cell subsets using a high-throughput microfluidics PCR platform (Fluidigm BioMark).

Results: SIV-negative SM and RM DN T cells upregulated CD40L and produced Th1 (IFN-γ, IL-2), Th2 (IL-13) and Th17 (IL-17) cytokines in response to superantigen or TCR stimulation. However, SM DN T cells produced significantly more cytokines at the single-cell level, showed greater polyfunctionality, and were functionally distinct from RM DN T cells with regards to production of multiple cytokines and chemokines, including IL-2, IL-4, IL-5, IL-13, IL-17, G-CSF, GM-CSF, MCP-1, and MIF. SM DN T cells also had significant population of Tregs and higher frequency of CCR6-positive cells. Ex vivo gene expression profiling of purified T cell subsets showed transcriptional similarity of SM DN T cells to CD4+ T cells and strikingly significant differences from

RM DN T cells. Surprisingly, RM DN T cells showed closest similarity to CD8+ and not CD4+ T cells. TCR-stimulated SM DN T cells showed 2- to 580-fold upregulation of 31 genes including effector molecules and activation markers in contrast to up to 9-fold upregulation of only15 genes in RM DN T cells. The genes showing greatest upregulation (>10-fold) in SM DN T cells included il22, il17a, ifng, tnf, il2, il4, il5 and il21, confirming their enhanced Th17, Th1 and Th2 functionality. Following SIV infection, profound DN T cell hypofunctionality was seen in SIV-infected RM but not SIV-infected SM.

Conclusions: Besides being significantly higher in frequency, SM DN T cells are functionally distinct from RM and may differ in their ontogeny. The diverse functional properties of SM DN T cells that are not affected by SIV infection likely play a role in regulating immune activation and preventing disease progression to AIDS in these natural hosts of SIV infection.

327 CD39/CD73/Adenosine Pathway in Progressive vs Non-Progressive Infections

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Background: The CD39/CD73/adenosine (ADO) pathway was associated with immunosuppression in multiple diseases; yet, its precise role in mediating immune activation and inflammation (IA/INFL) during HIV-1/SIV infection remains unclear.

Methodology: We compared and contrasted the expression of markers related to either ADO production (CD39 and CD73) or ADO breakdown (CD26) on both regulatory (Tregs) and conventional T cells isolated from blood, lymph nodes (LNs), and intestine of nonprogressive (African green monkeys-AGMs) and progressive (pigtailed macaques-PTMs) models of SIVagm infection. Expression of ADO-related markers was assessed by flow cytometry during acute, early and late chronic infection, compared to preinfection levels and correlated with T cell immune activation (CD38/HLA-DR and Ki-67), monocyte activation (sCD14 and sCD163), and inflammation (CRP and proinflammatory cytokines).

Results: Baseline expression levels of both CD39 and CD73 on CD8+ Tregs isolated from blood and in CD4+ Tregs isolated from LNs and intestine were intrinsically high in AGMs. However, CD39, CD73 and CD26 expression remained at baseline levels throughout SIVagm infection in all the cells from different compartments of the AGMs, which control chronic IA/INFL.

Conversely, in PTMs, which exhibit increasing IA/INFL markers with disease progression, CD39 expression on circulating conventional T cells and Tregs significantly increased during the late stages of SIV infection. In the LNs, expression of both CD39 and CD73 was significantly increased on conventional T cells and Tregs, while only CD73 significantly increased after infection on Tregs in the intestine. In the LNs, a dramatic increase of CD26 expression on CD39 and CD73 cells occurred only during acute infection, while being maintained throughout infection in the intestine. Increased CD39 and CD73 expression in SIV-infected PTMs did not positively correlate with control of IA/INFL.

Conclusions: CD39/CD73 expression on Tregs and T conventional cells undergo different dynamics among different lymphoid compartments and among different NHP species. Despite a higher baseline adenosine production in the AGM nonprogressive model, lack of variation of CD39/CD73 and CD26 markers suggest that ADO pathway is not critical for the control of IA/INFL in AGMs. Conversely in the progressive SIV infection of PTMs, significant changes in CD39/CD73 and CD26 expression occur in tissues rather than blood, suggesting that future studies of the ADO pathway should focus on the tissue sites of viral replication. In pathogenic infections, increased CD39/CD73 expression and subsequent ADO production may be counteracted by the early increases in the expression of CD26, which is associated with adenosine deaminase.

328 Dynamics of B Cell Subpopulations in Pathogenic and Nonpathogenic SIV Infections

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Background: We compared and contrasted the dynamics of B cells subpopulations in mononuclear cells from blood, lymph nodes (LN) and intestine (INT) in progressive SIV infection of pigtailed macaques (PTMs) and in non-progressive SIV infection of African green monkeys (AGMs) to elucidate the significance of B-cell changes observed in HIV/SIV infection.

Methodology: We assessed the changes in total B cells, as well as of naïve, resting, activated and tissue-like memory B-cell subpopulations using a combination of CD20, CD27 and CD21 monoclonal antibodies.The dynamics of Bregs ($CD20^{+}CD24^{hi}CD27^{hi}IL\text{-}10^{hi}$) were assessed by flow-cytometry. Activation, homing to the intestine, exhaustion and apoptosis status of total B cells were assessed as expression of Ki-67, TLR-2, $\alpha4\beta7$, PD-1 and Annexin V. CD4 T follicular helper (Tfh) cells were assessed with a combination of PD1, CXCR5, ICOS and Bcl-6. Binding anti-gp41 and neutralizing antibodies were assessed in the two species.

Results: A sigificant acute loss of total circulating B cells occurred in the progressive host, followed by restoration during chronic infection. Conversely, the total circulating B cells did not significantly change in AGMs but increased in the LNs during chronic infection. A transient acute increase of B cells occurred in the gut in both species. Naïve B cells decreased in all compartments in both species. Activated and resting memory B cells decreased in the blood but increased in the LNs and gut of PTMs. Circulating tissue-like memory B cells increased in blood only in PTMs, while in the gut, a similar increase was observed in both species. B cell proliferation post-SIV infection was similar in both species, the highest increases being detected in the LNs during chronic infection. Infected PTMs had elevated Bregs, which positively correlated with IL-10 xpression. PTMs had high baseline levels of $\alpha4\beta7$, but this marker did

not increased after SIV infection. Only PTMs showed significant increases in B cell activation and apoptosis. While the dynamics of both anti-gp41 and neutralizing antibodies was similar in AGMs and PTMs, rapid progressor PTMs lacked the ability to develop anti-gp41. An increase in CD4 Tfh cells was observed in the LNs, especially in PTMs.

Conclusions: In AIDS-susceptible species, but not in non-progressive hosts, SIV infection is characterized by B cell dysfunction defined by loss of total and memory B cells, increased numbers of Bregs and increased B cell activation and apoptosis. These changes do not appear to be correlated with production of neutralizing antibodies, which is similar in both species. Yet, the rapid progressor infection is associated with a severe incapacity to mount an Ab response against gp41.

Session P-D5 Poster Session
Thursday March 6, 2014, 2:30 PM–4:00 PM Exhibit Hall A
Compartmentalization

329 Transient Compartmentalization of SIV Variants in the Breast Milk of African Green Monkeys

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Background: In contrast to HIV-infected humans and SIV-infected rhesus monkeys, natural hosts of SIV, African green monkeys (AGMs), rarely transmit the virus postnatally. Previous studies in humans and rhesus monkeys revealed that breast milk populations of humans and rhesus monkeys are not genetically distinct from those in plasma. As the breast milk virus population of natural hosts of SIV remains uncharacterized, we sought to examine the genetic and functional diversity of breast milk SIV variants in this limited transmission setting.

Methodology: We intravenously infected six female hormone-induced lactating AGMs with the infectious molecule clone T/F SIV variant (SIVsab92018ivTF). Single genome amplification and sequencing was performed on the env sequences of virus variants in milk and blood of AGMs at five months and one year post-infection. Maximum likelihood trees of plasma and milk env sequences were constructed using PAUP*, and compartmentalization of the milk env variants was assessed using the Slatkin-Maddison test. Finally, plasma and milk env genes were cloned and used to produce Env pseudoviruses to assess for infectivity and neutralization sensitivity.

Results: The milk env variants in AGMs were largely compartmentalized from those in blood in four of five AGMs at five months post-infection. Notably, there was limited genetic diversity among milk virus variants as large numbers of identical sequences were observed among the milk virus lineages, suggesting clonal amplification of virus variants that seeded the breast milk compartment from blood. However, the milk virus lineages observed at five months post-infection did not persist at one year post-infection, and there was no signature env sequence or unique Env phenotype among milk virus variants. Furthermore, two of two plasma and one of two milk Env pseudoviruses from one monkey were functional, displaying similar infectivity in TZM-bl cells.

Conclusions: The compartmentalization of low diversity milk env variants in AGMs is transient and may be a result of the low number of CD4+ T lymphocyte target cells in the breast milk compartment of AGMs. This is in contrast with the limited compartmentalization previously observed in humans and rhesus monkeys. As there is a genetic bottleneck in postnatal virus transmission, the restricted diversity of milk virus variants and the limited number of CCR5-expressing CD4+ target cells in infant AGMs may together contribute to the rarity of postnatal transmission in natural hosts.

330 HIV Migrates Bi-Directionally Between Blood and Cerebrospinal Fluid and Between Blood and Semen

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Background: Once HIV infection is established, the virus persists in anatomic compartments, including the blood, central nervous system and genital tract. The dynamics of viral migration between these compartments remains poorly understood.

Methodology: We investigated partial HIV env sequences derived from paired cerebrospinal fluid (CSF) and blood samples from 11 ART-naïve, HIV-infected subjects and paired semen and blood samples from 4 subjects. Sequences were screened for hypermutation and duplication, aligned, and then analyzed by: (i) phylogenetic reconstruction using a Bayesian Markov-chain Monte Carlo approach, (ii) evaluation of viral compartmentalization using tree- and distance-based methods, and (iii) analysis of migration events using a discrete Bayesian asymmetric phylogeographic approach of diffusion with Markov jump counts estimation.

Results: Subjects were sampled longitudinally (range: 3-11 timepoints/subject) over a mean duration of 433 days (range: 9-2071 days). HIV-1 env sequences were isolated by clonal sequencing from blood plasma (range: 27-1520/subject), seminal plasma (21-85/subject) and CSF (11-59/subject). Mean env sequence length was 484 nucleotides (range: 333-648). The subjects had a mean CD4+ T-cell count of 541 cells/ml (range: 200-1123). Mean HIV RNA log10 copies/ml for blood plasma was 4.6 (range: 2.5-5.4), 3.4 for seminal plasma (2.5-4.0) and 3.8 for CSF (2.5-5.4). Compartmentalization was maintained throughout all sampled timepoints for 3 of the 4 individuals with paired blood and CSF samples but none of the subjects with paired blood and semen samples. We compared our Bayesian approach of inferred migration events with the Slatkin-Maddison test for compartmentalization, and the results were significantly correlated (Spearman $R=0.61$, $p<0.01$). We then estimated the direction of viral gene flow between compartments over time, and

observed bi-directional replenishment of viral compartments. Specifically, there was a mean of 15 migration events from blood to semen (range 0-34) and 8 migration events from blood to CSF (range: 0-16). Considering migration towards blood, we observed 14 migration events from semen to blood (range 1-43) and 11 migration events from CSF to blood (1-15). Temporal analysis showed asynchronous peaks of viral migration to and from blood over time, suggesting transient disruption of viral compartmentalization.

Conclusions: These results strongly suggest that HIV subpopulations migrate back and forth between blood and other anatomic compartments, and that viral populations in CSF and semen actively contribute to the contemporaneous HIV RNA population observed in the blood. These compartmental reservoirs may need to be targeted if eradication strategies are to be successful.

331 Pol Versus Env Genetics in SHIV-Infected Macaques Highlights Importance of Phylogenetic Signal

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Background: Previously we investigated HIV *pol* populations in SHIV-infected macaques by single-genome sequencing to determine if low-level replication was a source of residual viremia during ART and to investigate viral compartmentalization across tissues. Using this approach, we found no evidence for evolution during suppressive ART and little evidence of viral compartmentalization. To investigate the possibility that the low diversity in *pol* masked the emergence of new viral variants and/or compartmentalization, we applied the same methods to the more diverse *env* gene in the infected macaques.

Methodology: Two macaques (M03250 and K02396) received 20 weeks of ART (TNF, FTC, EFV) and one macaque (6760) was untreated. Longitudinal plasma samples (N=11) from treated macaques were analyzed by single-genome sequencing of a 1 kb pol fragment and a 2.5 kb *env* fragment. In the untreated animal 6760, tissues were collected at necropsy after infection for 30 weeks of infection and single-genome sequences were obtained from PBMCs, lymph nodes, spleen, thymus, gut tissues, bone marrow, and lung. The entire 2.5kb env fragment and the 101 nucleotide V3 region alone were evaluated separately for population diversity, divergence, and compartmentalization using phylogenetic and panmixia analyses, and compared to results from *pol*.

Results: Previously we found diverse variants in *pol* but no new variants emerged in the plasma during suppressive ART, and viral population differences across tissues were due to varying frequencies of the same viral variants. Similarly, new phylogenetic and panmixia analyses of 2.5kb *env* sequences in plasma did not reveal the emergence of new variants during ART, showing that the lack of evolution in *pol* was not due to low phylogenetic signal in this region. E*nv* populations analyzed in tissues from 6760 were highly diverse but showed similar population structures to *pol* and a lack of tissue compartmentalization. By contrast, phylogenetic analyses of only the V3 *env* region showed very weak phylogenetic signals and little diversity, indicating that the V3 region is not appropriate to evaluate intra-individual populations for diversity, evolution, and phylogenetic structure.

Conclusions: Comparisons of population genetics of *pol* and *env* in SHIV-infected macaques show that both regions have sufficient phylogenetic signal to assess evolution during ART and compartmentalization of virus populations. Although commonly used for genetic analyses, the V3 loop is under strong purifying selection that restricts its diversity and severely limits its usefulness for intra-individual analyses of viral genetics. These findings highlight the importance of performing single-genome and deep sequencing on regions of the viral genome with strong phylogenetic signal.

Session P-D6 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

New Themes in Host Control

332 Effect of CD8 Depletion On CD4+ T-Cell Subsets in SIV Infection

Timothy Hayes[1], Steven E. Bosinger[1], Ankita Chowdhury[1], Benton O. Lawson[1], Barbara Cervasi[2], Kiran Gill[2], Mirko Paiardini[1], Miles P. Davenport[3], Jacob D. Estes[4], Guido Silvestri[1]

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Background: Several studies indicated that CD8+ lymphocytes inhibit virus replication during HIV/SIV infection. CD8+ T-cells can directly kill HIV/SIV infected cells through MHC-I-mediated recognition of viral epitopes (i.e. cytotoxic T lymphocyte activity). Furthermore, CD8+ T-cells may inhibit viral replication via non-cytolytic mechanisms such as cytokine and chemokine production or by influencing the activation state of target CD4+ T-cells. Recent studies have revealed that CD8+ lymphocyte depletion does not affect the in vivo lifespan of productively infected cells in chronic SIV infection suggesting a role for non-cytolytic mechanisms of virus suppression. The goal of this study is to investigate the mechanisms by which CD8+ lymphocytes control virus replication in a series of experiments in which CD8+ lymphocytes were depleted in vivo in chronically SIV-infected rhesus macaques (RMs).

Methodology: 18 female adult RMs were infected i.v. with 3,000 TCID50 of SIVmac239. At day 70 post-infection, 15 animals were depleted of CD8+ lymphocytes by s.c. administration of the CD8 antibody M-T807R1. Three control animals were mock-depleted. Five animals each were sacrificed at day three, day seven, and 14 post-depletion. Multiple tissues and blood were collected at necropsy for further analysis.

Results: All 18 RMs were successfully infected, with 11 animals maintaining high plasma viral loads (VL) through chronic infection, and 7 animals controlling viral replication to levels below 1,500 SIV copies/ml. In all animals, the M-T807R1 antibody induced rapid and massive CD8 depletion that was followed by a rapid increase in plasma VL. A negative correlation was seen between pre-depletion VL and VL increase after depletion. After depletion, plasma levels of CCR5 ligands MIP-1α, MIP-1β, and RANTES did not change significantly while levels of CD4+ T-cell activation, as measured by Ki-67 expression, increased. Microarray analysis revealed a decrease in gene expression of CCR5 ligands in CD4+ T-cells post-CD8 depletion. Importantly, increases in cell-associated SIV DNA were detected in all sorted memory CD4+ T-cell subsets post-CD8 depletion, with the notable exception of central-memory CD4+ T cells in controllers, in which the frequency of SIV DNA+ cells declined despite the marked increase in VL.

Conclusions: In chronic SIV infection of RMs, CD8+ lymphocytes contribute to control of viral replication in a multi-factorial way that may have a different impact in the various subsets of CD4+ T cells.

333 Low Social Rank Prior To SIV or SHIV Infection Associates With Higher Viral Load in Chronic Infection

Gretchen N. Neigh[1,2], Timothy Hayes[2,3], Ronald Trible[2,3], Thomas H. Vanderford[2,3], Diane G. Carnathan[2,3], Constance S. Harrell[1], Kirk Easley[4], Mirko Paiardini[2,3], Guido Silvestri[2,3]

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Background: The tempo of disease progression in HIV-infected humans and SIV-infected macaques is quite variable among individuals, with high levels of virus replication predicting shorter survival. Prolonged exposure to stress may alter immune system function even in the absence of HIV or SIV infection, and disruptions in housing environment, a known stress stimulus, shorten survival time in SIV-infected macaques. Macaques housed in social groups establish a relatively stable matriarchal hierarchy. Within these hierarchies, subordinate animals consistently demonstrate elevated markers of chronic stress compared to dominant ones. In the current study we tested the hypothesis that stress history, as dictated by the subject's social rank prior to study assignment, predicts viral load during chronic SIV infection.

Methodology: All rhesus macaques originated from social groups housed at Yerkes National Primate Research Center with established rank systems prior to isolation for further studies involving SIV or SHIV infection. Viral loads from five previous studies (four involving SIVmac and one involving SHIVsf162p3) were measured by RT-PCR as copies of SIV RNA/ml of plasma, and the relative data were retrospectively compiled and analyzed. All animals' social and medical histories prior to study assignment were obtained from colony records. Retrospective individual animal meta-analysis was conducted on viral load data across the acute, early chronic, and late chronic phases of infection.

Results: A total of 62 macaques infected with SIV or SHIV were stratified based on the pre-infection social rank, and then evaluated longitudinally throughout infection for viral load in plasma. We found that, in the acute phase of SIV or SHIV infection, the level of virus replication was not predicted by social rank prior to study assignment ($p=0.37$). Interestingly, in both early and late chronic phases of the infection, social rank prior to study assignment significantly influenced the level of virus replication ($p=0.01$ and $p=0.002$ for subordinate vs. dominant/mid). In the early chronic phases of infection copies of SIV RNA/ml of plasma in subordinate subjects (mean = 5.202 log10 copies/ml) was elevated compared to subjects that originated from dominant/mid ranks (mean = 4.488 log10 copies/ml). Also during late chronic infection, higher viral loads were observed in subordinate subjects (mean = 5.806 log10 copies/ml) compared to subjects from dominant/mid social ranks (mean = 4.213 log10 copies/ml).

Conclusions: These data demonstrate that social history prior to SIV or SHIV infection can influence viral load in the chronic phases of the disease, with increased exposure to stress being associated with higher levels of virus replication during chronic infection.

334 Modulation of Natural Killer Cell Activity by Simian Immunodeficiency Virus Peptides

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Background: Natural killer (NK) cells recognize and kill virus-infected cells without prior antigenic stimulation. This recognition is achieved in part through the loss of interactions between inhibitory killer-cell immunoglobulin-like receptors (KIRs) on NK cells and their MHC class I ligands on virus-infected cells. MHC class I-bound peptides can affect NK cell activation by stabilizing or disrupting interactions with KIRs. We previously reported that the binding of a common MHC class I molecule in the rhesus macaque, Mamu-A1*002 (A1*002), to an inhibitory KIR, Mamu-KIR3DL05 (3DL05), is stabilized by certain SIV peptides, but not by others.

Methodology: Using an A1*002-expressing, transporter associated with antigen processing (TAP)-inhibited cell line pulsed with individual peptides, we evaluated 75 SIV peptides previously shown to bind to A1*002 (IC50<500 nM) for the ability to modulate the activity of primary 3DL05+ NK cells in cytotoxicity assays. Additional assays were also performed to identify peptide variants that differentially affect interactions with 3DL05 without altering binding to A1*002.

Results: We identified 26 SIV peptides that suppressed the cytolytic activity of 3DL05+ NK cells, three of which correspond to immunodominant CD8+ T cell epitopes that bind to A1*002 with a high affinity (IC50<10 nM), and are therefore likely to be among the most abundant epitopes presented on the surface of SIV-infected A1*002+ cells. An analysis of peptide variants revealed that substitutions at positions 7 or 8 could change a peptide that suppresses 3DL05+ NK cell activity into a peptide that does not, and vice versa, without affecting binding to A1*002. In competition assays, the suppressive peptide dominated to inhibit 3DL05+ NK cell activity when present at less than 2% of a mixture with a non-suppressive variant of the same peptide.

Conclusions: Our results demonstrate that viral peptides can modulate NK cell activation via KIR-MHC class I interactions. The dominance of suppressive peptides over non-suppressive peptides is consistent with the need to prevent NK cell activation in response to the complex repertoire of self peptides presented by MHC class I molecules on the surface of healthy cells. These observations also suggest that immunodeficiency viruses may acquire changes in epitopes that increase the avidity of MHC class I ligands for inhibitory KIRs as a mechanism of immune evasion to suppress the activation of certain NK cell subsets.

Session P-E1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Modulating Immune Activation

335 Rosuvastatin Reduces Immune Activation and Inflammation in Treated HIV Infection

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Background: Despite suppressive antiretroviral therapy (ART), elevated levels of immune activation and inflammation often persist in HIV-infected subjects. Statins have anti-inflammatory effects, and when given in combination with ART, may reduce immune activation.

Methodology: The 96-week 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 statins on markers of cardiovascular risk and skeletal health in HIV. This was a pre-planned analysis of the effect of rosuvastatin at week 48 on immune activation and inflammation. All subjects were on ART, and had HIV-1 RNA<1000 copies/mL, LDL-cholesterol ≤30mg/dL and evidence of immune activation (C8+CD38+DR+ ≥19% or hsCRP ≥2mg/L). Randomization was 1:1 to daily rosuvastatin 10 mg or placebo, and was stratified by protease inhibitor (PI) use. Tcell activation was measured by expression of CD38, HLA-DR, and PD1. Monocyte activation was measured with soluble markers (sCD14 and sCD163) and by real time enumeration of monocyte subpopulations and tissue factor (TF) expression. We also measured markers of systemic inflammation (hsCRP, sTNF-RI and II, IL-6, IP-10, sVCAM-1 and ICAM-1), vascular inflammation (Lp-PLA2), and coagulation (D-dimer, fibrinogen).

Results: 147 subjectsenrolled; 78% male, 70% black, 29% white, with median age 47 years and CD4 cells 613 cells/μL; 49% were on PI and 78% had HIV-1 RNA <50 copies/mL. Baseline characteristics were similar between groups, except for the % of $CD14^{Dim}CD16+$ monocytes that expressed TF (statin= 21.8% and placebo= 18.9%, p=0.05). Rosuvastatin use reduced sCD14 (p=0.006), Lp-PLA2 (p=0.0007), and IP-10 (p=0.03) levels. In addition, sCD163 and fibrinogen decreased within the statin arm (p=0.001 and p=0.015). The %TF+ $CD14^{Dim}CD16+$ monocytes was also reduced in the statin arm compared to the placebo arm (p=0.005). Within the statin arm, treatment reduced proportions of TF+ monocytes among all three subsets (CD14+CD16-, p=0.002, CD14+CD16+ and $CD14^{Dim}CD16+$, p<0.0001 for both). There was also a greater decrease in the proportions of activated T cells between the placebo and statin arms (p=0.009 for CD4+ cells and p=0.003 for CD8+ cells).

Conclusions: 48 weeks of rosuvastatin treatment reduced significantly several markers of inflammation and lymphocyte and monocyte activation in ART-treated subjects, whether these favorable changes translate to a clinical benefit remains to be elucidated.

336 Effects of Prednisolone On CD4 Counts and HIV Disease Progression: A Two-Year Clinical Trial

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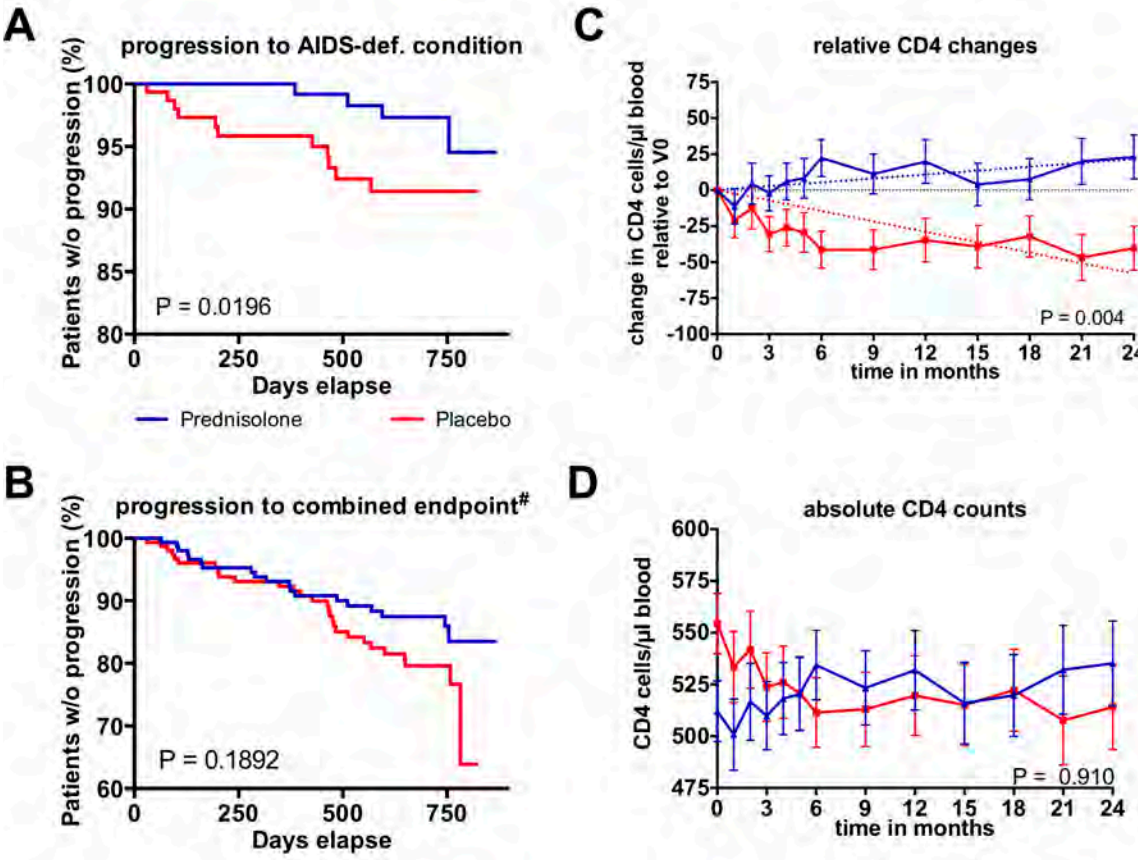
Background: HIV infection is associated with chronic immune activation, which may be a central mediator of HIV pathogenesis. Here we investigated the effect of the anti-inflammatory corticosteroid prednisolone on HIV disease progression.

Methodology: We conducted a randomized, double-blinded, placebo-controlled two-year clinical study in Tanzania to assess the effects of prednisolone on HIV disease progression in patients not yet eligible for antiretroviral therapy (HAART). A total of 326 HIV-infected patients were included in the study and randomly assigned to receive either 5 mg prednisolone per day or placebo for 24 months. Primary study end point was progression to an AIDS-defining condition or a drop of CD4 counts below 200 cells/μl, or death from any cause.

Results: Four patients receiving prednisolone and 11 patients receiving placebo developed an AIDS-defining condition (Fig. A) (P = 0.0196), and 16 and 18 patients respectively developed CD4 counts < 200 cells/μl. Average CD4 changes were +21.6 (± 4.4) cells/μl for prednisolone and -57.9 (± 8.9) cells/μl for placebo within two years (Fig. C). Prednisolone treatment was associated with a statistically significant increase in median HIV viral load between baseline and month 12 (1.7x10^4 copies/ml versus 3.7x10^4 copies/ml; p = 0.0247). Prednisolone-treated patients developed significantly fewer malaria episodes than placebo-treated patients (30 versus 60; P = 0.0016). No deaths occurred during the study.

Figure: Effect of Prednisolone on disease progression. A: Kaplan-Meyer estimate of progression to CDC stage C within the Intent to treat (ITT) population. B: Progression as defined by the combined primary clinical end point (#: onset of AIDS-defining condition AND/OR drop of CD4 counts < 200 cells/μl). C: Changes of CD4 counts relative to baseline of the ITT population. D: Absolute CD4 counts of the ITT population.

Conclusions: This study demonstrates that a non-antiretroviral, immunomodulating substance is able to attenuate HIV disease progression. Our findings emphasize the role of immune activation in HIV pathogenesis and may stimulate studies with low-dose corticosteroids as an adjunct to HAART with the aim of reducing residual immune activation and long-term morbidity. The combination of HAART and prednisolone may also open a new strategy to prolong AIDS-free survival in resource-restricted settings. (clinicaltrials.gov NCT01299948)



337 Sevelamer Does Not Decrease Plasma LPS or sCD14 But Does Decrease Soluble Tissue Factor and LDL

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Background: Inflammation is associated with increased morbidity and mortality in HIV-infected individuals. Microbial translocation may be a major driver of this inflammation. Sevelamer carbonate, a phosphate binder, decreases serum lipopolysaccharide (LPS), low-density lipoprotein (LDL) cholesterol, and inflammatory markers in hemodialysis patients. We hypothesized that sevelamer would reduce circulating LPS and monocyte and T cell activation in HIV-infected subjects.

Methodology: In this single arm study, HIV-infected participants not on antiretroviral therapy (ART) received sevelamer 1600 mg three times a day for 8 weeks and were followed for an additional 8 weeks off treatment. Circulating soluble CD14 (sCD14), LPS, IL-6, D-dimer, C-reactive protein (CRP), fetuin A, IL-1β, IP-10, soluble CD163 (sCD163), soluble tissue factor (sTF), and oxidized LDL (oxLDL) cholesterol were measured in centralized labs, and total, non-HDL, and LDL cholesterol at local research sites. HLA-DR+CD38+ and Ki67+ CD4 and CD8 T cells were measured by flow cytometry in a central lab. Statistical significance of changes in measurements between time points was determined using the sign test.

Results: 40 participants were enrolled; 4 were excluded from analysis because of missing key visits (n=3) or ART initiation (n=1). Of 36 evaluable participants, 72% were male; median age was 44 years; median CD4+ T cell count 585/mm3; median HIV-1 RNA 3800 copies/mL. Phosphate levels did not change significantly; 7 participants received phosphate supplementation per protocol due to serum phosphate <2.5 mg/dL; there were no other adverse events. Key results are shown in the table. LPS, sCD14, CD4+ T cell counts, and HIV-1 RNA levels did not change significantly with or after treatment. The frequency of HLA-DR+ CD4 T cells or Ki67+ CD4 or CD8 T cells or fetuin A, IL-1β, IP-10, or sCD163 levels did not change significantly during or after treatment.

Conclusions: In HIV-infected participants not on ART, sevelamer for 8 weeks does not appear to decrease microbial translocation or immune activation but appears to decrease LDL, oxLDL, and sTF. OxLDL induces TF expression in numerous cell types; sevelamer may reduce TF by decreasing OxLDL, suggesting that it might have beneficial cardiovascular effects. Further investigation into the effects of sevelamer on the coagulation cascade, including the biological relevance of the modest increase in D-dimer levels, is warranted.

The effect of sevelamer on key measures					
	Baseline (median)	Wk 8 (median)	Wk 16 (median)	Wk 8 vs Baseline, p=	Wk 16 vs Wk 8, p=
LPS (pg/mL)	25.2	25.3	26.4	0.87	0.30
sCD14 (µg/mL)	1.81	1.73	1.78	0.62	0.23
CD38+HLA-DR+ CD8 T cells (%)	36.0	36.1	34.3	0.73	1.00
IL-6 (pg/mL)	1.65	1.71	1.68	0.87	0.39
CRP (ng/mL)	1768	2199	2353	0.62	0.39
D-dimer (ng/mL)	184	201	199	**0.03**	0.39
sTF (pg/mL)	41.8	37.7	43.6	**<0.01**	**<0.01**
Total cholesterol (mg/dL)	172	155	169	0.18	**0.01**
LDL cholesterol (mg/dL)	101	81	94	**<0.01**	**0.01**
oxLDL cholesterol (mg/dL)	64.4	58.2	64.2	**0.01**	0.06
Wk 8=On sevelamer, Wk 16=8 weeks off sevelamer					

338 Reduction of sCD163, SP and PD1+ Th Cell Levels in a Phase 1B Trial of the NK1R Antagonist Aprepitant

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Background: Substance P (SP) is an undecapeptide produced in neurons and immune cells and involved in nociception and inflammation. The effects of SP are mediated by the neurokinin 1 receptor (NK1R). Increased levels of SP are present in HIV-infected individuals and NK1R antagonists have anti-HIV effects in monocyte-derived macrophages in vitro, by decreasing the expression of CCR5. Aprepitant is an NK1R antagonist approved by FDA as an antiemetic. Increased plasma levels of sCD163 are associated with HIV disease progression.

Methodology: We conducted a phase IB randomized, placebo controlled, double blind study to evaluate the safety, antiviral activity, pharmacokinetics and immune modulatory effects of aprepitant in HIV infected adults not on antiretroviral therapy, with CD4+ cell count ≥ 350 cells/mm3 and plasma viral load ≥ 2,000 copies/ml. Subjects were stratified by viral load (< vs. ≥20,000 copies/ml) and randomized to receive aprepitant 375 mg QD or placebo for 14 days, and followed for 42 days. Primary endpoints were Grade 2-4 adverse events (AE), change in viral load, plasma SP levels, cellular inflammatory markers and plasma sCD163 levels.

Results: Eighteen subjects were randomized (9 to aprepitant, and 9 to placebo); 72% male; 89% black; mean age 37 years. Median viral load (copies/ml) in log10 at baseline was 3.92 for aprepitant and 4.23 for placebo. There were no significant changes in plasma viremia during the dosing period: median (minimum, maximum) change in log10 viral load at day 14 was 0.03 (-0.32, 0.13) in the aprepitant arm and 0.02 (-0.10, 0.68) in the placebo (p=0.83). There were no significant changes in cellular inflammatory markers CD4+ or CD8 CD38+/HLA-DR+ cells or in in the frequency of CD4+/CCR5+ cells. Aprepitant was associated with significant decreases in percentages of CD4+ T cells expressing PD-1 (30% to 21%, p=0.04), plasma SP (-48.2 pg/mL, -10%, p=0.05) and sCD163 (-503 ng/mL, -22%, p=0.02), with no significant changes in the placebo arm. Mean peak aprepitant plasma concentrations on day 14 were 9.2 ± 3.6 µg/mL. There were no serious adverse events. Adverse events were equally frequent in both arms, mild and self-limited in nature. The use of aprepitant was associated with moderate increases in total and LDL cholesterol (+ 29 mg/dL, p=0.01; 24 mg/dL p=0.02 respectively), and increases in HDL cholesterol (4 mg/dL, p=0.02).

Conclusions: Aprepitant was safe and well tolerated. At the dose used in this proof of concept phase IB study, aprepitant did not show significant antiviral activity, but its use was associated with decreased levels of CD4+ PD-1 cells, SP and sCD163 suggesting that blockade of the NK1R pathway may have a role in modulating monocyte activation in HIV infection. Prospective studies in virologically suppressed individuals are warranted.

339 Rifaximin Has Marginal Impact On Immune Activation in Immune Non-Responders To ART - ACTG 5286

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Background: Immune activation (%CD38$^+$HLA-DR$^+$ on CD8$^+$ T-cells) predicts disease progression in untreated HIV-1 infection & CD4$^+$ T-cell rise with ART. Immune activation is associated with elevated markers of gut microbial translocation (MT) from HIV-induced gut mucosal CD4$^+$ T-cell depletion. HIV$^+$ persons with CD4$^+$ T-cell <350 cells/mm^3 despite suppressive ART, immune non-responders, have higher levels of immune activation and MT. Rifaximin, a non-absorbable antibiotic, decreases plasma LPS levels in cirrhotics. We hypothesized that rifaximin would decrease gut MT & immune activation in immune non-responders.

Methodology: ACTG 5286 was a randomized, open-label 2-arm study of rifaximin. 73 HIV$^+$ adults on ART for $\geq$ 96 weeks with CD4$^+$ T-cell < 350 cells/mm^3 and viral load (VL) below assay limit for $\geq$ 48 weeks were randomized 2:1 to rifaximin 550 mg BID vs no study treatment for 4 weeks. %CD38/HLA-DR$^+$ and %Ki67$^+$ on CD8$^+$/CD4$^+$ T-cells, plasma LPS, sCD14, IL-6, D-dimer, sCD163 and sTNFR-II were measured at baseline & week 4; Wilcoxon rank-sum tests compared changes between arms.

Results: At entry, subjects had a median age of 51 years, and median baseline and nadir CD4$^+$ T-cell of 223 and 40 cells/mm^3, respectively. Compared to no treatment (n=22), rifaximin (n=43) for 4 weeks was associated with a significantly lesser increase in both %CD38$^+$/HLA-DR$^+$ of CD8$^+$ T-cells [median change (Q1, Q3) in rifaximin: 0.0 (-1.7, 1.0) vs no treatment: 0.6 (0.1, 1.5); p = 0.028] and %Ki67$^+$CD8$^+$ T-cells [median change (Q1, Q3) in rifaximin: -0.1 (-0.3, 0.1) vs no treatment: 0.1 (-0.1, 0.3); p = 0.013], but not in other cellular markers of activation. Rifaximin use was not associated with a decline in plasma LPS [median fold-change (Q1, Q3) in rifaximin: 1.00 (0.83, 1.12) vs no treatment: 0.98 (0.91, 1.12); p = 0.45] or sCD14 [median fold-change (Q1, Q3) in rifaximin: 0.94 (0.85, 1.15) vs no treatment: 0.94 (0.89, 1.03); p = 0.97]. No significant differences between arms were identified in IL-6, D-dimer, sCD163 or sTNFR-II levels. Twenty-seven (55%) rifaximin-treated subjects reported a primary safety event (mostly grade 2); no grade 3/4 events were related to study treatment.

Conclusions: Rifaximin use for 4 weeks had a marginal impact on CD8$^+$ T-cell activation, and was not associated with significant changes in levels of markers of gut MT, inflammation or coagulation. In HIV$^+$ individuals with incomplete CD4$^+$ T-cell recovery despite suppressive ART, rifaximin was safe and well-tolerated.

340 Reduced Immune Activation During Tenofovir-Emtricitabine Therapy in HIV-Negative Individuals

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Background: Higher levels of immune activation are associated with an increased risk of HIV acquisition. Previous research *in vitro* has identified immunomodulatory properties of tenofovir (TFV) in various cell lines. However, it is unknown whether TFV influences immune activation *in vivo*. We aimed to evaluate the effects of TFV therapy on cellular immune activation in HIV-negative individuals.

Methodology: HIV-negative adults received daily co-formulated tenofovir disoproxil fumarate (TDF) 300 mg/emtricitabine (FTC) 200 mg for 30 days followed by a 30 day washout period. Whole blood for flow cytometry was collected at baseline and on days 30 and 60. Immune activation was determined by measuring % HLA-DR and CD38 expression on CD4$^+$ and CD8$^+$ T-cells. Additionally, intracellular TFV-diphosphate (TFV-DP) was quantified in purified CD4$^+$ and CD8$^+$ cells, which were collected at one study visit in each participant. Immune activation data were $\log_e$ transformed prior to analysis. Data were analyzed with one-way ANOVA for repeated measures and pairwise comparison for significant results between baseline, day 30 and day 60. The relationship between immune activation and intracellular CD4$^+$ and CD8$^+$ TFV-DP was assessed using the Spearman correlation coefficient. A p value $\leq$0.05 was considered significant. Data are presented as geometric mean (95% CI).

Results: Data were available from 19 participants (10 female; 1 Hispanic; 9 African American). Co-expression of CD38/HLA-DR on CD4$^+$ cells was reduced, but not significantly (ANOVA p=0.25); baseline 2.61% (2.1 to 3.2), versus 2.11% (1.64 to 2.70) at day 30 (30 days of daily TDF-FTC), and 2.13% (1.64 to 2.76) at day 60 (30 days off drug). Significant differences for immune activation markers on CD8$^+$ cells were demonstrated (ANOVA p=0.02). Co-expression of CD38/HLA-DR on CD8$^+$ cells was 3.97% (2.98 to 5.29) at baseline, 2.71% (2.01 to 3.66) at day 30, p=0.03, and 2.46% (1.65 to 3.53) at day 60, p=0.008. Differences between day 30 and day 60 were not significant (p=0.58). No significant correlation was identified between CD38/HLA-DR expression and intracellular levels of TFV-DP in CD4$^+$ (r=-0.18, 95% CI, -0.61 to 0.34; p=0.51) or CD8$^+$ (r=-0.01, 95% CI, -0.53 to 0.52; p=0.97).

Conclusions: Exposure to TDF-FTC was associated with decreased immune activation in HIV-negative individuals. The effect endured for 30 days after drug discontinuation, which parallels the long half-life of intracellular TFV moieties. A decrease in immune activation could contribute to the known antiviral effect of TDF-FTC as pre-exposure prophylaxis (PrEP) in HIV-negative patients.

341 Mesalamine To Reduce Immune Activation During HIV Infection: A Randomized Controlled Trial

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Background: Immune activation predicts morbidity and mortality in treated HIV infection and may contribute to persistent gut epithelial barrier defects and systemic microbial translocation. We hypothesized that the luminally active anti-inflammatory agent, mesalamine, might decrease mucosal inflammation in treated HIV infection, leading to decreases in microbial translocation and systemic immune activation.

Methodology: We performed a randomized placebo-controlled trial of mesalamine (Apriso) among HIV-infected individuals with incomplete CD4+ T cell recovery on suppressive antiretroviral therapy (ART). HIV-infected subjects with CD4 counts less than 350 cells/mm3 and undetectable plasma HIV RNA levels for greater than 1 year on ART were randomized to either mesalamine or placebo for 12 weeks followed by 12 weeks crossover to the other arm. Consenting subjects also participated in a serial rectal biopsy substudy. The primary outcome was the week 12 change in the percent of activated (CD38+ HLA-DR+) CD8+ T cells from baseline. Secondary outcome measures included changes in other immunologic markers in blood and gut as well as in markers of macro and microvascular function (flow-mediated dilatation [FMD] and hyperemic velocity).

Results: Of 33 subjects (24 in the rectal biopsy substudy), 15 were randomized to receive mesalamine and 18 placebo in the first 12 weeks. Compared to placebo-treated subjects, mesalamine-treated subjects experienced a similar median change in the percent of activated peripheral blood CD8+ T cells from baseline to week 12 (+0.9% vs. -0.4%, P=0.63). There was also no evidence for a difference between groups in treatment-mediated changes in the percent of activated peripheral blood CD4+ T cells, rectal CD4+ and CD8+ T cells, or in plasma sCD14 (P=0.14), IL-6 (P=0.07), d-Dimer (P=0.27), kynurenine to tryptophan ratio (P=0.87), FMD, change in FMD or hyperemic velocity (P=0.73), or rectal HIV RNA or DNA levels. There was also no evidence for a change in immunologic markers during mesalamine therapy when those with early vs. late therapy were combined.

Conclusions: Administration of a mesalamine preparation designed to release in the colonic mucosa does not significantly affect either systemic or colonic immune activation levels in HIV-infected individuals with incomplete CD4+ T cell recovery on suppressive ART. Alternative strategies to decrease microbial translocation and systemic immune activation are needed.

342 Decreased Levels of D-Dimer After Probiotic Supplementation in Patients Receiving ART

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Background: Despite efficient antiretroviral treatment (ART) HIV-infected patients have increased morbidity and mortality compared to HIV seronegative individuals. Gut microbiota composition has potential impact on HIV pathogenesis and cardiovascular risk. Notably, markers of inflammation, coagulation and microbial translocation have been reported to predict all-cause mortality. The aim of this study was to assess the efficacy of probiotic supplementation in HIV-infected individuals.

Methodology: Randomized, placebo-controlled trial, completed study. Thirty HIV-infected patients on ART (median age 50.3y, 22 men, 22 Caucasians) were included. Inclusion criteria were: HIV-RNA < 50 copies/ml, CD4 count < 500 cells/µl, no antibiotics or probiotics prescribed for the last 2 months, and no episodes of inflammatory bowel disease, immunomodulating therapy or infectious diarrhea for the last 6 months. Participants were randomized in a double blind fashion to the following study arms: i) probiotics (n=14), ii) placebo (n=8), and iii) controls (n=8). The probiotic consisted of 250 ml/day fermented skimmed milk supplemented with *Lactobacillus rhamnosus GG* (10^8 cfu/ml), *Bifidobacterium animalis* subsp. *lactis* B12 (10^8 cfu/ml), and *Lactobacillus acidophilus* La-5 (10^7 cfu/ml). Heat-treated fermented skimmed milk served as placebo. The intervention period was 8 weeks. LPS was analyzed by Limulus Amebocyte Lysate colorimetric assay (LAL) (Lonza, USA), soluble (s) CD14 and IL-6 by ELISA (R&D Systems) and D-dimer was measured by Asserachrom kits (Diagnostica Stago, Asnière, France). Non-parametric statistics were applied.

Results: Twenty-five completed the trial leaving 12 patients in the probiotic group, 7 placebo and 6 controls. No serious adverse events were recorded. In patients receiving probiotics, there was a 33% reduction from baseline to 8 weeks in the levels of the coagulation marker D-dimer, from a median of 320.3 ng/mL (239.8-474.7 IQR) to 214.2 ng/mL (142.0-392.6 IQR) (p=0.03, Wilcoxon). IL-6 levels decreased 13.8% from median 1.23 pg/mL (0.94-2.46 IQR) to 1.06 pg/mL (0.93-1.39 IQR) in the probiotic group (p=0.06, Wilcoxon). No changes were found in the placebo group or controls. CD4 counts, plasma LPS or soluble CD14 did not change significantly in any of the study arms.

Conclusions: Probiotic supplement significantly reduced D-dimer levels and possibly also levels of IL-6, both markers related to HIV-associated inflammation and cardiovascular disease. This reduction was apparently not related to changes in markers of microbial translocation. Additional studies to further elucidate mechanisms by which probiotics can influence upon gut microbiota, coagulation and inflammation are warranted.

Session P-E2 Poster Session
Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Therapeutic Vaccines and Immunotherapies

343 Immune Function and Viral Load Post AGS-004 Administration To Chronic HIV Subjects Undergoing STI

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Background: HIV infection induces immune dysregulation of both CD4 and CD8 T cell compartments. The anti-viral T cell pools in chronically infected patients are characterized by an exhausted activation phenotype, which is unable to control virus replication. ART can suppress HIV replication leading to

stabilizing of CD4 T cell numbers and improving immune function. However, latent virus is not eliminated and the residual T cell pools do not overcome this state of T cell exhaustion. During non-controlled viral replication, the expression of Programmed Cell Death-1 (PD-1) on activated T cells is associated with T cell exhaustion and poor viral control. AGS-004 is a personalized dendritic cell (DC) loaded with RNA encoding autologous Gag, Nef, VPR, and Rev. AGS-004-001 is a Phase 2 trial designed to assess the efficacy and safety of AGS-004 during a 12 Week ART structured treatment interruption (STI) in chronic HIV-1 infected subjects. The goal of this immunotherapeutic intervention is to reverse this induction of T cell exhaustion leading to control of viral replication by inducing long-term immunity.

Methodology: Longitudinal blood draws where collected prior to AGS-004 dosing, after four doses of AGS-004 administered during ART, and after two doses during STI. Phenotype of HIV-specific CD4 and CD8 T cells and their proliferation capacity where determined by multi-color flow cytometry to determine the activation state of HIV specific T cells. Measurements of viral load were performed during these same time-frames. Associations between T cell proliferation, T cell activation state and viral control were determined.

Results: Positive changes in the magnitude of T cell proliferation to viral antigens after AGS-004 administration were detected in subjects with extended time to viral rebound during STI. Both activated CD4 and CD8 T cells lacking PD-1 where increased after AGS-004 administration in subjects with an extended time to viral rebound versus subjects with faster time to viral rebound measured during STI. Furthermore, subjects displaying rapid viral rebound had a greater number of exhausted CD57+/PD-1+ CD4 and CD8 effector T cells compared to subjects with an extended time to viral rebound.

Conclusions: Taken together, these data suggest that in study AGS-004-001 subjects with an extended time to viral rebound during STI demonstrated increases in CD4 and CD8 T cells with an activated phenotype. Furthermore, these same subjects displayed lower numbers of T cells expressing PD-1, a marker associated with dysfunctional CD4 and CD8 T cell activation. The role AGS-004 plays in the induction of an anti-HIV response geared towards delaying viral rebound during STI will be elucidated in the double blind placebo controlled phase 2 study AGS-004-003, currently underway.

344 Immunogenicity of AGS-004 Dendritic Cell Therapy in Patients Treated During Acute HIV Infection

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Background: Enhancing HIV-1 specific immunity without CD4 T cell activation may clear productively infected cells, a key aspect of eradication strategies. We assessed the safety and immunogenicity of AGS-004 dendritic cell (DC) therapy in patients initiating ART during acute HIV infection (AHI).

Methodology: In an open-label, single arm sub-study of AGS-004-003, DC therapy was administered to patients who initiated ART within 45 days of AHI (HIV RNA <50 c/ml for > 6 months). AHI was defined as a negative/indeterminate EIA or negative HIV RNA test within 45 days of detectable plasma HIV RNA. AGS-004 consists of matured autologous DCs co-electroporated with in vitro transcribed RNA encoding autologous HIV antigens (Gag, Vpr, Rev, and Nef) plus synthetically derived CD40 ligand RNA to achieve DC functionality. Patients received monthly doses of AGS-004 on ART followed by measurement of immune responses after 3-4 doses (week 12 or 16). HIV RNA was measured at 4 time points by a single-copy assay (SCA). The frequency of resting CD4+ T-cell infection (RCI) was measured by quantitative viral outgrowth assay at baseline and after 3 doses (week 10) while on ART. Patients meeting a priori criteria for increased immune response after 3 doses were eligible for voluntary analytic treatment interruption (ATI) with continued monthly DC dosing. Criteria for restarting ART included CD4 count <350 cell/mm^3, >20% decline in absolute CD4 count or percentage, or confirmed HIV RNA ≥10,000 c/ml.

Results: Since January 2012, 6 male patients were enrolled with median age 35 (range 26-56) and median baseline CD4 T cell counts 618 cells/mm^3 (range 397- 937). All six (100%) demonstrated positive immune responses defined as ≥2-fold increase from baseline in the number of CD28$^+$/CD45RA-CD8$^+$ CTL that were also ≥3 standard deviations above the negative control. RCI was low in all 6 patients treated in AHI (0.043 to 0.767 infected resting CD4+ cells per million). Only one patient had a > 2-fold decrease in the frequency of RCI at week 10. HIV RNA by SCA was <1c/ml in 5 patients prior to ATI (6th pending). All 6 patients underwent ATI with a median duration off ART of 74 days (range 34 -152). One participant with the lowest RCI (0.046 IUPM) had the longest ATI (152 days), and another is still in ATI (120 days). The patient whose RCI declined > 2-fold (from 0.179 to 0.067 IUPM) underwent ATI for 90 days. All 5 patients who restarted ART suppressed viremia. The few treatment-related adverse events were all grade 1.

Conclusions: AGS-004 DC therapy was safe, well-tolerated, and led to increased HIV-specific immune responses, but did not allow sustained ART interruption. However, this DC therapy might result in depletion of persistent HIV infection in ART-suppressed patients following administration of anti-latency therapy.

345 Immunogenicity and VL Rebound After ATI in Chronic HIV Infected Patients Receiving MVA-B

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Background: Poxvirus-based vaccines have shown great potential as HIV vaccines. We present the safety and immunogenicity results of a phase I, double blinded, placebo-controlled therapeutical vaccine trial of an MVA vector expressing HIV-1 antigens from clade B (MVA-B) in successfully cART-treated HIV-infected patients who underwent cART interruption.

Methodology: Patients were randomly allocated to receive 3 intramuscular injections of MVA-B at 0, 4 and 16 weeks (n=20) or placebo (n=10). cART was discontinued in all patients 8 weeks after the last dose of MVA-B and viral rebound dynamics were assessed during the first 12 weeks of cART interruption. Immunogenicity to the vaccine insert and the rest of the HIV proteome was assessed using IFNg ELISPOT.

Results: Vaccinations were well tolerated with no grade 3 or 4 side effects reported and VL was maintained below detectable levels in all patients while receiving MVA-B. No major changes in total magnitude or breadth of HIV-specific responses were detected between vaccinees and placebos. Only a minor significant increase in the responses targeting vaccine inserts of Gag and Env-gp120 was seen after 2 vaccinations and was maintained over time (median Gag responses of 290, 403 and 435 SFC/M PBMC at baseline, w6 and w24 respectively, p=0.02 and p=0.04). No increases of functional avidity after vaccination. Unspecific immune activation in vaccines (measured by EBV-specific responses in IFNg ELISPOT) was ruled out. All patients rebounded after cART interruption. At week 12 after cART interruption, median reduction in VL (as compared to setpoint VL before any cART) was -0.24 vs -0.53 log copies/ml in MVA-B vs placebo, respectively (p=0.74). CD4 T cell counts declined similarly between groups. The dynamics of VL rebound did not correlate with the responses detected before cART interruption.

Conclusions: MVA-B vaccination was a safe strategy to increase Gag and Env-gp120 specific T cell responses in individuals with existing HIV-specific immunity but did not delay nor avoid viral load rebound after cART interruption.

346 Dynamics of VL Rebound After cART Interruption in HIV Patients Receiving MVA-B Plus Disulfiram

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Background: In vitro data suggest that stimulation of HIV-1-specific T lymphocytes with a therapeutic vaccine could facilitate elimination of latent viral reservoir after virus reactivation with drugs (i.e disulfiram). We present the results of a substudy of a phase I, doubled blind placebo-controlled trial of an MVA-B therapeutic trial combined with disulfiram virus-reactivation treatment in successful cART-treated HIV-infected patients.

Methodology: Patients were randomly allocated to receive 3 intramuscular injections of MVA-B at 0, 4 and 16 weeks (n=20) or placebo (n=10). Twelve patients (8 MVA-B, 4 placebo vaccinated) received a 4th dose of MVA-B at week 36 followed by 2 months of disulfiram (250 mg qd). cART was discontinued in all 30 patients 8 weeks after the last dose of MVA-B and viral rebound dynamics were assessed during the first 12 weeks of cART interruption.

Results: VL was maintained below detectable levels in all patients while receiving MVA-B or MVA-B/disulfiram on ART but rebounded in all patients after cART interruption. The dynamics of VL rebound were not significantly different between the disulfiram treated/untreated groups. Proportion of patients with VL rebound at weeks 2 and 4 after cART interruption was similar between groups (w2: 7/12 (58%) and 8/16 (50%), w4: 11/12 (92%) and 15/17 (88%), in MVA-B/disulfiram vs MVA-B, P = 0.66 and 0.74), respectively). At week 12 after cART interruption, mean (SE) change VL (as compared with set-point VL before any cART) was −0.72 (0.4) vs −0.35 (0.3) in MVA-B/ disulfiram vs MVA-B, respectively (P = 0.46). CD4 T cell counts declined similarly between groups after cART interruption.

Conclusions: A combination strategy of a therapeutic vaccine (MVA-B) plus disulfiram treatment neither prevented nor delayed viral load rebound after cART interruption as compared with MVA-B vaccination alone.

347 Vaccination With Autologous Dendritic Cells Pulsed With Autologous HIV-Infected Apoptotic Cells

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Background: We evaluated the safety, tolerability, and immunogenicity of a therapeutic HIV vaccine composed of autologous dendritic cells (DC) pulsed with autologous, inactivated, HIV-1 infected apoptotic cells (DC-HIV vaccine).

Methodology: Autologous HIV-1 was isolated from ART-naïve subjects who then initiated PI-based ART. DC-HIV vaccine was composed of autologous monocyte-derived DC (matured with TNFα, IL-1β, IFNγ, Poly I:C) pulsed with autologous lymphocytes infected with autologous HIV-1 and inactivated by UV/psoralen. After virologic suppression (<50 cps/mL) for at least 12 weeks, subjects received 3 doses (10^7 DC each) of DC-HIV vaccine subcutaneously, given at 2 week intervals, followed 6 weeks later by analytic treatment interruption (ATI). A 4th HIV-DC vaccine dose was given 2 weeks into ATI. The primary endpoint was change in HIV-1 RNA from pre-ART to 12 weeks after ATI. Polyfunctional CD8+ T cell responses to the vaccine (n=7) and to consensus HIV-1 Gag peptide pools (n=10) were evaluated before and after vaccination. Changes in T cell immune activation (DR+CD38+) and regulatory T cell (Treg) and myeloid-derived suppressor cell (MDSC) frequencies were also assessed.

Results: Ten male subjects were enrolled and received study vaccine (pre-ART median CD4= 486 cells/mm^3 and HIV-1 RNA=4.53 $\log_{10}$ copies/mL; median duration of HIV diagnosis= 27 mos). The DC-HIV vaccine was well-tolerated and caused only minor local reactions. All subjects remained off ART for the 12-week ATI. Three of 10 subjects had a ≥0.4 $\log_{10}$ decrease in HIV-1 RNA from their pre-ART baseline. CD8+ T cell polyfunctional response was increased in 3/7 subjects after ATI compared to the pre-vaccine response while on ART. Additionally, 4/10 subjects had an increase in CD8+ T cell polyfunctional response to Gag peptide but only 1/3 subjects with ≥0.4 log decrease in HIV-1 RNA had an increase in response to Gag peptide. There was an increase in CD4+ (p=0.006; Wilcoxon signed rank test) and CD8+ (p=0.007) T cell activation following the first vaccine dose but this returned to

pre-vaccine baseline 6 weeks after the 3rd vaccine dose. No change in Treg frequency after vaccination was observed but MDSC frequency was increased (median=2.67-fold; P<0.006). MDSC frequencies remained increased through the 12-week ATI.

Conclusions: DC-HIV vaccination was safe and well tolerated, and associated with a decrease in plasma HIV-1 RNA in some subjects and an early and transient increase in both CD4+ and CD8+ T cell immune activation. Modest increases in CD8+ T cell anti-HIV-1 responses and a subsequent decrease of T cell activation to baseline levels may be related to enhanced frequencies of MDSCs induced by the DC vaccine.

Session P-E3 Poster Session
Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**
New Technologies in Immunology

348 Systems Biology, HIV Disease, and RNAs Big and Small

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Background: Systems biology, encompassing high-throughput molecular profiling technologies and computational methods, provides the means for comprehensive interrogation of the host response to infection. My laboratory is using systems biology to understand and model integrated views of virus-host interactions, to computationally screen for antiviral drugs, and to identify correlates of immunity in nonhuman primate evaluations of new strategies for HIV vaccines.

Methodology: We are using new experimental systems and technologies, such as systems genetics, metabolomics, and next-generation RNA sequencing (RNA-seq), to provide systems-level views of virus infection that include host genetic variation, metabolic pathways, and noncoding RNA expression. We are using these approaches to study early events in the pathogenesis of HIV and simian immunodeficiency virus (SIV) as well as emerging pathogens such as influenza virus, SARS and MERS coronaviruses, and Ebola virus. Specifically, we are using RNA-seq (covering both polyA+ and polyA– transcripts) to obtain comprehensive views of the transcriptional response of CD4+ T cells to infection with HIV and of nonhuman primate rectal and peripheral blood mononuclear cell (PBMC) compartments to acute mucosal infection with SIV. We are also using RNA-seq and microarray-based approaches to study innate and adaptive immune responses of nonhuman primates vaccinated with candidate AIDS vaccines, thereby illuminating the events that lead to protective immune outcomes.

Results: We have observed changes in the expression of diverse classes of small and long noncoding RNAs in CD4+ T cells infected with HIV (including over 1,000 long noncoding RNAs) and in rectal and PBMC compartments of nonhuman primates infected with SIV. This included a phased pattern of microRNA expression, which when integrated with mRNA expression data indicated a role for microRNAs (including novel unannotated microRNAs) in transcriptional regulation, T cell activation, and cell cycle control. In peripheral blood from vaccinated animals, we have also identified early innate immune signaling responses associated with protection from repeated low-dose mucosal challenge with highly pathogenic SIV.

Conclusions: Our findings provide an unprecedented view into the complex early host transcriptional changes that occur in HIV-infected cells and suggest that a detailed knowledge of noncoding RNA regulation and function will be necessary for a full understanding of transcriptional control and viral pathogenesis. In addition, the combination of high-throughput datasets and computational methods provides new information for speeding HIV vaccine and drug development and for preparedness against future viral threats.

349 CoRSeq^{V3}: Novel Coreceptor Usage Prediction Algorithms for HIV-1 Subtypes B, C, D and CRF01_AE

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Background: Maraviroc (MVC) is a CCR5 antagonist used in HIV-1 antiretroviral therapy that can only be prescribed to patients with exclusively CCR5-using virus populations. Thus reliable determination of HIV-1 coreceptor usage in patients is clinically important for prescription of MVC. Genotypic coreceptor usage prediction algorithms, based on HIV-1 V3 sequence, have been developed as inexpensive and rapid alternatives to traditional phenotypic assays that, due to their cost and lengthy turn-around time, have limited prescription of MVC. Most algorithms are designed against and predict coreceptor usage of HIV-1 subtype B (B-HIV), but fail to reliably predict coreceptor usage of other HIV-1 subtypes, which constitute >85% of infections worldwide. We have developed a suite of V3 sequence-based coreceptor usage prediction algorithms ($CoRSeq_{V3}$) that are highly sensitive and specific for determining coreceptor usage of HIV-1 subtypes B, C (C-HIV), D (D-HIV) and CRF01_AE (AE-HIV).

Methodology: $CoRSeq_{V3}$ B-HIV, C-HIV, D-HIV and AE-HIV algorithms were designed and tested using every respective phenotypically characterised patient-derived V3 sequence in the Los Alamos Database, and from our recently published studies. Unique sequences were randomly assigned to "design" and "test" sets for each subtype and analysed for phenotype specific characteristics.

Results: Analysis of "design" sets revealed differing V3 characteristics for CCR5- and CXCR4-using viruses, including charge, length, glycosylation and amino acid mutations, which informed $CoRSeq_{V3}$ prediction criteria. $CoRSeq_{V3}$ predictive accuracy was then tested against independent "test" sequences. We found that $CoRSeq_{V3}$ algorithms have more favorable sensitivity and specificity profiles for predicting HIV-1 coreceptor usage than any alternative, including geno2pheno (Table).

Conclusions: Once clinically validated in future studies our highly sensitive and specific B-HIV, C-HIV, D-HIV and AE-HIV algorithms may enhance access to MVC and future coreceptor antagonists for countries where non-B HIV-1 strains predominate, and which have expanding economies and improving health care systems, such as India and China where C-HIV is endemic and Thailand, Indonesia and Vietnam where AE-HIV predominates. Developed nations with increasing AE-HIV prevalence such as Japan may also benefit from $CoRSeq_{V3}$. $CoRSeq_{V3}$ has been developed as an online platform that will soon be freely available at www.burnet.edu.au/coreceptor.

$CoRSeq_{V3}$ and geno2pheno sensitivity and specificity for predicting HIV-1 coreceptor usage

Coreceptor Usage Prediction Technique	B-HIV 185 CXCR4-using and 526 R5		C-HIV 80 CXCR4-using and 429 R5		D-HIV 57 CXCR4-using and 80 R5		AE-HIV 50 CXCR4-using and 126 R5	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
$CoRSeq_{V3\text{-}B}$	81.1	79.7	-	-	-	-	-	-
$CoRSeq_{V3\text{-}C}$	-	-	88.8	90	-	-	-	-
$CoRSeq_{V3\text{-}D}$	-	-	-	-	86	83.8	-	-
$CoRSeq_{V3\text{-}AE}$	-	-	-	-	-	-	92	92.1
geno2pheno 1% FPR	34.6	99.3	52.5	99.8	49.1	97.5	60	99.2
geno2pheno 2.5% FPR	58.4	97.2	67.5	99.8	70.2	87.5	78	92.9
geno2pheno 5% FPR	68.1	93.7	72.5	97.2	86	75	82	82.5
geno2pheno 10% FPR	74.1	85.3	80	93.7	89.5	53.8	88	57.1
geno2pheno 15% FPR	74.6	80.1	83.8	91.4	89.5	52.5	88	51.6
geno2pheno 20% FPR	77.8	69.8	85	85.8	89.5	48.8	90	40.5

350 Identification of Novel B*57:01 Restricted Peptides From HIV gp140 Using Immunopeptidomics

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Background: A small fraction of HIV-infected patients known as "elite controllers" maintain very low levels of plasma HIV and near normal levels of CD4+ T-cells without antiretroviral therapy. The majority of these long-term non-progressors possess HLA alleles such as HLA-B*57:01 or -B*27:05 that are thought to offer superior T-cell mediated immunity. The majority of peptide epitopes presented by these protective haplotypes have been identified using synthetic peptide libraries and no systematic study has been performed to identify the T-cell epitopes naturally presented by these apparently protective alleles. The use of synthetic peptides may fail to identify post-translationally modified epitopes, epitopes of non-canonical lengths and those arising from translation of alternative reading frames. We have used a mass spectrometry-based immunopeptidomics approach to identify the peptides naturally presented by protective alleles.

Methodology: HLA class I molecules were immunoaffinity purified from cells transfected with plasmids expressing HLA B*57:01 and HIV Env gp140, Rev and Vpu. HLA- bound peptide cargo was separated using reversed-phase chromatography and analyzed on a high resolution AB SCIEX 5600plusTripleTOF mass spectrometer. The data obtained was searched using ProteinPilot software. Peptides assignments were rigorously curated and validated with isotopically labeled HIV peptides.

Results: Over 2900 B*57:01-restricted human peptides were identified and we confirmed ten B*57:01 restricted, naturally presented HIV-gp140 peptides using synthetic peptides. Six of these peptides form part of a larger immunogenic region that was assigned on the LANL-HIV Epitope database. One of the four peptides is part of the Env signal peptide and has a post-translationally modified tryptophan residue. Additionally, one Rev peptide was identified and there were no peptides representing Vpu.

Conclusions: Using a cutting-edge immunopeptidomics approach we have identified novel epitopes that are non-conventional or post-translationally modified. Our methodology has enabled the identification of one of the largest sets of naturally presented human B*57:01 epitopes reported to date along with several novel B*57:01-restricted HIV peptides, setting the stage for elucidation of epitopes from other HIV proteins and analysis of T-cell responses.

351 New Summaries and Computational Tools at Los Alamos HIV Immunology Database

Karina Yusim[1], Shihai Feng[1], Hyejin Yoon[1], KumKum Ganguly[1], Jennifer Macke[1], James Szinger[1], Anthony P. West[2], Pamela Bjorkman[2], Brian Foley[1], Bette T. Korber[1]
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Background: Los Alamos HIV immunology database is an annotated, searchable inventory of more than 17,000 of entries of HIV-1 cytotoxic and helper T-cell epitopes and antibody binding sites, integrated with the sequence variability data from the HIV Sequence Database. The database is extensively used and is being cited in majority of publications on HIV. We strive to provide latest information, summaries and tools for the HIV field, and considering the literal explosion of HIV antibody research in the recent years, several global and useful computational tools are being added to the database to assist researchers worldwide.

Methodology: We used the vast body of information available in the database as well as extra extensive literature searches and analysis to launch new summary tables and analysis tools.

Results: We are introducing 3 new important resources. (i) New "Neutralizing Antibody Resources" page provides searchable summaries of broadly neutralizing HIV-1 antibodies, with links to papers, Ab sequences and structure, notes on breadth of neutralization, where to find Ab contacts or key residues, and heavy and light chain composition; exact coordinates of important neutralizing antibody binding sites and other HIV-1 Env features. (ii) To help systematize the diverse and ambiguous naming systems in different studies both for the new antibodies and the viruses used in large neutralization panels, we put together a relational database of HIV sequences, antibodies and neutralization data from these studies with an easy one-to-one correspondence between the various short names, database names and accession numbers, thereby simplifying analysis for many researches, and meta-studies in particular. (iii) Finally, the new global HIV genome browser tool is being released in the database. This tool retrieves and summarizes the vast and diverse information and tools available at HIV Immunology database. The browser allows users to look at the whole HIV genome as well as to zoom in to every HIV genome position or a region of interest and visualize all information we have in the database about this position (overlapping epitopes, antibody binding sites, antibody contact residues, functional domains, HIV sequence variability, database alignments etc). This tool also provides links to the database annotation and database tools, as well as pubmed and other sources.

Conclusions: The new summaries and tools developed in HIV Immunology database provide a user-friendly one-stop source of information about HIV genome and immunological data and promise to be very useful for HIV scientific community and for vaccine design efforts.

Session P-E4 Poster Session
Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall**

Monocytes, Dendritic Cells, NK Cells

352 Identification of Pattern Recognition Receptor for HIV-1 in Human Dendritic Cells

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Background: In attempt to identify putative intracellular pattern recognition receptors (PRRs) which recognize HIV-1 viral nucleic acids and trigger IFN mediated immune responses, we set up a si-RNA screen in MDDC cells where infection with Vsvg pseudotyped HIV-1 virus in the presence of VLP-Vpx particle induces ISG 54 expression.

Methodology: Targeted library of si-RNAs with known nucleotide binding domain and/or involvement in nucleotide metabolism are screened for inhibition on the infection mediated ISG54 induction. A knock-down efficiency of 70-90%, independent of donors, was achieved in MDDCs with transient transfection of si-RNAs. Further more, the ISG54 induction was IRF3 dependent and but independent of NFkB, p65 and the infection mediated induction was restricted to ISGs since pro-inflammatory cytokines such as TNFalpha and IkB are not induced. Initial hits were subjected to rigorous reconfirmation and deconvolution of pooled siRNAs for each hit gene as well as validation for their ability to enhance ISRE-reporter in 293T upon cDNA over-expression.

Results: Currently, we have several proteins that regulate innate responses in MDDCs to HIV-1 infection, and these factors are being characterized to determine if they play a direct role as a pattern recognition receptor to HIV-1.

Conclusions: Identification of PRR specific for HIV-1 virus will be a profound step in understanding innate response, or lack of the responses, upon HIV-1 infection.

353 Plasmacytoid Dendritic Cell Phagocytosis of IgG Anti-p24 Associates With Control of HIV Infection

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Background: Defining immune control mechanisms in patients with HIV infection will facilitate the development of HIV vaccines. Slower progression of HIV infection is associated with IgG antibodies to HIV Gag proteins. We have investigated this association by comparing functional characteristics of IgG antibodies to HIV p24, particularly phagocytosis by a plasmacytoid dendritic cell (pDC) cell line and the relationship with antibody isotype diversification, in HIV controllers and non-controllers.

Methodology: Sera from 59 HIV controllers (30 elite and 29 viremic) and 30 non-controllers were obtained from members of the SCOPE cohort. Phagocytic antibodies to HIV p24 (recombinant, baculovirus) were assayed using the Gen2.2 cell line, which we have shown to mediate phagocytosis via FcγRIIa. IgG1 (upstream) and IgG2 (downstream) antibodies to native HIV p24 were assayed by ELISA.

Results: Phagocytic antibodies against HIV p24 were higher in viremic controllers (p=0.0001) and, to a lesser extent, elite controllers (p=0.05) than non-controllers but did not correlate with plasma HIV RNA levels or $CD4^+$ T cell counts in viremic controllers. Both IgG1 and IgG2 antibodies to HIV p24 were detected in all patient groups and correlated strongly (r=0.63, p<0.0001). However, the antibody response was skewed away from IgG2 in non-controllers compared with controllers. Viremic controllers, but not elite controllers, exhibited higher serum levels of IgG1 and IgG2 anti-p24 than non-controllers (p=0.004 and 0.0004, respectively). Phagocytic antibodies against HIV p24 correlated with IgG1 and IgG2 anti-p24 (r=0.75 and 0.61, respectively; p<0.0001 for both). Neither IgG1 nor IgG2 anti-p24 correlated with plasma HIV RNA levels in viremic controllers or non-controllers but both correlated negatively with $CD4^+$ T cell counts in viremic controllers (r=-0.33, p=0.08 and r=-0.49, p=0.007, respectively).

Conclusions: Phagocytic antibodies (using a pDC cell line) and IgG1 and IgG2 antibodies to HIV p24 were higher in viremic controllers, but not elite controllers, compared with non-controllers. IgG antibodies to HIV p24 may, therefore, contribute to, or at least be a marker of, immune control mechanisms in HIV controllers who cannot achieve elite control. These antibodies might activate anti-viral accessory cell responses, such as those mediated by pDCs.

354 Recruitment of Functionally Different NK Cells To the Rectal Mucosa in Vaccinated Macaques

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Background: Increasing evidence suggest that HIV can be controlled by Natural Killer cells (NK cells), via multiple mechanisms including antibody dependent cellular cytotoxicity (ADCC). In the RV144 vaccine trial, that showed 31% protection from HIV acquisition, there was an inverse correlation between risk of infection and ADCC, suggesting the importance of NK cells. NKG2A+ NK cells express CD16 and mediate ADCC. Mucosal NKp44+ NK cells produce IL-17 and IL-22 are important for the homeostasis of mucosal compartments. Here we investigated whether the ALVAC/SIV gp120 vaccine regimen adjuvanted with ALUM or MF59 could affect vaccine efficacy and NK cell function in mucosa.

Methodology: Two macaque cohorts were vaccinated with ALVAC-SIV gp120 vaccines. One group was boosted with the gp120 protein, adjuvanted with ALUM (n=27) while the other group was given the gp120 formulated with MF59 (n=27). All the animals were challenged with low repeated dose of SIVmac251 intra-rectally. Rectal biopsies were analyzed at one week after the last immunization for the frequency and function of NK cells by flow cytometry.

Results: We observed a significant protection from SIVmac251 acquisition versus the 47 control animals in the ALUM but not in the MF59 group. Both vaccines recruited NKG2A+ and NKp44+ NK cells to the gut. However, the frequency of NKG2A+CD107a+ NK cells and NKG2A+TNFα+ NK cells were significantly higher in the MF59 group (p=0.015, P=0.0468) following stimulated with PMA/Ionomycin whereas the NKp44+IL17+ NK cells were significantly higher in the ALUM group when stimulated with SIV env peptides (p=0.0098).

Conclusions: Our results indicate that vaccination with ALUM recruits regulatory NKp44+IL17+ NK cells whereas vaccination with MF59 was associated with a higher recruitment of cytotoxic NKG2A+CD107+ NK cell subsets to the gut. However, none of the differences correlated with protection from SIV mac251 acquisition.

355 HIV Myeloid-Derived Suppressor Cells Inhibit the Protective Response To Cytomegalovirus

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Background: HIV infection is associated with diminished protective responses against opportunistic infections including cytomegalovirus (CMV). In this study, we examined the effect of HIV expanded myeloid derived suppressor cells (MDSCs) on CMV specific effector cells.

Methodology: Peripheral blood mononuclear cells (PBMCs) obtained from HIV seronegative, CMV seropositive healthy donors were cultured in presence of heat inactive HIV_{BaL}. After 5 days, cells were stained with anti-CD11b, anti-CD33, anti-CD14 and anti-HLA DR. $CD11b^+CD33^+CD14^+$HLA DR^{hi} (DR^{hi} monocytes) and $CD11b^+CD33^+CD14^+$HLA $DR^{-/lo}$ (MDSCs) cell subsets were sorted using flow cytometry. Sorted cell fractions were cultured with freshly isolated autologous PBMCs in presence or absence of a peptide pool of CMV pp65 antigen (1 µg/ml). IFNγ and IL-10 were determined by ELISPOT and expressed as spot forming units (SFU). Sorted cell fractions were cultured in presence of LPS (100 ng/ml) and IFNγ (2 ng/ml). IL-12p70 was determined in culture supernatants by ELISA and surface expression of HLA DR and CD83 (maturation markers) by flow cytometry. CD150 and B7H4 (leukocyte activation markers) expression on sorted cell fractions was determined by flow cytometry. Data were analyzed using two-tailed, paired Student's *t* test.

Results: Culture of PBMCs with heat inactivated HIV resulted in a significant expansion of MDSCs as compared to control PBMCs (p=0.003). Expansion of MDSC and DR^{hi} monocyte cell populations were comparable in the presence of HIV (p=0.74). PBMCs stimulated with the CMV pp65 peptide pool and cultured with sorted autologous MDSCs had fewer IFNγ SFU compared to PBMCs without MDSCs (p=0.03); however, PBMCs cultured with DR^{hi} monocytes did not significantly differ (p=0.37). Furthermore, pp65 stimulated PBMCs produced increased IL-10 SFU when cultured with MDSCs compared to cultures with the DR^{hi} monocyte subset. The MDSC subset exhibited a 2-fold increase in expression of surface CD150 and 1.3-fold increased expression of B7H4 as compared to the expression on the DR^{hi} monocyte subset (p=0.03). HIV MDSCs maintained HLA DR^{lo} and $CD83^{lo}$ expression as compared to the DR^{hi} monocytes, even when cultured with LPS and IFNγ. Furthermore, these cells produced 4-fold less of the T_H1 polarizing cytokine IL12p70 as compared to DR^{hi} monocytes (p=0.02).

Conclusions: These findings suggest that HIV infection results in a significant expansion of MDSCs and that MDSCs are involved in suppression of the immune response directed against CMV. Understanding the mechanism(s) responsible for the suppressed immune response against CMV will assist in the development of treatment strategies designed to improve the immunity to CMV and other opportunistic infections associated with advanced HIV infection.

Session P-E5 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall**

Pre-Clinical Vaccine Studies

356 Induction of Gut Anti-HIV Immune Response via Dendritic Cell Targeted Intranasal Vaccination

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Background: The mucosal surfaces of the gastrointestinal (GI) tract are preferentially targeted by HIV-1, resulting in profound depletion of GI CD4+ T cells and massive viral replication early in the course of infection. Therefore, the induction of an effective GI mucosal immune response is important for the HIV-1 vaccine effort. Here, we have employed a novel dendritic cell targeted vaccine strategy to induce GI mucosal immune responses to HIV gag p24 antigen.

Methodology: C57Bl/6 mice were immunized with either HIV gag p24 or dendritic cell (DC) targeted α-DEC-205 gag p24 in combination a microbial mimic, polyICLC. The vaccine was delivered via intranasal (i.n.), subcutaneous (s.c.), intramuscular (i.m.) or intraperitoneal (i.p.) routes in a prime-boost fashion. One week post boost, the small intestinal lamina propria (SILP) or colonic lamina propria (CLP) lymphocytes were isolated and cultured in the presence of either p17 (control) or p24 (immunizing) peptides to examine cellular recall responses. Subsequently, to determine the longevity of mucosal immune responses, mice were immunized as above, and recall responses were tested after six months.. The data was acquired using flow cytometry and analyzed using Flowjo (Treestar) and Prism (Graphpad Software) respectively

Results: We illustrate the capacity of an i.n. administered vaccine to induce robust and long-lived responses within the SILP and CLP, characterized by α-HIV specific CD4+IFN-γ+ cells. i.n. (1.5% CD4+IFN-γ+ cells) and i.p. (1.4%) routes of immunization were superior to systemic routes of vaccination such as s.c. (0.1%) or i.m. (0.1% $P < .0001$). We utilized a DC targeting technique to enhance the uptake of the antigen complex by DCs. The utilization of a α-DEC-205 gag p24 antibody significantly increased the potency of the α-HIV p24 response, exhibiting a two-fold increase in CD4+IFN-γ+ T cells (1.6% versus 0.8%), which was DC mediated. Characterization of the α-HIV specific CD4+ generated after i.n. vaccination revealed a predominant Th1 response, with enhanced levels of IFN-γ, IL-17, IL-1β producing T cells in the. In addition to CD4+ T cell responses, CD8+ responses were generated using a NYVAC-gag boost followingα-DEC-205 priming,. Furthermore, we observed that DC targeted vaccination induced immunity as long as six months following immunization at the site of the SILP (1.93%) and the Colonic LP (3.3%) and was significantly more potent than unconjugated gag p24

Conclusions: Robust and long-lived α-HIV immune responses can be generated in the GI lamina propria using a novel, DC targeted vaccine

357 Conserved Element DNA Vaccine based On HIV-1 or SIV sequences Increases T-Cell Breadth

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Background: HIV sequence diversity and potential "decoy" epitopes are hurdles in the development of an effective AIDS vaccine. We tested the hypothesis that a vaccine candidate composed of highly Conserved Elements (CE) of the HIV proteome excluding the variable regions would help overcome these problems. CE were selected based on both stringent conservation and association of specific elements with immune control. A prototype HIV DNA vaccine, expressing 7 CE identified in p24gag as a single protein, was able to induce robust cross-clade specific immune responses in mice.

Methodology: Macaques were immunized by IM injection followed by electroporation with two DNA plasmids providing potential epitopes found in >99% of all HIV-1 M group sequences. Cellular immune responses were compared to those obtained upon vaccination with gag DNA only. As a second test of this concept, we also developed SIVp27gag CE vaccine and tested immunogenicity in DNA vaccinated macaques.

Results: HIV CEgag DNA vaccination induced robust immunity in all 10 vaccinated macaques, whereas full-length gag DNA vaccination elicited CE responses in only 5 of 11 animals targeting fewer CE per animal. CE DNA vaccination elicited highly cytotoxic T cells against CE, capable of Granzyme B production and degranulation, desired features for an effective vaccine. Importantly, boosting CE-primed macaques with DNA expressing full-length p55gag increased both magnitude of CE responses and breadth of Gag immunity, demonstrating altered immunodominance hierarchy in the presence of pre-existing CE-specific responses. Similarly, we found the vaccination with SIV p27gag CE induced antigen-specific responses. In contrast, vaccination with SIV p57gag induced poor CE-specific responses found only in 50% of the vaccinees. As for HIV CE, the SIV CE-specific responses were boosted by vaccination with DNA expressing complete Gag.

Conclusions: Combination of conserved elements and full-length immunogen provides a novel strategy to increase the magnitude and breadth of immune responses to Gag, and allows for the development and expansion of subdominant responses. This vaccine allows the immune system to target the 'Achilles heel' of the virus, for which few escape pathways exist. Inclusion of a conserved element immunogen provides an effective strategy to broaden responses against any highly diverse pathogen by avoiding decoy epitopes, while focusing responses to critical and invariable viral elements.

358 DNA and Protein Co-Immunization Improves the Magnitude and Longevity of Humoral Immune Responses

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Background: Understanding the quality of immune responses induced by different vaccine regimens is essential for improving the prospects of AIDS vaccines.

Methodology: To identify optimal regimens, we compared vaccination protocols that used DNA, protein, or a combination of DNA and protein using a classical prime/boost strategy or delivered in a co-immunization regimen combining the two vaccine components. Magnitude, breadth, longevity and mucosal dissemination of anti-Env humoral responses were monitored in vaccinated macaques. Rhesus macaques were vaccinated using electroporation with either DNA, DNA/protein co-immunization, or DNA prime followed by protein boost or by protein alone. As protein source, we used AT-2 inactivated SIV particles or HEK293 produced HIV or SIV Env. Humoral (including neutralizing, linear epitope and V1V2 antibodies) and cellular responses were followed over time. Some of the vaccinated macaques were challenged to determine immune correlates of protection.

Results: Protein only vaccination induced robust humoral responses, which rapidly declined. In contrast, co-immunization with DNA (IM delivered by needle) and protein induced long-lasting responses. We expanded on these observations and implemented several vaccine improvements, i.e. better env DNA plasmids, inclusion of IL-12 DNA as adjuvant and improved in vivo DNA vaccine delivery by intramuscular injection followed by in vivo electroporation (IM/EP) and inclusion of protein as boost or co-immunization regimen. Although DNA only vaccination achieved strong humoral responses, protein boost after DNA vaccination greatly increased Ab levels. Importantly, a co-immunization strategy of DNA/protein injected in the same muscle the same time induced highest and broad humoral responses. Similar data were obtained using either purified Env proteins or inactivated viral particles. Inclusion of DNA in the vaccine promoted persistence of plasma antibody levels for greater than 2 years. SIV DNA/protein vaccination induced: higher SIV Env-specific IgG in saliva; more responders with higher SIV Env-specific IgG in rectal fluids; higher and longer-lasting plasma bAb and Nab to homologous and heterologous Env; and Ab to V1/V2. Systemic and mucosal vaccine-induced Ab responses against SIVsmE660 correlated with slower virus acquisition upon challenge. In addition, vaccinated macaques showed strong protection against chronic viremia compared to controls. Similar to SIV, HIV DNA/protein (purified Env) vaccination also induced higher Ab levels compared to DNA only, including significantly higher levels of V1/V2 Abs.

Conclusions: DNA/protein co-delivery increases the magnitude and longevity of systemic and mucosal humoral immune responses in immunized rhesus macaques.

359 The Adjuvant Used in an ALVAC/gp120 Regimen Alters Plasmablast Homing Markers in Macaque and Humans

Luca Schifanella[1], Shari Gordon[1], Monica Vaccari[1], Georgia Tomaras[2], Mangala Rao[3], David Venzon[1], Susan Barnett[4], James Tartaglia[5], Silvia Ratto-Kim[6], Genoveffa Franchini[1]

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Background: An ALVAC-HIV/gp120 vaccine provided limited but significant protection against HIV-1 acquisition (31.2%) in RV144 trial. Antibodies against the envelope were associated with reduced risk of HIV acquisition. The frequency of plasmablasts (PBs) has been shown to correlate with protection from SIV acquisition in macaques. Increasing evidence indicates that chemokines and their receptors have a central role in regional targeting PBs to hematopoietic, mucosal or inflammatory sites. The homing of vaccine-induced PBs could affect vaccine efficacy.

Methodology: 2 groups of 27 macaques each were immunized 4 times with ALVAC-SIV and received 2 boosts of gp120 formulated in ALUM or MF59. 1 month post immunization all animals and 47 controls were challenged with repeated low doses of SIVmac251 by intra-rectal route. We studied the vaccine efficacy and the frequency of PBs expressing alpha4beta7, CXCR4 and CXCR3. The frequency of the same markers in PBs was measured in 2 clinical cohorts (n=17 each) that were immunized with ALVAC HIV and boosted with 2 gp120 formulated in ALUM or MF59 together with ALVAC-HIV (RV132 and RV135)

Results: In macaques both strategies induced high titer of binding antibodies to SIV-gp120 and a similar frequency of specific PBs; however only ALUM group significantly reduced rate of SIV acquisition when compared to 47 unvaccinated controls (Log rank p=0.021). We found that, in naïve animals, the frequency of total PBs was correlated with the subset of PBs expressing alpha4beta7 (a mucosal homing marker) (CC=0.55, p=0.0001). 7 days after last vaccination the MF59 group showed an increased frequency of circulating PBs expressing CXCR3 (an inflammatory site homing marker) and a significant decrease in the frequency of the alpha4beta7 PBs (p=0.0001, p=0.001). The frequency of vaccine-induced alpha4beta7 PBs was higher in ALUM group while the frequency of CXCR3 PBs was higher in the MF59 group (p=0.01, p=0.03). Only in the ALUM group the frequency of PBs expressing alpha4beta7 was correlated with the amount of rectal IgA and IgG against the V2 region of mac251 (p=0.04 and p=0.02)

In the clinical cohorts we observed a significant higher frequency of circulating alpha4beta7 PBs in the ALUM group when compared with the MF59 group (p=0.03); however, no differences in CXCR3 expression was observed between the 2 groups.

Conclusions: Our data indicate that different adjuvants alter the expression of chemokine and integrin receptors on PBs that, in turn, affect their homing potential to tissues. We found no correlation between the expression of homing markers on PBs and reduced rate of SIV acquisition. Boosting with gp120 with ALUM adjuvant induces a significant higher frequency of alpha4beta7 PBs than boosting with gp120 with MF59 when measured in the two clinical cohorts.

360 ALVAC-SIV/gp120 Efficacy Is Not Improved by the Increase of Anti-Envelope B and T-Cell Responses

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Background: A prime-boost regimen of recombinant canarypox priming (ALVAC-HIV) with HIV (Clade B and E) -gp120 protein boosting formulated in Alum resulted in significant but limited protection from HIV acquisition in the Thai Trial (RV144).

We hypothesized that the use of the Th1/Th2- adjuvant MF59 as an alternative to the Th2- Alum, could improve the protection elicited by the ALVAC-SIV/gp120 vaccine platform, by increasing envelope specific antibody and T cell responses.

Methodology: We vaccinated 54 macaques four times (0,4, 12 and 24 weeks) with the identical ALVAC backbone used in RV144, expressing SIV mac251 Gag-pro and gp120TM (instead of the HIV-1 Envs used in RV144), and then boosted 27 macaques twice (12 and 24 weeks) with both SIVmac251- and SIVsmE660- gp120 proteins formulated either with Alum or with MF59. A total of 24 adjuvanted or naïve animals were included as concurrent controls and additional 23 as historical controls. All the animals were exposed to 120 TCID50 of SIVmac251, by the intra-rectal route, once a week, at 4 weeks after the last immunization.

Results: ALVAC-SIV/gp120 adjuvanted in MF59 significantly increased env-specific binding antibodies, ADCC, neutralizing antibodies, and CD4+ T-cell responses compared to the identical regimen adjuvanted in Alum. However the Alum-group induced significantly higher titers of envelope specific IgG3 antibodies in the plasma and cyclic V2 responses in mucosal compartments compared to the MF59-group. In addition, the Alum-group (RV144-like) resulted in significant protection from SIVmac251 acquisition (log rank $p=0.021$) while the MF59-group did not improve the efficacy of the ALVAC/gp120 regimen (log rank $p=0.56$)

Conclusions: The combination of ALVAC-SIV-gp120/MF59 was overall more immunogenic than that of ALVAC-SIV-gp120/Alum; however it did not increase protection against SIVmac251 acquisition and altered both the IgG subclass and mucosal V2 responses.

361 Altering the Prime Affects ALVAC-SIV/gp120 Immunogenicity and Efficacy

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Background: The 31.2% efficacy afforded by ALVAC-HIV/gp120 in the RV144 Thai Trial needs to be improved. ALVAC-SIV/gp120 vaccines tested in a SIVmac251 macaque model also demonstrated partial efficacy ~40% at each challenge. DNA vaccines and alternate adenoviral vectors such as Adenovirus 26 are clinically relevant vaccine candidates that could be used in combination with ALVAC/gp120. Thus we used the macaque model to test if priming the immune system with DNA or Ad26 as opposed to ALVAC would improve the immunogenicity and efficacy of ALVAC-SIV/gp120 vaccines.

Methodology: Twenty-seven macaques were given four vaccinations with ALVAC expressing SIV genes. A second cohort of twenty-four macaques had the two initial ALVAC vaccinations replaced with either two intramuscular DNA injections or a single intramuscular injection with Adenovirus 26, all expressing SIV genes. All vaccinated animals were boosted with ALVAC-SIV and gp120 protein in alum. Four weeks post immunization, vaccinated macaques and 41 controls were given repeated low-dose intra rectal challenges with SIVmac251. The immunogenicity and efficacy of each regimen was evaluated.

Results: DNA-ALVAC-SIV/gp120, Ad26-ALVAC-SIV/gp120 and ALVAC-SIV/gp120 vaccines all induce high titer gp120 binding antibodies that recognize the V1/V2 region. The Ad26 primed group demonstrated significantly greater neutralization of SIV tier 1-like viruses, ADCC and increased SIV specific T cell responses. To evaluate efficacy, we compared the rate of SIV acquisition of each vaccination regimen to controls and found that both ALVAC-SIV/gp120 and DNA-ALVAC-SIV/gp120 vaccines significantly delayed SIV infection with an estimated efficacy of 40.2 and 51.2% respectively. However the rate of SIV acquisition was not significantly different between the Ad26-ALVAC/SIV+gp120 regimen and controls.

Conclusions: Priming with DNA or ALVAC followed by ALVAC/gp120 boosting resulted in a significant reduction in the rate of SIV acquisition. However, we observed a lack of protective efficacy when Ad26 was combined with ALVAC-SIV/gp120. This finding differs from other studies that demonstrated protective efficacy with an Ad26-MVA regimen using an alternate SIVmac251 challenge stock 3-9 months post vaccination. Understanding the evolution of protective responses and vaccine combinations that enhance efficacy can inform the design of human trials that use these vaccine modalities.

362 Immunization of Humanized BLT Mice Against HIV Influences Early Immune Responses and Viral Loads

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Background: The precise specificity of humoral and cellular immune responses has been shown to affect the control of SIV/HIV replication. While the SIV-infected rhesus macaque model has proven invaluable for elucidation of the mechanisms of HIV disease pathogenesis and vaccine efficacy, differences in host and viral genetics limit the model's use for the study of human HIV-specific immune responses elicited by infection or immunization.

Recent studies have shown that the immune system in the humanized BLT mouse model is functional and HIV specific cellular immune responses elicited during infection of these mice appear to accurately reflect those of humans, indicating that this model may be useful for HIV vaccine studies.

Methodology: Four sets of mice reconstituted from distinct human donors were immunized with a PLGA-Gag microparticle prime and then boosted with a replication-defective HSV viral vector encoding HIV Gag (d106S-Gag). Mice were then challenged four weeks later with the HIV molecular clone JR-CSF, 2 groups with a moderate dose of 20,000 TCID50 intravaginally (Experiments #1 and #2) and 2 groups with a high dose of 50,000 TCID50 intraperitoneally (Experiments #3 and #4).

Results: Gag immunized mice exhibited a stronger and more rapid cellular immune response against Gag versus mock or GFP-immunized mice, indicative of an anamnestic response.

Gag immunization in Experiment #1 produced a delay in detectable plasma viremia by up to 6 weeks in 3/6 mice, with a mean difference in viral loads of 1.7 log10 ($p \leq 0.03$) during this period, while in Experiment #2 1/9 mice exhibited a delay in plasma viremia by up to 4 weeks and the group had a 0.4 log10 mean difference at 6 and 10 weeks post-challenge ($p \leq 0.03$). Following a high-dose intraperitoneal challenge (Experiments #3 and #4) we observed a more modest 0.5 log10 difference in the mean viral loads at weeks 2 and 6 post-challenge ($p = NS$ and $p < 0.04$, respectively). Overall, the combined results show that Gag immunization was highly associated with lower viral loads ($p = 0.003$) over the 12 week challenge period.

Conclusions: The detection of anamnestic responses and the consistent reduction in viral loads across numerous groups illustrate that humanized BLT mice can be successfully utilized for HIV vaccine studies. This small animal model of HIV infection and immunology may therefore play an important role in the development of HIV vaccines, including efforts to redirect immunity towards more critical targets of the virus.

Session P-E6 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall**

Human Vaccine Trial Results

363 Antibody Responses in Anogenital Secretions of RV305, a Late Boost Vaccination of RV144 Volunteers

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Background: Anogenital mucosae are the primary sites of HIV-1 acquisition. RV144 is the only HIV vaccine trial to show efficacy to date. HIV uninfected RV144 volunteers (n=162) who completed all vaccinations 6-8 years earlier, were enrolled into the RV305 and were randomized to receive 2 injections of ALVAC-HIV or AIDSVAX B/E or a combination of both, or placebo, at day 0 and 6 months. We measured serial antibody responses in anogenital secretions.

Methodology: IgG and IgA responses in cervical vaginal mucus (CVM), seminal plasma (SP), and rectal secretion (RS) at study entry and 2 weeks post first and second injection were tested by ELISA against HIV-1 envelope gp120 CRF01_AE (A244gD), and gp70V1V2 scaffold proteins derived from CRF01_AE (92TH023) and subtype B (CaseA2).

Results: Prior to boosting, IgG A244gD responses in CVM were similar in all vaccination groups with geometric mean titers (GMT) range of 61-66. GMT increased to 1745 and to 904 two weeks after the first boost, but decreased to 994 ($p=0.01$) and 556 ($p=0.10$) following the second boost in AIDSVAX B/E and ALVAC-HIV/AIDSVAX B/E groups, respectively. Gp70V1V2 IgG responses in CVM were undetected in all groups prior to boosting. After the first injection, responses were higher in AIDSVAX B/E followed by ALVAC-HIV/AIDSVAX B/E; gp70V1V2 B, GMT=35 and 28, respectively; gp70V1V2 AE, GMT=228 and 133, respectively. After the second boost, responses to gp70V1V2 AE decreased to GMT=65 ($p<0.01$) and 50 ($p=0.04$), respectively, but responses to gp70V1V2 B remained unchanged. In SP, IgG responses to A244gD and gp70V1V2 AE were detected after the first boost in the AIDSVAX B/E and ALVAC-HIV/AIDSVAX B/E groups with A244gD GMT=125 and 126, respectively, and for gp70V1V2 AE GMT=28 in both groups. IgG GMT to A244gD decreased to 62 ($p<0.01$) and 70 ($p<0.01$), respectively, while gp70V1V2 AE reactivity was undetectable after the second boost. SP IgG responses to gp70V1V2 B were not detected in either group. In the ALVAC-HIV group, CVM and SP IgG responses were undetectable for all proteins tested. IgG responses were not detected in RS from any vaccination group and no IgA responses were detected in any of the samples tested (1:100 sample dilution).

Conclusions: Antibodies induced in RV305 anogenital secretions indicate that IgG responses to HIV-1 gp120 and to gp70V1V2 scaffold proteins in CVM and SP were inducible after being boosted with AIDSVAX B/E or ALVAC-HIV/AIDSVAX B/E. We did not detect IgG antibody responses in mucosal secretions from the group receiving ALVAC-HIV only and in RS from all groups. IgA responses were absent in mucosal secretions from all groups. The induction of HIV-1 antigen specific IgGs in CVM and SP suggests a possible mechanism by which the RV144 regimen provided protection from HIV-1 acquisition in heterosexual couples.

364 Divergent HIV-Specific CD4 T-Cell Response Profiles in HIV Vaccine Trials

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Background: A fundamental goal for an HIV vaccine is to induce long-lived protective immunity. However, in HIV vaccine trials conducted to date, humoral responses are modest and appear to wane rapidly after vaccination. Given the critical role of CD4 T cell help in the induction of affinity-matured, long-lived antibody responses, we extensively characterized CD4 responses developed using a wide range of previously studied vaccine candidates and adjuvants.

Methodology: Cryopreserved peripheral blood mononuclear cells were obtained from samples corresponding to peak immunogenicity times of several HIV vaccines including ALVAC alone delivered via different routes, ALVAC prime/ AIDSVAX boosts, ALVAC prime/ Env protein boosts, DNA prime/ Ad5 boost, subtype B gp120 alone, and MVA alone. Chronically infected HIV specimens were used as reference. HIV-specific CD4 T cell responses were assessed by intracellular cytokine staining using multicolor flow cytometry.

Results: HIV-specific CD4 T cell responses were detectable in all vaccines and patients, however, the magnitude, cytokine profile and protein dominance varied substantially. Overall, PBMC from vaccine recipients primarily targeted Env, compared to chronic HIV specimens that primarily targeted Gag. ALVAC immunizations delivered intradermally or loaded on autologous dendritic cells generated CD4 T cell responses to Env-derived peptides while intramuscular delivery elicited responses targeting Gag peptides. Env protein boosting of intramuscular ALVAC primes overwhelmingly shifted the response to Env. In this regard, boosting with oligomeric gp160 had a stronger effect than bivalent gp120. CD4 T cells responding to ALVAC vaccination alone predominantly produced TNFα and IL-21 in response to Env, whereas Gag invoked more IFNγ than IL-21. Oligomeric gp160-boosted PBMCs produced TNFα and IFNγ in response to both Env and Gag, while the response in bivalent gp120-boosted PBMC consisted of TNFα, IFNγ, and IL-21, albeit as mostly single-cytokine producing cells. MVA immunizations, either intradermal or intramuscular, overwhelmingly generated more to Env peptides than Gag specific responses. Using principal component analysis (PCA), the induced response patterns showed a very distinct cytokine profile that only partially overlapped with the CD4 T cell responses seen in natural HIV infection.

Conclusions: Immunization vectors and antigens differentially influence the CD4+ T cell response. Vaccine-specific immune responses vary drastically from those developed through natural HIV-1 infection. Ongoing analyses of specific CD4 T cell responses induced by various vaccination vectors and delivery routes may elucidate optimal means of invoking strong antibody responses in HIV vaccine recipients.

365 Immunogenicity and Reactogenicity of Cervarix® Versus Gardasil® in HIV-Infected Adults: An RCT

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Background: Most human papillomavirus (HPV)-related cancers are potentially vaccine-preventable. Persons infected with HIV have excess risk of developing HPV-related cancers but are often hyporesponsive to immunization. We hypothesized that in HIV-infected adults the TLR4 agonist-adjuvanted bivalent HPV vaccine would be more immunogenic than the alum-adjuvanted quadrivalent HPV vaccine.

Methodology: We performed an investigator-initiated, double-blind, controlled trial randomizing HIV-positive adults to receive either three doses of the bivalent HPV vaccine (Cervarix, GlaxoSmithKline) or the quadrivalent HPV vaccine (Gardasil, Sanofi Pasteur MSD) at 0, 1.5 and 6 months. Immunogenicity and safety were evaluated for up to 12 months. Primary endpoints were serum neutralizing anti-HPV-16 and anti-HPV-18 antibody geometric mean titers (GMTs) at 7 months measured by pseudovirion-based neutralization assay (PBNA). The HPV-DNA status of the participants was determined before and after immunization.

Results: Ninety-two participants were included in the study. Anti-HPV-18 GMTs were higher in the bivalent HPV vaccine group compared with the quadrivalent HPV vaccine group at 7 and 12 months, and no significant differences were found in anti-HPV-16 GMTs among vaccine groups. In the bivalent HPV vaccine group, female compared with male participants had higher anti-HPV-16/-18 GMTs . No gender-specific differences in GMTs were found in the quadrivalent HPV vaccine group. Mild injection site reactions were more common in the bivalent HPV vaccine group than in the quadrivalent HPV vaccine group (91.1% vs. 69.6%; P = .02). No serious adverse events occurred.

Conclusions: Compared with the quadrivalent HPV vaccine, the bivalent TLR4-adjuvanted HPV vaccine induced superior vaccine responses among HIV-infected women whereas in HIV-infected men the difference in immunogenicity was less pronounced. Both vaccines were well tolerated. Comparative efficacy trials of HPV immunization in HIV-infected individuals are warranted.

366 The Specificity of V3 Antibodies in RV144 Plasma Implicated in Reducing HIV Infection

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Background: The RV144 clinical trial was shown to have an estimated vaccine efficacy of 31%. IgG antibodies (Abs) to V2 significantly inversely correlated with infection risk. Recently it was shown that Abs to V3 also inversely correlated with infection risk when vaccinees had low levels of Env-specific plasma IgA, and ADCC and neutralizing Abs. In addition, sieve analysis of breakthrough viruses identified significant differences in vaccine- and placebo-recipients in the proportion of certain residues present at positions 307 and 317 in V3. Studies were therefore performed to determine the fine specificity of V3 Abs in RV144 plasma and their possible role in reducing HIV infection.

Methodology: Plasma specimens drawn two weeks after the last immunization from 40 vaccinees and 20 placebo recipients were tested in ELISA at a 1:100 dilution for reactivity vs. biotinylated cyclic V3 peptides (cV3s).

Results: Of 8 cyclic V3 peptides studied, reactivity was strongest vs. clade B cV3s. The next strongest responses were with clade A, AG and C cV3s. The weakest responses were seen vs. clade AE cV3s (92TH023 & A244). The relative strengths of responses were consistent with analyses of the distance between the V3 sequences used in the assays. Plasma from placebo recipients were non-reactive. Seven variants of BaL and A244 cV3s with substitutions for I^{307} and F^{317} were also tested. Vaccinees' plasma were most reactive with cV3 peptides containing I^{307} (which was present in the vaccine), and much less reactive with substitutions (V, T or M) that were more frequent in vaccinees' breakthrough viruses than in those from placebo recipients. In contrast, plasma were equally reactive with wildtype A244 cV3 containing F^{317} and with A244 cV3 containing L^{317} despite the fact that vaccinee breakthrough viruses more frequently contained F^{317} than those from placebo recipients.

Conclusions: RV144-induced V3 Abs were cross-reactive with cyclic V3 peptides from clades A, AG, B, C, and AE. Data are consistent with V3 Abs being induced primarily by the clade B gp120 boost and suggest that Abs that target I^{307} provided immune pressure. In contrast, since vaccinees' plasma did not distinguish between A244 cV3s containing F^{317} or L^{317}, and since the proportion of F^{317} was increased in vaccinees' breatkthough viruses, it is possible that the presence of F^{317} confers an advantage to the virus, possibly by obscuring the epitope in the N-terminal V3 beta-strand that includes I^{307}.

Session P-E7 Poster Session
Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall**

Immune Response To Infection

367 HIV Cell Tropism Dependent Impact of CTL Escape Mutations in Gag On Viral Replicative Capacity

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Background: KK10 (K263-K272) within the N-terminus of HIV p24/Gag represents the immunodominantly targeted CTL epitope in HLA-B27+ HIV-infected individuals. Due to its association with delayed disease progression B27 is considered to be protective during HIV infection. The stereotypical escape mutation R264K alters the KK10 epitope in a way that it is no longer presented by B27, in vitro causing a substantial reduction in viral replicative capacity in targeted lymphocytes at the same time. This replication defect can be attributed to an altered interaction between p24 and the cellular protein Cyclophilin A. Efficient replication of the R264K escape variant can be restored in vivo and in vitro by the selection for the secondary compensatory mutation S173A.

So far, in vitro analyses of the phenotype of R264K have been performed with X4 tropic viral strains using primary lymphocytes or cell lines as target cells. Since the R5/X4 tropism shift usually occurs rather late in the course of HIV infection and R5+ cells are a major reservoir for HIV it would be important to confirm these findings with R5 tropic viruses and their respective target cells.

Methodology: Chimeric HIV-1 proviruses were engineered fusing a backbone of the X4 tropic NL4-3 strain (containing the respective mutations of interest in Gag) with an Env coding part of the R5 tropic YU2-strain. Chimeric NL4-3/YU2 viruses were used to infect PMA-stimulated THP1 cells (macrophage-like cells). Relative replication capacities of the viral variants were compared to that of NL4-3/YU2 chimeric virus without additional Gag mutations (wild-type). Viral replication was monitored over a period of several days by measuring p24 content in supernatant by ELISA. Similar experiments were performed with various NL4-3 variants in CD4+ T-cell lines.

Results: In CD4+ T-cells the R264K variant replicates with about 10% efficiency compared to wild-type NL4-3. In contrast, Gag mutation R264K in context of a R5 tropic chimeric NL4-3/YU2 virus mediates no reduction in viral replicative capacity when infecting macrophage-like cells.

Conclusions: This striking difference in viral replication capacities of specific viral variants with HLA-B27 associated Gag mutations in context of differential viral cell tropism raises questions about the nature of the observed protective phenotype of HLA-B27. Mutational escape from the immunodominant CTL pressure against the KK10 epitope in HLA-B27+ individuals seems to be restricted in lymphocytes while macrophages could be permissive for replication of the respective variants. Our observations strongly suggest that also specific Gag mutations can influence cellular tropism of HIV.

368LB Epitope Targeting and the Antibody-Dependent Cellular Cytotoxicity Response Against HIV-1

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Background: Antibody-dependent cellular cytotoxicity (ADCC) has been linked with protection against HIV-1. In the RV144 trial that showed an estimated efficacy of 31%, high levels of ADCC inversely correlate with infection risk. Non-neutralizing epitopes in the C1 region of gp120 have been implicated as potential targets for protective antibody responses elicited by vaccination, although antibody-binding titers against these epitopes do not correlate with protection. We hypothesized that differences in the mode of epitope recognition may be responsible for large differences in ADCC activities between antibodies targeting the C1 region of gp120.

Methodology: For atomic level definition of binding epitopes, we determined the structures of two monoclonal antibodies (mAbs), N5-i5 and 2.2c, that target the C1 region of gp120, in complex with gp120 core in the CD4-trigerred conformation. ADCC measurements were carried out using CEM-NKr-CCR5 target cells sensitized with recombinant gp120 from the HIV-1Ba-L isolate. Fluorescently labeled N5-i5 was used in a competition strategy to measure N5-i5 and 2.2c binding to CEM-NKr-CCR5 target cells sensitized with gp120.

Results: Monoclonal antibodies (mAb) N5-i5 and 2.2c differed 75-fold in their ADCC potency. N5-i5 and 2.2c recognized overlapping but distinct epitopes in the C1-C2 region of gp120. While N5-i5 contacted topological layers 1 and 2 of gp120, 2.2c contacts were restricted predominantly to layer 1 with few contacts with layer 2. We also found that the heavy and light chains of bound N5-i5 and 2.2c were switched. Hybrid variants of the antibodies with their VH and VL domains swapped, showed no difference in cell surface binding. While the ADCC potency for N5-i5 did not show any significant difference between the wild-type and the VH/VL swapped version, swapping VH and VL domains improved ADCC potency of 2.2c by 7-fold.

Conclusions: The ability of antibody to cross-link antigen and positioning of its CH2 domain were found to contribute to ADCC potency, indicating that ADCC function depends on the orientation of antibody binding even when overlapping epitopes are involved. These data provide a framework for understanding the discordance between epitope-specific binding assays and ADCC as correlates of reduced infection risk in the RV144 trial. Further, they set the stage for an atomic level understanding of the role of precise epitope targeting in ADCC and similar Fc-mediated effector functions of antibodies.

369 Complex Impact of Reversion Mutations and CD8+ T Cell Escape Mutations On HIV-1 Fitness

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Background: Mutations that revert back to the ancestral state frequently occur in the HIV-1 genome during infection and have been considered to render the viruses more fit. However, their impact on viral fitness and interactions with the immune escape mutations have not been evaluated in their cognate transmitted/founder (T/F) viral genomes.

Methodology: Our previous study showed that viruses containing both cytotoxic T lymphocyte (CTL) escape mutations and reversion mutations are as fit as the T/F viruses. To precisely determine the role of reversion mutations, we generated the T/F mutants that contained either reversion mutation alone or together with CTL escape mutations and determined its impact on the viral fitness in primary CD4+ T cells using the PASS fitness assay.

Results: The reversion mutation V247I in the TW10 CTL epitope in Gag could partially restore the fitness loss caused by the CTL escape mutation T242N in the same epitope. However, the reversion mutation V247I or I64T in Tat/Rev alone had no impact on fitness of the T/F virus. The CTL escape mutations G248A in Gag and R355K in Env did not have any fitness cost. Interestingly, the CTL escape mutation G248A, like the reversion mutation V247I, could also partially compensate the fitness loss caused by the T242N mutation. Both the V247I and G248A mutations together fully restored the fitness loss of the T242N mutant. Positions 242, 247 and 248 are not located at p24 pentamer or hexamer interfaces and therefore should not affect the capsid assembly. In addition, homology modeling of p24 monomers demonstrated that mutations at these positions are not expected to significantly affect stability of the helix 6 structure.

Conclusions: Our results showed that reversion mutations might not render their cognate T/F virus more fit in vitro but could partially restore the fitness loss caused by the CTL escape mutation, and a CTL escape mutation could also partially compensate the fitness loss due to the other CTL escape mutation. These findings demonstrated that the overall viral fitness is influenced by the complex interplay of different mutations.

370 CD4+ and CD8+ T-Cells of HIV+ and HIV- Men Who Have Sex With Men Respond To a Broad Array of CMV Epitopes

Huifen Li[1], Joseph B. Margolick[1], Jay H. Bream[1], Tricia L. Nilles[1], Susan Langan[1], Hanhvy T. Bui[1], Andrew W. Sylwester[2], Louis J. Picker[2], Sean X. Leng[1]
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Background: Cytomegalovirus (CMV), a β-herpesvirus, can establish a chronic/latent infection in peripheral blood monocytes, leading to significant T-cell clonal expansion and possibly T-cell immunosenescence and chronic inflammation in aging and HIV infection. While CMV is a large virus with many immunogenic regions, little is known about T cell responses of HIV+ individuals to CMV epitopes other than those in pp65 (encoded by region UL83 in the CMV genome) and IE-1 (region UL123). The aim of this study was to investigate $CD4^+$ and $CD8^+$ T-cell responses to major CMV epitopes in HIV- and HIV+ men who have sex with men (MSM) in the Multicenter AIDS Cohort Study (MACS).

Methodology: Stored peripheral blood mononuclear cells (PBMCs) from HIV+ (n=12) and HIV- (n=10) men were stimulated with 26 pools of peptides (15-mers with 10 amino acid overlap) derived from 19 CMV open reading frames (ORFs). These ORFs were studied because they accurately predicted total $CD4^+$ and $CD8^+$ T-cell anti-CMV responses in young healthy adults (Sylwester et al, *J. Exp. Med.* 2005; 202:673). $CD4^+$ and $CD8^+$ T-cell responses to each peptide pool were assessed by multicolor flow cytometry and intracellular cytokine staining for IFN-γ, TNF-α, and IL-2.

Results: The total proportion of T cells that responded to any of the CMV peptide pools ranged from 0.2% to 40.3%. $CD4^+$ T-cells responding to UL83 or UL123 represented <10% of the total CMV-specific $CD4^+$ T-cell response measured in both HIV+ and HIV- men. This proportion was higher for $CD8^+$ T-cells, but was still <40%. These figures may overestimate the proportion of T cells reacting to UL83 and UL123, because other immunogenic ORFs demonstrated by Sylwester et al were not analyzed here. Several men demonstrated robust total IFN-γ responses to CMV despite minimal or no response to either UL83 or UL123 peptides, particularly in $CD4^+$ T cells. IFN-γ and TNF-α responses were very similar and were more likely to be due to UL83 and UL123 than were IL-2 responses. CMV-induced responses did not differ significantly between HIV+ and HIV- men, except for the IL-2 response of $CD4^+$ T cells to UL83 which was higher in HIV+ men ($p < .04$).

Conclusions: These findings indicate that the impact of CMV on T-cell immunity is much broader than what would be seen if only responses to pp65 and IE-1 were measured. They suggest that the assessment of CMV-directed T-cell immunity based on responses to epitopes derived from UL83 and UL123 alone is inadequate at best and may be misleading, especially for CD4 T-cell responses. More detailed characterization of CMV-induced immunity is needed in people with and without HIV infection.

371 Linkage Between Disease Status and a Naturally Arising Mutation in Functional Region of HIV-1 Nef

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Background: HLA class-I(HLA-I) downregulation by HIV-1 Nef has been shown to protect infected cells from CTL killing, thereby contributing to viral persistence in vivo. It achieves this through a number of highly conserved sequence (functional) domains. However, the in vivo implication(s) of naturally arising polymorphism(s) in HIV-1 Nef's published functional domains associated with HLA-I down-regulation, still remain(s) elusive.

Methodology: We enrolled a total of 658 treatment-naive, chronically HIV-1 infected subjects. Plasma samples were collected after obtaining informed consent, HLA-typed, viral RNA extracted and amplified by nested RT-PCR. The resultant nef amplicons were directly sequenced by Sanger's method. Only clade-B sequences with intact ORF (n=406) were included in the further analysis.

Results: The molecular epidemiology of our data set revealed a less conserved Met20 of Nef (78%; which is one of the HLA-I downregulation functional domains) than the subtype-B Nef sequences published in Los Alamos Database (91%, n=1467 ; http://www.hiv.lanl.gov). There is a preponderance of Ile20 (18%) in our dataset, than in the Los Alamos sequences (7%), p<0.0001. Ile20 was found to be associated with higher plasma median viral load (p=0.009). Other codons which were associated with Ile20 show no contributory effect on the viral load enhancement of Ile20. There is also enrichment of HLA-C*03:03 in subjects harboring Ile20 (p= 0.0161).

Conclusions: Taken together, we identified a naturally arising polymorphism, Ile20, within HIV-1 clade-B nef's functional domain associated with HLA-I down-regulation, that has a propensity for higher viral load in vivo.

372 Characterizing Acute HIV-1B CTL Escape by Full-Genome "Deep" Sequencing

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Background: The cytotoxic CD8+ T lymphocyte (CTL) immune response is implicated in the suppression of acute HIV-1B plasma viral load from peak to set-point. The magnitude of this post-peak decline, and by extension the load at which set-point is established, varies widely across infections, but the determinants of this variation are incompletely defined. The well-documented capacity of HIV-1 to escape from CTL responses implicates differential loss of acute CTL response efficacy resulting from rapid HIV CTL escape as a potential determinant of CTL-mediated control. Here, we investigate the relationship between the timing of acute HIV-1B escape from the earliest CTL responses and the acute viral load trajectory.

Methodology: We comprehensively characterized HIV-1B CTL escape in acute subjects (Fiebig I-III) by longitudinal, near full-genome, deep sequencing (200-fold average depth per site) across 4-6 time points per subject in the first 180 days post-infection (dpi). The acute CTL response was quantified by autologous IFN-g ELISPOT assay during the first 90 dpi for all HIV epitopes defined for each subjects' HLA class I genotype (LANL A list).

Results: Acute CTL escape was observed in all subjects (range: 3-6 epitopes) and impacted 20-70% of the targeted epitopes and 27-93% of the total acute CTL response. Extremely rapid escape was detected at 28 dpi in two subjects at which time escape variants already comprised as much as 48% of the plasma virus population. The overlay of modeled CTL escape kinetics curves on acute viral load trajectories reveals an apparent temporal relationship between CTL escape and deflections in post-peak viral load declines.

Conclusions: These preliminary data suggest that the loss of efficacy of acute CTL responses resulting from rapid CTL escape by HIV may contribute disproportionately to the overall capacity of the acute CTL response to suppress virus replication and control viral load.

373 HIV-1 gp120-Specific Antibody Dependent Cell-Mediated Cytotoxicity in HIV-1 Elite Controllers

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Background: In the Thai RV144 HIV vaccine trial, antibody dependent cell-mediated cytotoxicity (ADCC) is the only vaccine induced immunological parameter that correlates inversely with infection. This suggests that protective HIV specific ADCC can be stimulated by vaccination. We hypothesized that natural production of HIV-specific ADCC antibodies may also be protective and that these antibodies may be at least partially responsible for HIV viral control observed in women who naturally control the virus without antiretroviral drugs, Elite controllers (EC).

Methodology: We compared the ADCC response of antibodies in the serum and cervicovaginal lavage (CVL) from 35 EC, 34 HIV-infected HAART initiators, and 35 HIV-uninfected women in a standard 51Cr-release assay. All were participants in the Women's Interagency HIV Study (WIHS), the largest ongoing prospective cohort study of HIV among US women. The 35 EC in our study had stable or increasing CD4 T cell numbers, were not on antiretroviral therapy and had undetectable HIV RNA for ≥1.5 years. HAART initiators were evaluated at three visits: visit 1, an asymptomatic visit with comparable CD4 T cell count to the EC group; visit 2, the last visit before HAART; and visit 3, a progressing visit during treatment. Statistical comparisons were conducted using the Mann-Whitney or Wilcoxon Paired Test. Significant differences were considered when p<0.05.

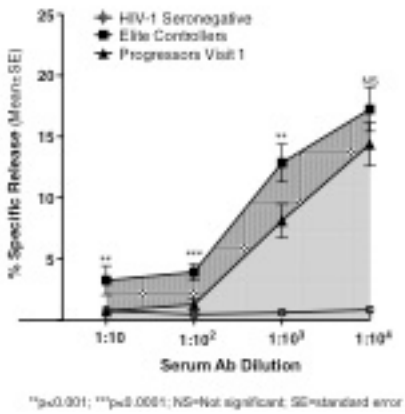

Fig.1

Results: EC had significantly higher serum (see Fig.1) and CVL ADCC activity than HAART initiators ($p \leq 0.009$ at 1:10 CVL dilution); this difference was most prominent at visit 1, the asymptomatic visit. Another measure of this activity, serum ADCC antibody titer, was significantly higher in EC than in HAART Initiators: visit 1, $p \leq 0.003$; visit 2, $p \leq 0.04$; visit 3, $p \leq 0.006$. While 97% of EC and 77% of HAART Initiators (Visit1) had a detectable serum ADCC titer, CVL titers were present in 40% of the EC and 27% of the HAART Initiators (Visit 1). CVL ADCC antibody titers were detected in 17% of the women immediately prior to HAART and increased to 32% during HAART treatment. The HIV-1 seronegative women had no detectable gp120-specific ADCC.

Conclusions: HIV EC have higher serum and CVL ADCC antibodies against HIV-gp120 than HAART initiators. ADCC may contribute to the ability of EC to control viral load. Evidence that the proportion of women with CVL ADCC activity increases after the initiation of treatment suggests that HAART may facilitate a rebound in ADCC antibodies.

374 CD8 T Cell Responses Emerging During Acute HIV Infection Drive Long-Term Control

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Background: The emergence of HIV-specific CD8 T cell responses during acute HIV infection has been previously associated with a post peak decline of HIV viremia, resolution of clinical symptoms and the development of a semi-stable viral setpoint; this early viral setpoint has been shown to be highly predictive of disease outcome. Given the importance of early HIV-specific CD8 T cell responses, we assessed which particular HIV-specific CD8 T cell responses contribute to long-term control.

Methodology: 622 predominantly male (97%) Caucasian (83%) individuals with primary HIV-1 infection (Fiebig: n= 152 (2/3), 61 (4), 277 (5), 87 (6), 23 (nd)) were screened by IFNγ Elispot for HLA class I-restricted, epitope-specific CD8+ T cell responses using optimally defined epitopes approximately 2 months post initial presentation. Longitudinal viral load, CD4 count and time to HAART were collected of all patients over an average period of 1000 days post presentation.

Results: Initial viremia and early viral set points were significantly associated with HLA class I expression ($p<0.0001$). Similarly, the time patients remained off antiretroviral therapy also showed significant association with HLA class I. In particular, patients with HLA-B57 and -B13 initiated HAART significantly later than individuals expressing HLA-B8 and B7 ($p<0.0001$). However, no association of HLA with initial CD4 count was found. Interestingly, among the HLA class I alleles, the presence or absence of individual HIV-specific CD8 T cell responses had a significant impact on disease progression. A larger breadth of HIV-specific CD8 T cell responses during primary HIV infection was associated with significantly slower disease progression. Moreover, the induction of certain HIV-specific CD8 T cell responses significantly influenced disease progression, while others had little to no impact. For example, HLA-B27+ individuals that generated an HLA-B27-KK10 response during primary HIV infection had significantly slower disease progression than patients that did not mount this response ($p=0.0002$). In contrast, CD8 T cell responses against epitopes such as HLA-B8-EI8 (p24) or HLA-B57-HW9 (Nef) did not show any influence on disease progression.

Conclusions: Our data demonstrate strong associations of CD8+ T cell responses against specific epitopes with long-term HIV control, while others did not show any association despite being restricted by the same HLA class I allele. Thus, engineered proteins focusing the immune response towards specific epitopes might provide an important approach for vaccine design strategies.

375LB Modification of Antibody 10E8 To Improve HIV-1 Neutralization

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Background: Neutralization of HIV-1 by antibodies that target the membrane-proximal external region (MPER) of the gp41 subunit of the HIV-1 envelope glycoprotein has been shown to correlate with their capacity to recognize MPER in a membrane context. We sought to assess if modification of the broad and potent MPER-specific HIV-1 neutralizing antibody 10E8 could enhance its recognition of MPER in a membrane context and potentiate its neutralization of HIV-1.

Methodology: Antibody residue positions in the vicinity or co-planar with the gp41 contact interface, though not within it, were chosen for modification. Antibody variants were tested for HIV-1 neutralization and for MPER recognition in soluble and lipid contexts. Crystallization of the 10E8 variant with the greatest effect on virus neutralization was undertaken in complex with gp41 MPER to decipher its mechanism of action.

Results: Six residue positions within the 10E8 heavy chain were chosen for mutagenesis. Aromatic residues were introduced into these positions either individually or in combination. Up to 9-fold improvements in neutralization potency over wild-type 10E8 were observed against individual strains of a 5-isolate panel, and up to 4-fold mean improvements observed against all strains combined. Improvements in neutralization did not directly correlate with antibody recognition of MPER in a lipid context. The crystal structure of the most potent 10E8 variant was determined in complex with a peptide of gp41 MPER, though no additional contacts between the antibody and gp41 were observed.

Conclusions: We have defined residue modifications within the 10E8 heavy chain that improve antibody-mediated HIV-1 neutralization. Binding studies suggest improvements in neutralization were not associated with enhanced antibody recognition of MPER in a lipid context. The crystal structure of the most potent 10E8 variant in complex with gp41 MPER did not reveal additional contacts with the gp41 peptide, suggesting other mechanisms within the virion context are likely at play in the improved neutralization potency observed.

376 Association of Gag-Specific CD28+CD95+ CD8+ T-Cell Responses in Lymph Nodes With Lower Viral Loads

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Background: Cumulative studies have suggested that HIV replication can be controlled by potent $CD8^+$ T-cell responses. Individual viral proteins show different kinetics of expression and degradation, which affect efficacy of protein-derived epitope presentation to $CD8^+$ T cells. Thus, some viral proteins can be the targets for effective $CD8^+$ T cells more frequently. $CD8^+$ T-cell responses have been examined in peripheral blood, but those in lymph nodes (LNs) have not been analyzed fully. Here, we investigated the relationship between viral loads and individual protein-specific $CD8^+$ T-cell responses in LNs in a macaque AIDS model.

Methodology: We used peripheral blood mononuclear cells (PBMCs) and lymphocytes in the inguinal LNs obtained in the chronic phase of SIVmac239 infection from 36 Burmese rhesus macaques. We examined viral protein-specific $CD8^+$ T-cell responses in these PBMCs and LN-derived lymphocytes by detection of IFN-γ induction after stimulation with overlapping peptide pools and performed correlation analyses between these responses and viral loads.

Results: Analyses using PBMCs revealed inverse correlation between viral loads and frequencies of $CD8^+$ T cells, in particular central memory $CD28^+CD95^+CD8^+$ T cells, specific for the N-terminal half of Gag (Gag-N). Analyses using LNs showed more significant inverse correlation between viral loads and Gag-N-specific $CD28^+CD95^+CD8^+$ T-cell frequencies (Fig. 1). In contrast, frequencies of effector memory $CD28^-CD95^+CD8^+$ T cells specific for the N-terminal half of Env (Env-N) in LNs as well as in PBMCs positively correlated with viral loads (Fig. 1). Percents of the $CD28^-CD95^+$ subset in Env-N-specific $CD8^+$ T cells were significantly higher than those in any other viral protein-specific $CD8^+$ T cells. LNs without detectable SIV capsid p27 antigens had significantly higher frequencies of Gag-N-specific $CD28^+CD95^+CD8^+$ T cells and lower frequencies of Env-N-specific $CD28^-CD95^+CD8^+$ T cells than those with detectable p27.

Conclusions: This study revealed the association of Gag-N-specific $CD28^+CD95^+CD8^+$ T-cell frequencies in LNs with lower viral loads, supporting the notion that Gag-specific $CD8^+$ T-cell responses can often contribute to HIV control. Interestingly, we further found positive correlation of Env-N-specific $CD28^-CD95^+CD8^+$ T-cell frequencies with viral loads, implying that Env-N-specific $CD8^+$ T-cell responses may not be effective against HIV/SIV replication.

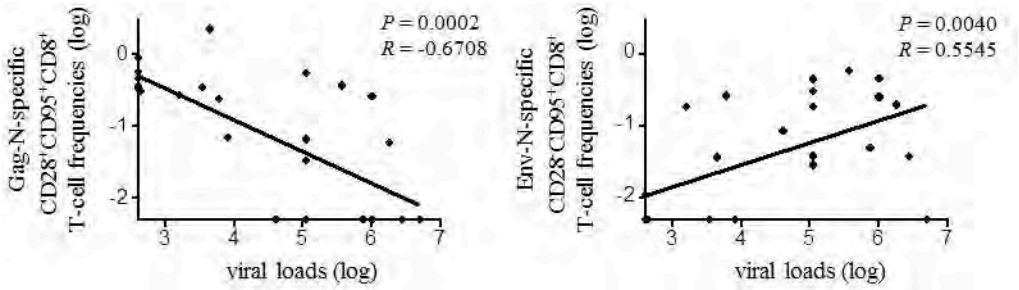

Fig.1. Correlation of antigen-specific CD8+ T-cell frequencies with viral loads.

377 Distinct Functional Properties of HIV-Specific Cytolytic CD4 T Cells Compared To Th1 or CD8 T Cells

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Background: Control of HIV replication mediated by CD8 T cells is well documented, though some evidence suggest that CD4 T cells with cytolytic properties (CD4 CTL) may also contribute to control of viral replication. Indeed, reports have shown that HIV controllers possess higher frequencies of CD4 CTL than progressors. However, very little is known about the immunobiology of CD4 CTL and how to generate them with an HIV vaccine. Moreover, it is unclear whether they are actively infected and depleted by HIV.

Methodology: To further define HIV-specific CD4 CTL, we assessed gene and surface expression patterns of relevant markers in PBMCs, from chronically HIV-infected patients, responding to HIV-Gag peptide pools. We compared HIV-specific CD4 CTL versus HIV-specific CD8 CTL and T-helper cells using Fluidigm Technology and multicolor flow cytometry. We further evaluated susceptibility to HIV infection and by assessing the infectability of sorted HIV-specific CD4 CTL using a panel of four R5 primary isolates.

Results: Using index-cell-sorting paired with Fluidigm Technology as well as flow cytometry, we demonstrated that HIV-specific CD4 CTL have a distinct expression profile, which clearly distinguishes them, not only phenotypically, but also functionally from HIV-specific CD8 T cells and Th1 CD4 cells without cytolytic activity. In particular, expression of surface markers CD57 and KLRG1 was significantly higher on HIV-specific CD4 CTL ($p=0.0036$, $p=0.0263$ respectively) than on Th1 CD4 cells. Moreover, we found that both t-box transcription factors T-bet and eomesodermin (Eomes) are involved in the cytolytic program of CD4 T cells, similar to cytotoxic CD8 T cell. In contrast to CD4 CTL, HIV-specific CD8 T cells expressed NKG2D with higher level of Eomes, KLRG1 and CD57. Even though HIV-specific Th1 CD4 cells expressed T-bet, Eomes expression was absent in those cells, suggesting a role of Eomes in the cytolytic program of CD4 CTL. Nevertheless, HIV-specific Th1 CD4 cells are characterized by high expression of CD161. Interestingly, the expression levels of CCR5 were the lowest on CD4 Th1 cells and the highest on CD4 CTL. In a viral replication assay, we found that CD4 CTL, defined as expression of CD57 or KLRG1 on CD4 T cells, have a lower infectability than CD57- or KLRG1- CD4 T cells suggesting a distinct HIV-specific CD4 T cell subset that resists HIV infection.

Conclusions: Our data demonstrate that HIV-specific CD4 CTL have a distinct functional and phenotypic profile compared to HIV-specific CD8 CTL and CD4 Th1 cells. Furthermore, CD4 CTL express higher levels of CCR5 and are less prone to HIV infection compared to general Th1 CD4 T cells suggesting a CD4 T cell population that is more likely to persist during HIV infection.

378 CD8+ T Cells From HLA-B*57 Elite Suppressors Inhibit Replication of HIV-1 Escape Mutants

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Background: Elite Controllers or Suppressors (ES) are individuals who maintain undetectable plasma viral loads by standard clinical assays in the absence of antiretroviral therapy. Multiple lines of evidence suggest that the control of viral replication in these patients is due to a strong and specific cytotoxic T lymphocyte (CTL) response. Escape mutations are believed to impair the ability of CD8+ T cells to control HIV-1 replication. Interestingly, viruses isolated from the plasma of ES have been shown to contain several escape mutations; it is not clear how immunologic control is maintained despite this virologic escape.

Methodology: Using site-directed mutagenesis, we constructed six NL4-3 based viruses with canonical escape mutations in one to three HLA*B-5703 Gag p24 epitopes. To determine the ability of CD8+ T cells to suppress replication of HIV-1 containing escape mutations, unstimulated CD4+ T cells of seven HLA*B5703+ ES were infected with either wild type or one of the constructed escape mutant variant viruses and cocultured with autologous CD8+ T cells at three target to effector ratios. Effector CD8+ T cells were either used directly ex vivo or first stimulated with peptides corresponding to either wild type or escape variant HLA-B*5703 Gag epitopes to see if this would induce stronger suppression of replication. Intracellular cytokine staining was performed in order to determine the mechanisms involved in the suppression of these escape variants.

Results: In this study, we investigated the effect escape mutations within HLA*B-57+ restricted Gag epitopes have on the ability of ES CD8+ T cells to suppress replication of HIV-1 in autologous CD4+ T cells. Unstimulated CD8+ T cells suppressed replication of all six escape mutants at levels that were comparable to the level of suppression of wild type virus. Intracellular cytokine staining revealed low baseline CD8+ T cells responses to wild type and escape variant peptides; however, culture of PBMC with peptides corresponding to either wild type or escape variant HLA-B*57 Gag epitopes for seven days resulted in increased IFN-γ and perforin expression in response to overnight stimulation with either wild type or escape variant peptides.

Conclusions: Our data demonstrate that CD8+ T cells from ES are capable of suppressing replication of virus harboring escape mutations in HLA-B*57 restricted Gag epitopes. Additionally, our data suggest that ES CD8+ T cells are capable of generating effective de novo responses to escape mutants. These results may explain why ES are able to control viral replication despite virologic escape.

Session P-F1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Mechanisms of HIV Latency

379LB The Tat Inhibitor, Cortistatin A, Suppresses Transcription and Reactivation of HIV Latent Cells

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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. Current therapies are unable to inhibit reactivation of transcription from latently infected resting cells as well as production from active persistent cellular reservoirs. Thus, novel classes of compounds are needed to eliminate this low level viremia that also contributes to persistent and damaging chronic immune activation.

The HIV Tat protein, a potent activator of HIV gene expression, is essential for integrated viral genome expression. Tat binds the 5' terminal region of HIV mRNA's stem-bulge-loop structure, the Trans-activation Responsive (TAR) element to activate transcription. Given Tat's crucial requirement for virus replication, it has been the target for the development of small molecule compounds, however so far none has yet reached the clinic.

Methodology: We found that didehydro-Cortistatin A (dCA), an analogue of a natural steroidal alkaloid is the most potent Tat inhibitor described to date, it binds selectively to the basic domain of Tat, the region responsible for the interaction with TAR, at subnanomolar concentrations. dCA reduces Tat mediated transcriptional initiation/elongation from the viral promoter to inhibit HIV-1 replication in acutely and chronically infected cells. Here we show that dCA can reduce residual viremia in HIV latently infected cells and block viral reactivation.

Results: dCA reduces residual viral production from several cell models of HIV latency, establishing a state of "super latency", rendering very difficult viral reactivation into a productive infection using the usual panel of activators (HDAC inhibitors, PKC activators, cytokines, etc). A concomitant reduction of RNA polymerase II recruitment to "super latent" promoters is observed. Only a strong activator such as Tat can reactivate the virus temporarily. Furthermore, arrest of dCA treatment does not result in viral rebound, as the promoter is transcriptionally shut-off. As expected, latent cell lines either mutated in TAR or Tat are insensitive to dCA. Most importantly, dCA inhibits HIV reactivation upon homeostatic and antigenic stimulation of CD4+T cells isolated from virally suppressed patients undergoing ART.

Conclusions: In sum, dCA is an exciting anti-HIV molecule that could inhibit and persistently abrogate residual HIV production from cellular reservoirs in blood and possibly tissues from virally suppressed subjects. Our experiments provide a proof-of-concept for the use of transcriptional suppressors in novel therapeutic strategies with the long-term goal of obtaining a functional cure for HIV.

380 Mechanisms by Which Negative Elongation Factor (NELF) Establishes and Maintains HIV Latency

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Background: Understanding events which contribute to HIV latency is critical for improving current treatments and potentially eradicating HIV infection. Events that contribute to HIV transcriptional latency include repressive chromatin structure, transcriptional interference, the inability of Tat to recruit P-TEFb and poor processivity of RNA polymerase II (RNAP II). Previously, we have established an important role for promoter proximal pausing in regulating HIV transcription. In this study we investigate whether RNAP II pausing is operative in the context of different cell models of latency, including transcriptional interference. Our data support that RNAP II pausing via NELF recruits co-repressor complexes and transcription factors which influence T cell commitment to repress HIV transcription.

Methodology: We have identified novel NELF interacting factors via Mass Spec analysis and have used immunoprecipitation and ChIP analysis to verify physical and functional interactions. We utilized multiple infected cell models including HIV infected Jurkat T cells, the latently infected ACH2 cell line, latently infected transcriptional interference cell lines and primary CD4+ T cells to further investigate NELF's involvement in HIV transcriptional latency.

Results: We have identified novel NELF interacting partners NCoR1-GPS2-HDAC3, a known co-repressor complex, and Bcl11b, a T cell commitment factor. HDAC3, GPS2 and Bcl11b bind latent HIV LTR. When the latent HIV LTRs are induced with PMA binding of these factors to the LTR is diminished. In addition, we have investigated NELF's involvement in regulating HIV transcription in cell lines where the latent HIV LTR is integrated into a transcriptionally active gene, resulting in transcriptional interference of the provirus. Treatment of these cell lines with a HDAC inhibitor such as TSA did not induce HIV transcription, however, when we knock down NELF in this model HIV transcription is induced. Furthermore, overcoming HIV proviral transcriptional interference correlates with diminished NELF binding to the HIV LTR.

Conclusions: Our data indicate that NELF is coordinating multiple mechanisms responsible for transcriptional silencing of the HIV LTR. Key factors involved in NELF induced repression of the provirus are NCoR1-GPS2-HDAC3 and Bcl11b. NELF coordinates chromatin organization through the NCoR1-GPS2-HDAC3 complex and the recruitment of Bcl11b. These data support that RNAP II pausing is a major checkpoint in the establishment of HIV latency and a potential target by which to purge latent HIV reservoirs.

381 Differential Role of Bromodomain Proteins in HIV-1 Latency

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Background: Small molecules targeting bromodomain (BRD) proteins, a well-conserved class of transcriptional regulators distinguished by the presence of bromodomains, have recently emerged as novel epigenetic therapeutics in hematological and virological disease. Bromodomains are small helical interaction modules that specifically bind acetylated lysines in histones and nonhistone proteins. We recently tested the effect of bromodomain inhibitors JQ1, I-BET, I-BET151 and MS417 on HIV latency. We and others showed that these compounds effectively reactivate HIV from latency in cell culture cells and select primary T cell models of latency. We hypothesize that bromodomain inhibitors target BRD proteins to neutralize their suppressive action and activate HIV from latency.

Methodology: We performed a comprehensive lentiviral shRNA screen of BRD proteins in J-Lat cells to identify which BRD protein is involved in the regulation of HIV latency. We also performed co-immunoprecipitation experiments to test for interaction of P-TEFb and BRD proteins.

Results: We tested two independent shRNAs against BRD1-9 in J-Lat A2 and A72 cells and tested reactivation from latency by flow cytometry of GFP with and without JQ1. Knockdown of BRD8 resulted in activation of the HIV LTR, similar to activation observed with BRD2 knockdown, however, this reactivation was still responsive to JQ1. In contrast, knockdown of BRD3 resulted in a decrease of basal HIV transcription, and the activatory potential of JQ1 was unchanged. Co-treatment of cells with JQ1 and DRB, a CDK9 inhibitor, resulted in a decreased ability of the cells to respond to JQ1 treatment. Similar results were observed when Cyclin T1 was knocked down with two independent Cyclin T1 shRNAs, indicating that the JQ1 effect in latent cells requires intact P-TEFb.

In co-immunoprecipitation experiments we found that BRD2, which lacks a bone-fide P-TEFb interacting domain and has not been associated with P-TEFb-binding, efficiently co-immunoprecipitated with the P-TEFb component Cyclin T1, an interaction that was enhanced in the presence of JQ1. This interaction also depended on intact acetylation sites in Cyclin T1, indicating that BRD2 interacts with P-TEFb via acetylated Cyclin T1 and the BRD2 bromodomain.

Conclusions: Our data indicate that bromodomain inhibitors activate HIV latency by a Tat-independent mechanism and implicate a thus far unrecognized bromodomain family member BRD8 in the establishment and/or maintenance of HIV latency. Further, we confirm BRD2 as a candidate target of bromodomain inhibitors in the reversal of HIV latency.

382 The NCOR2-Nurr1-CoREST Axis Impairs HIV Reactivation in Latently Infected Microglial Cells

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Background: Whereas the incidence of HIV-associated dementia (HAD) has declined due to successful anti-retrovirals treatment, prevalence of milder forms of HAD, which include asymptomatic neurocognitive impairment (ANI) and minor neurocognitive disorder (MND) has increased. Both ANI and MND are part of what is known as HIV-associated neurocognitive disorders (HAND). However, the molecular mechanisms explaining regulation of HIV activation in the brain remain ill-defined. The Nurr1/CoREST transrepression pathway has been recently described as a regulator of glial cells response to brain inflammation by limiting over-reactivation of NF-κB-dependent pro-inflammatory genes.

Methodology: Microglial cell culture, pharmacological inhibition, shRNA-mediated knockdown, and chromatin immunoprecipitation/sequencing.

Results: We report here that, unlike in latently-infected T-cells, in latently-infected microglial cells (CHME-5/HIV), HIV is induced by pharmacological inhibitors of the CoREST complex chromatin-modifying enzymes LSD1 and G9a/GLP; these inhibitors also sensitized CHME-5/HIV cells for LPS or IL-1β-mediated HIV reactivation. shRNA-mediated knockdown of Nurr1, LSD1, or CoREST yielded similar results. Chromatin immunoprecipitation analysis followed by high throughput next generation sequencing revealed that upon microglia treatment with TNFα, the nuclear receptor co-repressor 2 (NCOR2/SMRT), which strongly interacts with Nurr1 to facilitate transrepression, is present at the HIV promoter before activation, then recruited at the earliest time points, and then its presence fluctuates over time. Likewise, Nurr1, CoREST, LSD1, and G9a are recruited to the HIV promoter, changing the epigenetic signature (lower H3K4Me/higher H3K9Me2). The repressor role of these proteins in regulating HIV emergence from latency has been confirmed by unbiased shRNA screens for factors involved in maintaining HIV silenced in latently-infected microglial cells.

Conclusions: Our data indicate that the NCOR2-Nurr1-CoREST axis plays a role in preventing HIV over-reactivation in microglial cells, and studying this mechanism in detail may provide therapeutic targets for the treatment of HAND.

383 Repression of HIV Transcription in Memory CD4+ T Cells by Blimp-1

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Background: A barrier to eradicating HIV infection is targeting and eliminating latently infected memory CD4+ T cells, which are the main reservoir of latent virus. Our goal is to determine if T cell specific transcription factors restrict HIV transcription in specific T cell subsets to establish and maintain HIV latency. The transcription factor B Lymphocyte-Induced Maturation Protein 1 (Blimp-1) is expressed in B and T cells and upregulated in patients chronically infected with HIV. Blimp-1 inhibits IL-2 transcription and the IL-2 promoter and the HIV long terminal repeat (LTR) share common cis-elements. We hypothesize that Blimp-1 binds to the HIV LTR, inhibits HIV transcription and contributes to HIV latency.

Methodology: We used T cell lines and primary human CD4+ T cells to study the role of Blimp-1 in HIV transcription. HIV replication was monitored using luciferase reporters, RT-PCR, and HIV p24 ELISA assays. Binding of Blimp-1 to the HIV LTR was determined using chromatin immunoprecipitation assay. Blimp-1 expression was diminished using shRNA. The levels of Blimp-1 in different T cell subsets were measured using flow cytometry and immunoblots.

Results: We show that Blimp-1 is expressed in primary peripheral blood CD4+ T cells and is further induced by T cell activation. However, infection of CD4+ T cells with HIV inhibits the induction of Blimp-1. Importantly, Blimp-1 is differentially expressed in T cell populations and in particular is highly expressed in memory CD4+ T cells which do not support robust HIV replication. Ectopic expression of Blimp-1 in CD4+ T cells represses HIV transcription, whereas decreasing Blimp-1 in memory CD4+ populations activates HIV transcription. Blimp-1 binds downstream of the HIV 5'-LTR in resting primary CD4+ T cells and represses Tat-dependent HIV transcription. Upon T cell activation with anti-CD3 and anti-CD28 antibodies Blimp-1 is released from the HIV LTR and this correlates with significant increase in HIV transcription.

Conclusions: We propose a model in which Blimp-1 acts as an HIV restriction factor in memory CD4+ T cells through binding downstream of the HIV LTR and remodeling chromatin. Intrinsic inhibitors of HIV transcription, such as Blimp-1, may provide novel therapeutic targets for purging latent virus from specific cells.

384 HIV-1 Reactivation and Autophagy Inhibition Synergize To Cell Death via Amino Acid Deprivation

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Background: Reactivation of latent provirus is considered a critical approach in modern strategies to purge latent HIV reservoir. Although histone deacetylase inhibitors (HDACi) demonstrated promising results in HIV-1 virus reactivation, the killing of the infected cells, which appears to be a key step in the elimination of HIV reservoir, remains an issue. Recently the cellular degradation pathway of autophagy, an essential process allowing cells to survive amino acid deprivation has been implicated in HIV viral cycle and homeostasis. We hypothesized that latent HIV-1 reactivation as well as autophagy inhibition may sensitize infected cells to amino acid deprivation.

Methodology: Analyses were performed using latently infected cell lines J-lat full length clones (6.3; 8.4; 9.2; 10.6; 15.4) expressing HIV-R7/E-/GFP. Provirus reactivation was achieved using sodium valproate (VPA) (0.4, 2 and 10mM), vorinostat (SAHA) or panobinostat (Pano)(0.4, 2 and 10μM). Autophagy was inhibited using 3-MA (3 -10mM), LY294002 (7 - 20μM) or chloroquine (CQ)(4 - 100μM). Autophagy was measured using flow cytometry, fluorescent microscopy and western blotting. Apoptosis and cell viability were measured by propidium iodide (PI) nuclear staining, PI exclusion assay, Annexin V staining or by changes of cellular FSC vs SSC.

Results: VPA, SAHA or Pano exposure for 24h induced up to 3 fold ($p=0.017$), 41 fold ($p<0.0001$) and 55 fold ($p<0.0001$) reactivated HIV-1 expression correspondingly. Provirus reactivation appeared dependent on autophagy as it was reduced by co incubation with autophagy inhibitors. SAHA or Pano mediated reactivation of HIV-1 expression (for 14h) rendered cells highly sensitive to CQ induced inhibition of autophagy as additional co incubation with 20μM CQ for 8h synergized with viral reactivation and decreased cellular viability by 2.1% (Control; $p=0.057$), 61% (SAHA; $p=0.057$) and 60% (Pano; $p=0.072$). Importantly upon HIV-1 reactivation, cells appeared unable to survive amino acid deprivation (8h) as this led to a decrease in cell viability by 3.5% (Control; $p<0.0001$), 47% (SAHA; $p=0.0024$) and 75% (Pano; $p=0.0022$). The level of provirus reactivation nicely correlated with sensitization to amino acid deprivation. Furthermore CQ exposure synergized with provirus reactivation in sensitizing cells to amino acid deprivation.

Conclusions: Autophagy inhibition synergizes with HIV-1 cytopathic effects upon latent HIV-1 virus reactivation. Latent HIV-1 reactivation sensitized the infected cells to amino acid deprivation, which was further exacerbated by CQ mediated suppression of autophagy. These *in vitro* results may serve as a proof of concept study opening an avenue for the development of new strategies for the elimination of latent HIV reservoir upon reactivation.

385 JAK Inhibitors Tofacitinib and Ruxolitinib Block T-Cell Activation Mediated HIV Replication

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Background: Despite the successful suppression of plasma viremia, persistent immune activation and inflammation in HIV infected is associated to HIV persistence and increased morbidity. Targeting immune activation/inflammation using JAK inhibitors represents a rationale way to reduce inflammation-driven residual viral replication and/or viral persistence due to homeostatic proliferation. Tofacitinib and ruxolitinib are FDA-approved Jak1/2 inhibitors for treatment of rheumatoid arthritis and myelofibrosis; we evaluated them for their ability to block cytokine-mediated activation of JAK/STAT signaling pathway(s), T-cell activation and viral replication in HIV-infected primary human lymphocytes.

Methodology: We developed two models to evaluate the impact of Jak inhibitors on viral production/replication and T cell activation. In the ex vivo model, CD4 T-cells isolated from viremic subjects were stimulated for 3-6 days with anti-CD3/28, +/- antiretroviral agents and increasing concentrations of Jak inhibitors. In the in vitro model, CD4 T-cells isolated from healthy subjects were treated with increasing concentrations of inhibitors (0.1-10 uM) for 3-6 days after infection with HIV-1 NL4-3-GFP. Viral production was quantified by p24-ELISA or by evaluating the frequency of GFP+ cells using FCM. HIV-1 co-receptors and markers for T-cell activation and proliferation were measured by FCM.

Results: Addition of tofacitinib and ruxolitinib to primary CD4 T cells from HIV infected subjects or cells infected ex vivo demonstrated a concentration dependent reduction of HIV production and replication in both models (EC50 0.1 μM, $p < 0.05$). Inhibitor concentrations ≥ 0.01 μM demonstrated more than 50% inhibition of anti-CD3/CD28 induced activation/proliferation of CD4 cells (CellTrace™ Violet low, CD38, CD25, CCR5, HLA-DR,PD-1) and >50% inhibition of viral production measured by p24 ($p < 0.05$). Exogenous addition of 10-100 ng/mL IL-2 overcomes inhibition of cell activation and viral production mediated by Jak inhibitors at < 0.03 μM suggesting that these inhibitors act either by increasing levels of CCR-5, by expanding the number of cells producing virus or by protecting these cells from death.

Conclusions: Tofacitinib and ruxolitinib at physiologically relevant concentrations inhibited multiple signaling pathways associated with viral persistence. Selective blocking of JAK/STAT signaling pathway(s) could prevent persistence of cells producing virus, thereby reducing viral reseeding and reservoir size mediated by persistent immune activation and inflammation leading to a functional cure.

386LB Human Genome shRNA Screen Identifies Cellular Factors Controlling Latency

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Background: There is a "silent" population of HIV infected cells that remains in the host even after anti-retroviral therapy. This "silent" or latent population prevents the eradication of HIV in treated patients. Several mechanisms have been proposed to explain HIV latency. In order to identify the full set of cellular factors that control HIV latency, we have used a systems biology approach.

Methodology: A human genome-wide shRNA library containing 25 shRNAs per gene and a complexity of 495,000 shRNAs was transduced in a Jurkat T cell model for HIV latency (J-Lat). This cell line contains a latent HIV genome with a GFP reporter. The shRNAs contain an mcherry marker for easy identification. GFP and mcherry containing double positive cells were sorted by FACS after transduction of the library. DNA was extracted from the double positive population and from the unfractionated population and analyzed by deep sequencing for the presence of unique shRNAs. shRNAs were found to be either enriched or disenriched.

Results: The screen yielded several genes that have been previously reported in controlling HIV latency as well as HIV transcription. These included single genes such as MBD2, Eed and CHD1 and protein complexes such as Nurd complex and the Polycomb group complex (PrC2). Notably, the p-TEFB complex, which is the most well known positive regulator of HIV transcription, was also identified. In addition to known genes and complexes, there were also several unknown factors. These included factors that controlled T cell activation, differentiation of T cell subsets as well as T cell cytoskeletal rearrangement among others. Some of these factors have been further confirmed both in the J-Lat model as well as the primary latency model.

Conclusions: The human genome wide shRNA screen yielded a broad map of the genes, complexes and pathways that could be controlling the maintenance as well as the exit from HIV latency. These novel complexes could serve as useful drug targets to test in future studies involving patient samples.

Session P-F2 Poster Session
Tuesday March 4, 2014, 2:30 PM–4:00 PM Exhibit Hall A
Dynamics of Persistent and Rebound HIV

387 Incomplete Adherence To cART Is Associated With Higher Levels of Residual HIV-1 Viremia

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Background: The persistence of HIV-1 in the latent reservoir is reflected in the frequent detection of residual HIV-1 viremia below 50 copies/m despite long-term antiretroviral therapy (ART). Incomplete ART adherence is common even in individuals who maintain virologic suppression <50 copies/mL, but its effect on residual viremia is unknown. We hypothesize that incomplete ART adherence may lead to active viral replication and higher levels of residual HIV-1 viremia, even for individuals with apparently successful virologic suppression.

Methodology: Medication adherence and residual viremia <50 copies/mL were quantified in participants of the REACH cohort of homeless and marginally housed individuals with HIV/AIDS. Participants (N=64) had at least 6 months of virologic suppression <50 copies/mL and were in the adherence monitoring cohort with unannounced pill counts on a random day at the participants' usual place of residence every 3-6 weeks. Residual viremia was measured by the single-copy assay.

Results: The median duration of virologic suppression was 10.5 months [Q1-Q3: 7.5-18.4 months] and the median average ART adherence over the prior 1 and 2 months was 94% [Q1-Q3: 79%-100%] and 93% [Q1-Q3: 82%-98%], respectively. Average ART adherence over the past 2 months was associated with levels of residual HIV viremia (Spearman r = -0.25, P=0.04). One-third of participants with 100% ART adherence over the previous 2 months had detectable residual viremia. In multivariate regression analysis, ART adherence over the past 2 months, but not duration of virologic suppression, CD4+ T cell count, or ART regimen, was significantly associated with levels of residual HIV-1 viremia (P=0.004). Detectable residual viremia was associated with virologic failure (>50 copies/mL) in univariate Cox proportional hazard analysis (HR 2.08, P=0.02). However, in multivariate analysis, only ART adherence was associated with risk of virologic failure (HR 1.21, P<0.001).

Conclusions: Incomplete ART adherence was associated with higher levels of residual HIV-1 viremia, which may reflect new rounds of HIV replication even when an individual's viral load is <50 copies/mL. However, residual viremia was also detected in some individuals despite 100% measured ART adherence, suggesting that a component of residual viremia may originate from ongoing release of HIV-1 from the latent reservoir.

388 Viral Dynamics of HIV-1 Rebound Viremia

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Background: When combination antiretroviral therapy (cART) initiated in chronic HIV-1 infection is interrupted, virus quickly rebounds to near pre-treatment levels. The functional latent reservoir is challenging to measure during suppressive cART; rebound HIV-1 virus populations arise directly from the functional latent reservoir, are the actual viruses that curative strategies need to interdict and may be more readily defined. Here, we report a pilot study using single genome sequencing on plasma samples obtained shortly after cART interruption to characterize the clonality and kinetics of rebound virus populations arising from latency.

Methodology: We performed single genome sequencing on plasma samples obtained from four deindentified HIV-1 infected subjects who underwent analytical treatment interruption through other protocols. Viral RNA was extracted, cDNA synthesized and limiting dilution PCR performed to amplify HIV-1 env sequences. Sequences were aligned and analyzed phylogenetically.

Results: Between 20 and 30 gp160 or gp41 env sequences were generated from the first vRNA-positive plasma obtained after treatment interruption (during ramp-up), and 4, 8 and 12 weeks subsequently. Virus populations from the first vRNA-positive sample had maximum diversities ranging from less than 1% to greater than 5% diversity. Phylogenetically, sequences clustered into distinct low-diversity lineages, each indicating origin from a single latently infected cell or rebound founder population. The four subjects had 4, 4, 8 and >10 distinct founder populations, respectively. Over 12 weeks, founder virus populations expanded rapidly due to the introduction of novel founder virus populations and recombination. Strikingly, we observed complete replacement of initial virus populations with genetically distinct virus populations in some subjects.

Conclusions: Our findings demonstrate that single genome sequencing can be used to identify and characterize rebound founder virus populations. Despite earlier reports suggesting a mono- or oligoclonal viral population during initial rebound viremia (Joos et. al., PNAS 2008), we found a greater range in numbers of founder populations during virus ramp-up in the first days to weeks after treatment interruption. Further, rebound founder virus populations expanded more rapidly than previously suggested. We also identified complete replacement of initial virus populations indicative of potent immunological sweeps in the first weeks post-treatment interruption. The study of rebound founder virus populations is a novel strategy to characterize the functional latent reservoir and the immune pressures present upon treatment interruption, both of which have great relevance to curative efforts.

389 Transcripts Associated With the HIV Reservoir Correlate With the Pool Size of Long-Lived CD4 T Cells

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Background: Although active HIV-1 replication can be effectively suppressed by antiretroviral therapy (ART), the virus persists despite treatment and rapidly rebounds once treatment is discontinued. Prolonged ART initiated early after infection has been shown to reduce the size of the HIV-1 reservoir, however it does not eradicate the viral infection. This long-term viral persistence is mainly due to the presence of latently infected CD4 T cells, but host factors that modulate the size of the latent viral reservoir are incompletely understood.

Methodology: CD4+ cells were sorted after a median of 10 years of undetectable viremia from 37 treatment-naive Elite Controllers (EC), 10 patients who initiated ART in the chronic phase of infection (CT) and 8 patients initiating ART within 90 days of infection (ET). Following mRNA extraction, whole-genome transcriptional profiling was performed using Illumina HumanHT-12 microarrays according to standard procedures and differentially expressed genes were defined as having >1.5-fold differences in gene expression intensity and an FDR-corrected p-value of < 0.05. A linear regression model in R was used to identify gene transcripts associated with viral reservoir size in CD4 T cells.

Results: Principal component analysis suggested that long-term ART initiated in primary HIV-1 infection induced gene expression patterns in CD4 T cells that closely resemble those of EC. Notably, linear regression analysis demonstrated that 163 out of 215 of the differentially-expressed transcripts between ET and CT were negatively correlated to the total viral reservoir size (HIV-1 DNA copies/cell) in total CD4 T cells. Interestingly, many of the transcripts associated with the viral reservoir size in total CD4 T cells were also significantly correlated to the relative proportion of CD4 T memory stem cells and of central-memory cells within the total CD4 T cell pool, but not with any other tested immunological characteristics of the patients, including total CD4 T cell count or levels of immune activation in CD4 or CD8 T cells.

Conclusions: Gene transcripts associated with the size of the viral reservoir frequently correlated with the pool size of the long-lived CD4 T cells, suggesting that maintenance of the viral reservoir is guided by shared molecular pathways that also regulate homeostasis and pool size of these long-lasting T cell populations. This suggests that specific therapeutic intervention targeting the most durable CD4 T cell subsets will likely be necessary to reduce HIV-1 persistence in a clinically significant way.

390 Massive Expansion of HIV Infected Cells With Identical Proviruses in Patients On Suppressive ART

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Background: Studies of HIV-1 population genetics during ART have shown the emergence of groups of identical sequences in plasma and PBMCs after long-term suppression. To investigate the mechanisms for the emergence of identical sequences on ART, we identified 14 patients with clonal HIV sequences during long-term therapy and determined their relationship to CD4+ T cell count and HIV DNA copy number.

Methodology: Single-genome *pro-pol* sequences from PBMCs were obtained from 14 subtype B-infected patients at the time of initiating ART and during suppression for 4-12 years. Clusters of identical sequences were identified and the proportions of identical sequences were plotted against baseline and change in CD4+ T cell count and the HIV DNA copy number. Estimates for the total number of CD4+ T cells with clonal proviruses were determined by multiplying the fraction of identical sequences by the normalized HIV DNA copy number and the estimated total body CD4+ T cells.

Results: The fraction of identical sequences in PBMCs during long-term ART ranged from 7% to 55% of the total HIV DNA. In 3/13 patients who started therapy during chronic infection with T cell counts <100/ul, there was an apparent positive relationship between the change in CD4+ T cells following ART initiation and the emergence of identical sequences and a negative relationship with the HIV DNA copy number. There was no obvious relationship between the CD4+ T cell count or the HIV DNA copy number in patients who initiated ART during chronic infection with >100 CD4+ T cells/ul or in patients who initiated ART during early infection. Estimates of the total body number of CD4+ T cells carrying clonal HIV sequences ranged from $1.3x10^9$ to $6.9x10^{10}$.

Conclusions: Analyses of the genetics of HIV proviruses during ART suggests a relationship between the change in the CD4+ T cell count and the total DNA copy number with the emergence of identical sequences during therapy in those patients initiating ART with very low CD4+ T cell copy number. This finding suggests that increasing numbers of CD4+ T cells on ART is due, in part, to the expansion of infected cells. Estimates on the number of CD4+ T cells carrying identical HIV proviruses suggests that infected cells expand massively before and during ART generating billions of new infected cells from a single initial infection event despite suppressive therapy.

391 Effects of CCR5-Δ32 Heterozygosity On HIV-1 Reservoir Size and Immune Activation

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Background: The CCR5-Δ32 mutation in humans decreases cell surface expression of CCR5. To date, all three reported cases of HIV-1 eradication via bone marrow transplantation have been documented in CCR5-Δ32 heterozygotes. The contribution of CCR5-Δ32 heterozygosity to the observed eradication is as yet unknown. In this study, we examined the impact of CCR5-Δ32 heterozygosity on HIV-1 reservoir size and immune activation. We hypothesized that lower CCR5 cell surface expression may reduce susceptibility to infection by CCR5-tropic viruses, thereby modulating the size of the reservoir, the distribution of infected cell types, and/or the contribution of infection to immune activation and inflammation.

Methodology: 18 CCR5-Δ32 heterozygotes and 59 CCR5 wildtype homozygotes from the SCOPE cohort were selected for analysis. Subjects were treatment-naïve upon enrollment in the cohort, had documented pre-treatment plasma viral loads, and were fully suppressed for more than 1 year, with treatment duration of 1-2 years. Cryopreserved PBMCs were enriched for CD4+ T cells prior to nucleic acid extraction. HIV-1 pol and 2-LTR circle DNA were quantified by droplet digital PCR and cell-associated HIV-1 RNA was quantified by ultrasensitive real-time PCR. Flow cytometry was used to measure CD3, CD4, CD8, CCR5, CD38, HLA-DR, and PD-1, and T-cell subset markers on unfractionated PBMCs.

Results: The frequency of CCR5-positive CD4+ T cells ($p=0.016$) and CCR5 mean fluorescence intensity (MFI) ($p=0.027$) were significantly lower in CCR5-Δ32 heterozygotes compared to wildtype individuals. Cell-associated HIV-1 RNA was significantly lower in CCR5-Δ32 heterozygotes ($p=0.047$), despite similar levels of pol and 2-LTR circle DNA in both genotype groups. Cell-associated HIV-1 RNA was positively correlated with CCR5 MFI ($r2=0.12$, $p=0.003$) and frequency of HLA-DR+ CD38+ CD4+ T cells ($r2=0.09$, $p=0.001$), and inversely correlated with frequency of CD4+ T cells ($r2=0.17$, $p<0.0001$) across the entire cohort of both CCR5-Δ32 heterozygotes and wildtype individuals. CCR5 MFI was positively correlated with frequency of HLA-DR+ CD38+ CD4+ T cells ($r2=0.46$, $p<0.0001$).

Conclusions: Reduced HIV-1 RNA expression despite similar HIV-1 DNA levels indicates that the average per cell transcription of HIV-1 is likely reduced in CCR5-Δ32 heterozygotes. The molecular and mechanistic basis for this suppression should be explored in greater detail. Correlations between cell-associated HIV-1 RNA and both cellular activation and CCR5 expression suggest that reduced CCR5 availability in CCR5-Δ32 heterozygotes may limit the size of the functional HIV-1 reservoir and decrease immune activation, thereby enhancing the probability of achieving viral eradication.

392 Seminal CMV Replication, Immune Activation, and Higher Proviral HIV DNA During Suppressive ART

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Background: CMV replication is frequent in the genital tract of HIV infected men, and is associated with increased immune activation and HIV disease progression. We hypothesized that CMV-associated immune activation could influence the size of the HIV DNA reservoir during suppressive antiretroviral therapy (ART).

Methodology: Paired blood and semen samples from 53 HIV infected men on long-term ART with undetectable HIV RNA in blood plasma were studied. Levels of CMV DNA were measured in seminal plasma by RT-PCR. Total HIV DNA (pol), 2-long terminal repeat (2-LTR), and cellular HIV RNA (unspliced [us] gag and multiply-spliced [ms] encoding for tat/rev) were measured in peripheral blood mononuclear cells (PBMC) by droplet digital PCR. Levels of CD4+ and CD8+ T-cells immune activation (CD38+HLA-DR+) and proliferation (Ki67+) were determined from PBMC by multicolor flow-cytometry. Associations between levels of proviral HIV DNA, cellular HIV RNA, immune activation and proliferation in blood, time on ART, CD4+ T-cells counts and the presence of CMV replication in semen were investigated using univariate and multivariate non-parametric statistics.

Results: Detectable CMV DNA was found in 44% of seminal samples, and was associated with higher levels of proliferating (Ki67+) and activated (CD38+HLA-DR+) CD4+T-cells ($P<0.01$), and a trend towards higher levels of proliferating CD8+ T-cells ($P=0.1$) in blood. Subjects with detectable seminal CMV had higher levels of proviral HIV DNA (2.84 versus 2.11 log10 copies/million CD4+, $P=0.05$) and higher levels of cellular [ms] HIV RNA ($P=0.04$) compared to those without seminal CMV. Levels of [us] HIV RNA, 2-LTR and average cellular transcription (i.e. cellular HIV RNA/DNA ratio) were not different between subjects with and without CMV. There was a weak correlation between seminal CMV DNA and CD4-associated HIV DNA levels ($P=0.06$, $r= 0.26$). Among subjects with detectable CMV in semen, there was a significant correlation between HIV DNA levels and frequency of activated ($P<0.01$, $r=0.6$) and proliferating CD4+ T-cells ($P<0.01$, $r=0.64$). In multivariate analysis, presence of seminal CMV ($P=0.04$), and detectable 2-LTR ($P<0.01$) were independent predictors of higher HIV DNA in PBMC.

Conclusions: Asymptomatic seminal CMV replication is associated with higher levels of systemic CD4+T-cell immune activation and proliferation and with a greater size of the HIV DNA reservoir in PBMC. Average HIV transcription was not increased in CMV positive samples, suggesting that CMV is not directly associated with low-level HIV replication but more likely with homeostatic proliferation of HIV-infected CD4+ T-cells. Interventions aimed at reducing seminal CMV replication and associated immune activation could be important for HIV curative strategies.

393 Persistent HIV in Plasma During cART Can Lead To Rebound Viremia After Treatment Interruption

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Background: Combination antiretroviral therapy (cART) suppresses but does not eradicate HIV infection. Analysis of HIV variants during cART has revealed populations of identical sequences, suggestive of clonally expanded populations, which have been found in plasma, in peripheral blood mononuclear cells (PBMC), as well as in anatomic compartments. HIV emerges rapidly after treatment interruption; rebound viremia also includes clonally expanded populations, but it is not known whether these clonal variants arise from persistent viremia during suppression, or from clonal sequences present in PBMC. To investigate the source of early rebound virus, we compared HIV in plasma and cells prior to and following a short structured treatment interruption (STI).

Methodology: Stored plasma and PBMCs were obtained from patients (N=13) with viremia <50 c/ml on cART for ≥1 y enrolled in a STI. PBMCs were obtained on the day of drug interruption, and plasma samples obtained prior to and 7, 14, and 28 days after STI. DNA from PBMC and RNA from plasma was subjected to single genome sequencing (SGS) to obtain pro-RT sequences, which were aligned by Clustal W; phylogenetic analyses were performed using MEGA 5.2.

Results: A total of 13 patients were enrolled (median age 38.7 y, CD4= 611 cells/µl, 39%, duration of suppression 2.7 y prior to STI); 6 patients have been analyzed and 467 SGS obtained thus far. Prior to STI, HIV population structure in PBMC was complex, and included groups of identical sequences in 5 of 6 patients as well as individual variants; viral populations in plasma prior to STI were more restricted with a limited number of variants detected. All patients rebounded within 7-14 days of treatment interruption. As expected, rebound viremia consisted of both individual variants and groups of identical sequences in all patients. In 2 of 6 patients, sequences present during rebound were identical to an HIV variant detected in plasma prior to the STI. In contrast, variants present in rebound viremia were only rarely detected in PBMC-derived DNA.

Conclusions: Early rebound HIV consisted of individual and clonal sequences. PBMC populations were diverse and included clonal sequences. Rebound viremia included clonal sequences, but these populations were distinct from those detected in PBMC, and clonal sequences in PBMC did not give rise to clonal sequences in rebound viremia. These data suggest PBMC associated populations are large and diverse, and rebound viremia likely emerges from a small minority of infected cells. Some variants present in rebound viremia were detected in plasma prior to STI, demonstrating that rebound viremia emerges, at least in part, from expansion of low-level persistent viremia.

Session P-F3 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Effect of ART Early in HIV Infection

394 How To Characterize Post-Treatment Controllers in Patients Treated During Primary HIV Infection?

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Background: Post-treatment control (PTC) has been described in HIV-infected patients treated during primary HIV-infection (ANRS Visconti cohort). Characteristics of these patients differ from elite controllers. Markers associated with PTC were normal CD4 cell counts at the time of treatment interruption, normal CD4/CD8 ratio, low levels of immune activation and low cell-associated HIV-DNA levels. We evaluated the respective parameters in patients (pts) of the New Era Study, an ongoing, prospective 7-year clinical trial initiated in 2009 using 5-drug HAART in pts with primary HIV infection (PHI, ≤2 Western blot bands) and in pts with chronic HIV-infection on suppressive PI-based HAART for ≥3 years without prior virologic failure (CHR). The primary objectives of the study were to halt residual viral replication in plasma and to achieve depletion of cell-associated HIV-DNA ('proviral DNA') as a step towards (functional) HIV cure which should be proven by treatment interruption.

Methodology: Eligibility criteria of the New Era Study were CD4 nadir >200/µL, no history of AIDS, CCR5 tropism. PHI pts received 5-drug HAART including 2 NRTIs + 1 PI + Maraviroc + Raltegravir. In CHR pts, HAART was intensified with MVC + RAL. HIV-DNA in peripheral blood mononuclear cells (PBMC) was measured as described by the French ANRS group. Here we describe proviral DNA outcomes and CD38+CD8+ cells at month 24 for PHI and CHR pts stratified by CD4 ≥900/µL and CD4/CD8 ratio ≥1.

Results: In total, 20 CHR and 22 PHI pts were included. PHI pts were started on 5-drug HAART within ≤2.6 weeks after diagnosis. Western blot was negative in 12 PHI pts. 2 PHI pts discontinued before month 24. At month 24, median proviral DNA levels were significantly lower in PHI than in CHR pts (2.1 vs 2.6 log cp/10^6 PBMC, p=0.001). Significantly more PHI pts had a CD4/CD8 ratio ≥1 (90% vs 30%, p<0.001). CD4 count was ≥900/µL in 55% of PHI and 40% of CHR pts (p=n.s.) 50% vs 20% of PHI and CHR pts fulfilled both criteria (p=0.096). Proviral DNA levels and CD8 cell activation are shown in the Table.

	CHR		PHI	
	CD4 ≥900/µL and CD4/CD8 ratio ≥1	Others	CD4 ≥900/µL and CD4/CD8 ratio ≥1	Others
n/N	4/16*	12/16*	10/20	10/20
Cell-associated HIV-DNA [log cp/10^6 PBMC], (median, range)	2.7 (2.3 - 3.1)	2.6 (1.6 - 3.6)	1.9 (1.3 - 2.6)	2.3 (1.8 - 2.5)
Cell-associated HIV-DNA ^{6} PBMC (n)	0/4	2/12	6/10**	1/10**
CD38+CD8+ [cells/µL], (median, range)	125 (85 - 366)	135 (20 - 366)	75 (8 - 487)	71 (6 - 244)
CD38+CD8+ [%], (median, range)	9 (3 - 15)	13 (1 - 23)	9 (1 - 24)	14 (2 - 20)
* four missings			**P=0.0.57	

Conclusions: In both groups, early treated PHI pts and selective control pts continuously on suppressive HAART, patients with a CD4 cell count ≥900/µL and a CD4/CD8 ratio ≥1 were found. Only for PHI pts, cell-associated HIV-DNA levels were lower in case of normal CD4 count and normal CD4/CD8 ratio supporting that preservation of immune functions during PHI and/or early immune reconstitution are associated with a lower HIV reservoir size and potentially higher rates of PTC.

395 Loss of HIV Serological Markers Following Early Treatment of Acute HIV Infection

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Background: Early initiation of highly active antiretroviral therapy (HAART) during acute HIV infection (AHI) may alter the natural history and progression of HIV infection, modify disease outlook and affect the emergence of serological markers of infection. In this study 33 AHI subjects in Bangkok, Thailand in whom HAART was initiated early were followed and tested for serological markers of HIV and compared with a similar AHI population not on early HAART.

Methodology: Volunteer samples were screened for HIV infection by a 4th generation antigen/antibody combo EIA assay. Non-reactive samples were retested by pooled HIV-1 qualitative RNA (Gen-Probe Aptima) assay. Acute HIV infection was classified by Fiebig stage using RT PCR, p24 antigen, EIA, and Western blot assay results. Plasma samples collected at Weeks 0, 2, and 12 were tested by EIA 1/2 Plus O (3rd Gen), HIV-1/2 Ab/Ag Combo (4th Gen), p24 Ag (RUO); HIV-1 Western blot (WB), and Multispot assays (Bio-Rad Laboratories, Inc; Redmond, WA).

Results: Of volunteers who initiated HAART, one Fiebig I (RNA +) volunteer failed to develop a serological response and three others were transiently EIA (3rd Gen) repeat reactive (RR) at Week 2, but reverted to EIA non-reactive (NR) status by Week 12. Two of 15 Fiebig II volunteers were EIA NR, and an additional 2 EIA RR but WB Indeterminate (IND) by Week 12. Of 14 Fiebig III-V volunteers (all EIA RR as defined for these stages), one reverted to EIA NR, three remained WB IND, while one WB positive at Week 2 reverted to WB IND by Week 12. Delayed positivity on the Multispot assay was observed in 10 of 33 individuals. Five volunteers positive by Multispot at Week 2 reverted to negative status by Week 10. In contrast, a similar population of AHI patients that was not on HAART, demonstrated 3rd Gen EIA, 4th Gen EIA and Western blot positivity by Week 2-3; no seroreversions were observed.

Conclusions: Initiation of antiviral therapy at very early stages of infection (Fiebig I) impeded seroconversion to anti-HIV antibody. Initiation of therapy at Fiebig II-V delayed evolution of serological markers as detected by WB and Multispot, and in some cases, resulted in complete seroreversion of initial antibody response. Additional studies investigating initiation of HAART early in AHI on the course of infection and impact on the evolution of serological response is warranted.

396 Early Antiretroviral Therapy Prevents the Establishment of HIV-1 Infection in Humanized-BLT Mice

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Background: People who are living with HIV-1 have to maintain a lifetime of antiretrovirals, medication side effects and unsustainable costs to individual and society. Recently, "cure or functional cure" of HIV-1 infections was accomplished with the "Mississippi pediatric case", proved that curing HIV-1 is possible. However, the cure treatment window, and the mechanisms of cure are unknown. In this study, curing HIV-1 with early treatment was tested in the humanized-BLT (hu-BLT) mouse model.

Methodology: Six adult hu-BLT mice with good immune reconstitution were randomly divided into Early Treatment (Rx, n=3) and Control (Ctr, n=3) groups. Both groups were inoculated intraperitoneally (IP) with a mixture of two transmitted/founder HIV-1 viruses (2.5e3 TCID50 each). Six hours later, animals in the Rx group started daily treatment for two weeks with TDF, 5 mg/mouse, IP and 3TC, 4 mg/mouse, IP; Ctr animals received solvent IP. Three weeks after the antiretroviral drug therapy stopped, CD8+ T cells from both groups were depleted using two dose of anti-CD8 antibody (M-T807R1, 5mg/kg, IP) to test whether undetectable plasma viral load (PVL) was due to CD8+ T cells mediated viral control. Human CD8+ T cells in peripheral blood mononuclear cells (PBMCs) were quantified before and weekly after administration of anti-CD8 antibody using FLOW. Plasma viral RNA load (PVL), monitored weekly post inoculation (PI) using droplet digital PCR (ddPCR). HIV-1 viral DNA in PBMCs was monitored by ddPCR at 5 weeks post-CD8 depletion.

Results: Ctr group PVL was positive from 7-10 days PI throughout the entire experiment (mean PVL 6.98e4 copies/ml week 1, increased to 2.5e6 copies/ml at one month PI). In contrast, the Rx group had undetectable weekly PVL, including 3 weeks off therapy. To discriminate CD8+ T cells mediated cure

in the Rx group, CD8+ T cells in both groups were depleted. CD8+ T cells comprised 27.6% +/-14.9% of total human CD3+ T cells in PBMCs before administration anti-CD8 antibody. After administration anti-CD8 antibody, 99.5 percent of CD8+ T cells were depleted over 5 weeks. CD8+ T cell depletion significantly increased PVL (mean +SD) in Ctr group (4.0e5 +/- 2.3e4 copies/ml before depletion to 2.7e6 + 2.7e5 at 3 weeks post depletion). In contrast, Rx group PVL remained undetectable and HIV-1 vDNA was undetectable in PBMCs.

Conclusions: Early antiretroviral treatment can cure transmitted/founder HIV-1 infection in hu-BLT mouse model. Furthermore, CD8+ T cells depletion significantly elevated the PVL in Ctr animals, but did not modify the undetectable PVL in Rx group, suggesting early treatment achieved cure of HIV-1 infection. Studies are ongoing to further define the cure window and mechanisms involved.

397LB Lack of Detectable HIV DNA in a PrEP Study Participant Treated During "Hyperacute" HIV Infection

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Background: The study of ART initiation during "hyperacute" HIV infection may provide insights into a functional cure. We report such a case from The PrEP Demo Project, a pre-exposure prophylaxis program in at-risk MSM. This individual was HIV-uninfected (by pooled RNA, 4thgeneration EIA, and rapid antibody) at 2 pre-enrollment visits (21 and 13 days prior to PrEP baseline) but was found to be in Fiebig stage I HIV infection (RNA 220 copies/mL, 4th generation EIA negative, rapid antibody negative) at the PrEP baseline visit(estimated ~10 days after infection). The individual received PrEP (tenofovir/emtricitabine) for 7 days, at which time PrEP baseline test results returned and conventional ART was initiated. The patient was asymptomatic during this time and remains on ART.

Methodology: Single genome sequencing was conducted from the PrEP baseline plasma sample. Colorectal biopsy (~1.9 months after infection) and leukapheresis (~2.1 months after infection) were conducted and a large-volume blood sample (240mL, ~5.8 months after infection) was analyzed for replication-competent virus.

Results: Plasma HIV RNA levels were 220 copies/mL (PrEP baseline), 120 copies/mL (7 days after PrEP initiation), and "detected <40 copies/mL" (~32 days after infection); all subsequent plasma RNA levels have remained negative. There was a single occurrence of low-level cell-associated HIV RNA (4.7 copies per million CD4+ T cells) ~32 days after infection. All other HIV RNA/DNA tests have been negative, including those performed in colorectal biopsy samples enriched for total CD4+ T cells. Total CD4+ T cells and CD4+ T cell subsets (Tn, Tcm, Ttm, Tem) from the leukapheresis sample were also negative for HIV RNA and DNA (analyzed at 2 independent laboratories), including total DNA, integrated DNA, and 2-LTR circles. The viral outgrowth assay did not detect any replication-competent virus from 62 million purified resting CD4+ T cells. HIV western blot assays were repeatedly indeterminate (p55 only) but eventually became non-reactive. The individual was CCR5 wild-type and HLAB5701 negative. Analytic treatment interruption is planned after 12 months of ART.

Conclusions: We report a case of extremely early initiation of ART (immediately after the "eclipse phase," at approximately 10 days of HIV infection) in a PrEP participant. Whether very early ART exposure through PrEP or conventional ART contributed to this unique outcome remains unknown and warrants further study. PrEP programs should consider testing participants for acute HIV prior to and during PrEP use, and consider immediate conversion from PrEP to conventional ART following a diagnosis of acute HIV. Although HIV may persist indefinitely in this individual, a continuum may exist across PrEP, PEP, and curative early ART strategies.

398 Early HAART in Primary HIV Infection Protects TCD4 Central Memory Cells and Can Induce HIV Remission

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Background: Post treatment controller status has been associated with a low HIV reservoir, particularly in the CD4 T central Memory. We explored the characteristics of the subsets reservoir after 2 years of early HAART during PHI.

Methodology: 12 patients (PHI2) from the OPTIPRIM-ANRS147 trial were enrolled in this substudy (early HAART HIV-1 western-blot (WB) ≤4 antibodies (Ab) and positive HIV-RNA + in case of asymptomatic PHI CD46 years (PHI6) and for 11 post-treatment controllers (PTC) having a viral control for > 9 years.

Results: At baseline, among the 12 PHI2 (median age: 32 years, time from estimated date of infection: 36 days), 11 were symptomatic, 11 had HIV-1 WB ≤3 Ab; median CD4 counts was 376 cells/mm3 [IQR: 341;516], HIV-RNA 5.4 log cp/ml [5.0;5.8] and HIV-DNA 3.9 log cp/106PBMC [3.48;4.30]. One woman stopped the trial regimen before M24 due to pregnancy. From day 0 to M24, CD4 subset numbers increased ($p<0.004$) and HIV-DNA median level decreased in PBMC of -1.43 [-1.74;-1.21] ($p=0.001$), in TN of -0.74 [-0.9;-0.27], in TCM of -1.45 [-2.09;-1.34], in TTM of -1.48 [-1.97;-1.23] and -1.34 [-1,81;-1.2] in TEM (all $p<0.004$). There was no evolution of the viral diversity and viral production was induced by in vitro activation in all CD4 subsets at M24. At M24: long-lived TN and TCM were less infected than TTM and TEM (all $p<0.009$), less contributed to the reservoir than TTM ($p=0.019$) while TCM infection level was higher than TN, and similar to the shorter-lived memory subsets at PHI. Despite a significant decrease after 2 years early-HAART, HIV-DNA levels in all CD4 subsets in PHI2 were higher than levels observed in PHI6 and PTC (all $p<0.019$). Interestingly HIV-DNA levels in PHI6 were similar to those in P2 PHI2 reached a PTC status (HIV-RNA 1 year after treatment interruption), with very low HIV-DNA levels in all CD4 subsets, similar to the11 PTC.

Conclusions: We show that two years of an early treatment during PHI protected the long life TCM and TN from infection. A more prolonged treatment aiming to reach deeper reduction of HIV reservoir would probably more increase the chance to induce cases of patients presenting the characteristics of a HIV functional cure as observed in PTC.

Session P-F4 Poster Session
Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**
Methods for Measuring Reservoirs

399LB A Scalable RNA RT-PCR Based Assay To Quantify Latency Disruption in HIV-1 Infected Cells

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Background: Antiretroviral therapy (ART) provides suppression of HIV-1 below the limits of standard clinical assays, but virus promptly resurfaces upon interruption of ART due to viral persistence in stable reservoirs. A commonly used method to quantify cells in such reservoirs is HIV DNA PCR due to ease-of-use, however most of these cells are unlikely to ever produce replication-competent virus. On the other hand, viral outgrowth assays provide virologic realism, but are resource intensive. Detection of RNA by RT-PCR is a balanced approach that provides for some virologic realism while allowing for high throughput.

Methodology: Here we describe a method in which flow cytometry purified resting memory CD4+ T cells from ART treated patients are placed in a limiting dilution culture for 4 days in the presence of stimulation with bead-bound antibodies to CD2, CD3, and CD28. Viral replication is inhibited by the inclusion of a non-nucleoside reverse transcriptase inhibitor. The viral RNA is purified from the culture supernatant using a paramagnetic nanoparticle based method that is scalable to robotic automation. The extract is DNAse treated and then real time quantitative RT-PCR is performed using a primer and probe set specific for HIV gag. Statistics were performed with the R package for Extreme Limiting Dilution Analysis (ELDA).

Results: This assay is sensitive enough to detect 47 copies of HIV RNA produced from a single activated cell from the ACH-2 HIV latency cell line. Using this method with resting memory CD4+ T cells from virally suppressed patients, the frequency of induced HIV RNA production varied from 1 in 40,000 cells to fewer than 1 in 1,000,000. There was no correlation between frequency of HIV RNA producing cells and frequency of proviral DNA.

Conclusions: This assay represents a scalable bench-to-bedside method for quantifying the frequency of HIV producing cells in the blood and tissues of patients with viral suppression and for evaluating reservoir elimination strategies for such patients.

400 HIV Antibody Characterization To Quantify Reservoir Size During Curative Interventions

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Background: Since most routine and scalable assays of HIV persistence have sensitivities at or near the level of HIV found in most treated adults, there is intense interest in developing novel methods to characterize viral reservoir during therapy. The host response to residual virus may be a sensitive measure of reservoir size. We quantitatively analyzed the level and distribution of anti-HIV antibody profiles in serum samples of a diverse cohort using Luciferase immunoprecipitation systems (LIPS).

Methodology: Using the LIPS assay, antibody responses against nine different recombinant HIV proteins were quantitatively analyzed in uninfected blood donors (n=10), elite controllers (n=10), HIV-infected adult patients (n=9) from before and after several years of ART-induced virologic control (n=9) and in the Berlin patient who was cured following a delta32/delta32 CCR5 stem cell transplant. Heatmap and principal component analysis (PCA) was also used to analyze the antibody data.

Results: Quantitative humoral profiling of five, recent serial serum samples collected 51-67 months after the transplant from the Berlin patient revealed no antibodies against p24, matrix, nucleocapsid, integrase, protease and gp120, but persistent albeit low levels of antibodies against reverse transcriptase, tat and gp41. In contrast, antibody levels to these HIV proteins persisted at high and stable levels in most non-controllers and antiretroviral-treated subjects. However, five of the ten elite controllers had low levels of antibodies against matrix, reverse transcriptase, integrase and/or protease. PCA and heatmap analysis revealed that the uninfected blood donors and the Berlin patient clustered together and were in close proximity to the five elite controllers with low anti-HIV antibody levels. Since all ten elite controllers showed similar viral loads (<50 copies/ml), these data also highlight the heterogeneity of anti-HIV antibody responses in the elite controllers. Additionally, three of the ART-treated subjects who demonstrated a decrease in HIV antibodies following treatment showed a shift in their PCA profile closer to the uninfected controls following treatment. Across all proteins, responses to gp41 tended to show the most consistent group-to-group differences, with increasing responses across the uninfected subjects, the Berlin patient, the controllers and the treated group readily apparent.

Conclusions: Monitoring the host humoral response to individual HIV proteins, particularly gp41, may provide a practical tool to longitudinally monitor HIV persistence during curative interventions. The mechanism which accounts for uniquely low levels of antibodies towards certain proteins among some controllers is unknown, but may reflect very low reservoirs.

401 High-Throughput Analysis of Full-Length Proviral HIV-1 Genomes From PBMCs

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Background: HIV-1 proviruses in peripheral blood mononuclear cells (PBMCs) are felt to be an important reservoir of HIV-1 infection. Given that this pool represents an archival library, it can be used to study virus evolution and CD4+ T cell survival. Accurate study of this pool is burdened by difficulties encountered in sequencing a full-length proviral genome, typically accomplished by assembling overlapping pieces and imputing the full genome.

Methodology: Cryopreserved PBMCs collected from a total of 8 HIV+ patients from 1997-2001 were used for genomic DNA extraction. Patients had been receiving cART for 2-8 years at the time samples were obtained. 7 patients had pVL >50 copies/mL (mean: 312,282, range: 18,372-683,400) and 1 had pVL <50. Genomic DNA was subjected to limiting dilution prior to amplification of near-full-length genomes by a newly developed nested PCR. The predicted size of the PCR product was 9.0 kb, spanning from the 5' LTR through the 3' LTR. Single molecules were sequenced as near-full-length amplicons directly from PCR products without shearing using commercially available P4-C2 reagents and standard protocols on a PacBio RS II instrument. Quality of the genomes was validated by clonal positive controls and synthetic mixtures.

Results: Near-full-length provirus genome sequences were successfully obtained from all 8 patients as continuous long reads from single molecules. PacBio sequencing required approximately 10% of the PCR product needed for Sanger sequencing and generated 325MB per 3-hour run including 1,800 full-length intact genome reads on average. One patient's sample was not at a limiting dilution and analysis revealed multiple subspecies. For 8 near-full-length provirus genomes derived from the other 7 patients, large internal deletions were noted in 2 proviruses; APOBEC-mediated hypermutations were seen in 2 proviruses; and 4 proviruses appeared to be intact genomes. All of the defective proviruses showed a complete absence of resistance mutations in either RT or protease, even after 2-8 years of cART. On the contrary, all of the intact proviruses contained evidence of ART-resistance associated mutations suggesting that they represented relatively recent variants.

Conclusions: Combining a novel protocol for full-length limiting dilution amplification of proviruses with PacBio SMRT sequencing allowed for the generation of near-full-length genomes with good quality and an ability to detect minor variants at the 1-10% level. Preliminary data analyses suggest that defective proviruses may represent archival variants that persist long-term in host cells, while intact proviruses within the PBMC pool showing evidence of active virus replication may represent more recent variants.

402 Using Antibodies To Detect HIV Persistence in Treatment Intensification and Eradication Studies

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Background: Quantifying the degree of HIV persistence during therapy is challenging due to low viral burden and the intracellular sequestration of virus. An alternative or complementary approach is to quantify the host response to HIV. HIV incidence assays have been developed to measure antibody (Ab) evolution during HIV seroconversion. We used HIV incidence assays to investigate the association between HIV Ab levels, avidity and HIV antigen specificities in a diverse cohort of treated and untreated adults.

Methodology: HIV incidence assays included: dilution (1:400 dilution in buffer; increased cutoff) for the VITROS® Anti-HIV1+2 assay; an avidity (DEA-incubation/PBS-incubation; avidity index) modification for the BIO-RAD GS HIV-1/2 assay; and an index summing HIV-specific band intensities targeting p31, gp160, gp41 for the Geenius™ HIV1/2 supplemental assay. Using these methods we characterized HIV Ab responses from 280 long-term infected untreated individuals, 280 treated and suppressed individuals, 100 suppressed elite controllers (EC) and one potentially eradicated individual (the Berlin patient). We also observed responses in longitudinal follow-up after HAART.

Results: Compared to individuals with untreated HIV infection, EC exhibited lower levels of HIV Ab by both LS-VITROS ($p<0.001$) and Geenius ($p=0.01$) quantitative assays, but no difference in antibody avidity by the Bio-Rad avidity assay. EC had higher Ab levels compared to ART-treated suppressed patients in all assays ($p<0.001$). Subjects treated in acute infection had lower Ab levels on all assays compared to those treated in chronic infection. Among subjects treated with suppressive ART after complete seroconversion, increasing time on treatment was correlated with lower Ab levels by LS-VITROS ($p=0.001$) and Geenius ($p=0.01$), but no decline was seen in Ab avidity by the Bio-Rad assay. The Berlin patient has low-level Ab that has progressively declined over time on these assays, consistent with complete absence of virus (eradication).

Conclusions: There are reductions in Ab titer but not in avidity in treated compared to untreated individuals that correlates with time on treatment. Although EC had undetectable or very low VL, Ab levels remained elevated compared to individuals on ART, demonstrating maintenance of Ab stimulation from persistent viral replication in reservoirs. Measuring the quantity, quality and diversity of Ab to HIV may be used as a marker for monitoring viral persistence in studies of eradication and treatment.

403LB HIV DNA in PHI Associates With T Cell Immunity and Predicts Disease Progression and Rebound Viraemia

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Background: There are no comprehensive analyses of HIV proviral DNA in Primary HIV Infection (PHI) that include inflammation, HIV-specific immunity and clinical progression. We present analyses from the SPARTAC trial characterizing immunological and virological associations with proviral DNA in PHI, and exploring the impact of proviral DNA on clinical progression and virological rebound on stopping ART.

Methodology: Participants with PHI in SPARTAC were analysed for HIV proviral DNA ('integrated' and 'total' in CD4 T cells), HIV CD4 and CD8 T cell immune responses (by ELISpot), immune activation (HLA DR, CD38), immune exhaustion (PD-1, TIM-3, LAG-3) and generalized markers of inflammation (D-dimer, IL-6). Outcome measures included time to trial primary endpoint and time to plasma viral load rebound on stopping ART. Statistical associations were determined using linear regression and Cox proportional hazard models.

Results: Baseline samples at trial enrolment were available from up to 154 participants with subtype B infection. 'Integrated' and 'Total' HIV DNA levels were closely correlated (r=0.85; P<0.001) and associated with baseline CD4 count (P<0.001) and plasma viral load (P<0.001).

CD8 and CD4 T cell activation (CD38, HLA DR) were significantly associated with HIV DNA (P<0.01), the association being stronger for CD8s. There was a strong association with HIV DNA and D-dimer (P<0.01), but not IL-6. Both CD8 PD-1 and Lag-3 (not TIM-3) were significantly associated with HIV DNA, but there was no evidence for an association with proviral DNA and CD4 T cell exhaustion.

Participants making a CD4 T cell ELISpot response to HIV Gag had significantly lower HIV DNA levels (p<0.05; Mann Whitney), with weaker evidence for an association with CD8 T cell immunity (P=0.03 and 0.05 for responses to 0 vs 3 Gag overlapping peptides for 'total' and 'integrated' DNA, respectively).

In univariable analyses of untreated individuals at PHI, both 'total' and 'integrated' DNA were significant predictors of clinical progression. In multivariable analyses, 'total' DNA remained strongly associated with trial outcome (HR 3.6; P=0.002), whereas integrated DNA and plasma viral load did not.

In patients receiving 48 weeks of suppressive ART, total HIV DNA at time of stopping therapy was predictive of trial end-point (HR 3.6; p=0.01) and time to plasma viral load rebound (HR 2.5; P=0.007).

Conclusions: This is the first comprehensive analysis of the HIV reservoir in the context of HIV-specific immunity, inflammation and clinical progression in a large randomized clinical trial in PHI. The data confirm the close relationship between immunity, inflammation and the reservoir in PHI, and show that reservoir size is a key predictor not only of progression but also of viraemic control on stopping ART.

404 Next Generation Plasma HIV-1 RNA Single Copy Assays

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Background: A qPCR assay with single copy sensitivity targeting HIV-1 gag (gSCA) has been widely used to quantify plasma HIV-1 RNA below the limit of clinical assays. However, with current extraction methods, gSCA incompletely recovers a spiked internal standard (avian sarcoma virus, RCAS), and fails to efficiently amplify 15-30% of HIV-1 subtype B sequences due to mismatches in the gag primer/probe binding sites. To address these limitations, we developed a next generation SCA with improved extraction efficiency and primers/probes targeting highly conserved sequences in integrase (iSCA). We also explored assaying larger plasma volumes to increase iSCA sensitivity (Mega-iSCA).

Methodology: Primers/probe for qPCR were designed to target a highly conserved 3' region of HIV-1 integrase away from drug-resistance sites. Recovery of the spiked internal standard RCAS was used to optimize the extraction method. Paired plasma samples from 30 consecutive donors (25 with suppressed viremia for >2 years; 5 with viremia >50 copies/mL) were obtained to compare iSCA versus gSCA. For viremic patients, HIV-1 RNA recovery <10% of Roche TaqMan v2.0 was scored as inefficient amplification. Between iSCA and gSCA, >3-fold differences in HIV-1 RNA were considered significant. Large plasma volumes (up to 34 ml) were assayed by Mega-iSCA to achieve a theoretical limit of detection (LOD) of 0.05 copies/mL.

Results: Testing of the plasma panel from 30 donors revealed that the median recovery of the internal standard was 1.5 times higher with iSCA compared to gSCA (p<0.001, signed rank test). In samples from the 5 patients with viremia >50 copies/mL, gSCA efficiently amplified 2 of 5 whereas iSCA efficiently amplified all 5 compared with TaqMan (p=0.01, exact binomial test). In samples from all 30 patients, 12 of 30 had >3-fold recovery of HIV-1 RNA with iSCA versus gSCA, while 3 of 30 had >3-fold recovery with gSCA (p<0.001, exact binomial test). Using gSCA, 11 of 30 samples were undetectable compared with 7 of 30 samples using iSCA (p=0.088, exact binomial test). Large volume plasma samples from 7 patients with HIV-1 RNA <50 copies/mL were assayed by Mega-iSCA (4 of 7 were negative by standard iSCA). Mega-iSCA detected HIV-1 RNA in 6 of 7 samples including 3 of 4 negative by standard iSCA.

Conclusions: An optimized extraction method and primers/probe targeting highly conserved sequences in the 3' region of pol improved viral RNA recovery and decreased false negatives. Assaying larger plasma volumes by Mega-iSCA lowered the theoretical limit of detection for HIV-1 RNA to 0.05 copies/mL and improved sensitivity for persistent viremia. iSCA and Mega-iSCA should be useful for measuring the impact of therapeutic interventions and in differentiating between "functional" and "sterilizing" cures of HIV-1.

405 Assessment and Quantification of Cell Associate Unspliced HIV-1 RNA Using RT-ddPCR

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Background: Quantification of cell-associated HIV-1 RNA is critical to understanding how HIV-1 latency is established and maintained in a reservoir of infected cells during antiretroviral therapy. Droplet digital polymerase chain reaction (ddPCR) can detect and precisely quantify the target nucleic acids without the need for a calibration curve. Previous studies demonstrated that ddPCR is generally comparable to traditional qPCR methods for the quantification of both total HIV-1 DNA and episomal 2-LTR circles. In this study, we developed a reverse transcriptase (RT) ddPCR assay and compared to quantitative reverse transcriptase-PCR(qRT-PCR) for detection and quantification of unspliced cell-associated HIV-1 RNA in both HIV-uninfected cell lines spiked with HIV-infected cells and clinical samples from patients on antiretroviral therapy (ART) with very low-level viremia.

Methodology: To evaluate the ability of RT-ddPCR to measure cell-associated HIV-1 RNA, serially diluted (2.5 to 10^8 copies/10 ul RNA input) in vitro transcribed HIV-1 RNA was quantified by RT-ddPCR and qRT-PCR. We analyzed 8 replicates of the 100-copy standard to assess the accuracy and reproducibility of RT-ddPCR. Levels of cell-associated HIV-1 RNA were determined in clinical samples from patients on suppressive ART, and from MT2 cells spiked with the latently-infected cell line ACH2.

Results: RT-ddPCR accurately quantified HIV-1 RNA transcripts; the dynamic range was 10 to 10^5 copies per 10 ul RNA input (R2 > 0.99), which represented similar sensitivity as qRT-PCR. The 100-copy input showed that the percentage of positive droplets most closely correlated with the expected copy number. For samples with input RNA of 10^3 to 10^5 copies, the copies detected was ~10% lower than expected; for samples with <100 copies of input RNA the calculated copy number was slightly higher than expected (mean 1.9-fold difference). Linearity decreased significantly when greater than 10^5 copies due to saturation of positive droplets formation. HIV-1 RNA measured by RT-ddPCR and qRT-PCR in samples from co-culture of serially diluted reactivated ACH2 cells together with MT2 cells lines were highly correlated (R2=0.9668). HIV-1 RNA was detected by RT-ddPCR in 14/20 samples (range, 4-284 copies/million PBMC) and by qRT-PCR in 13/20 samples (range, 6-479 copies/million PBMC), respectively.

Conclusions: The RT-ddPCR assay detected and accurately quantified cell-associated HIV-1 RNA with a dynamic range down to 10 copies per reaction. RT-ddPCR demonstrated similar accuracy and sensitivity compared to qRT-PCR in the measurement of cell-associated HIV-1 RNA in both cell-lines spiked with HIV-infected cells and in patient samples. RT-ddPCR is a promising tool for the quantification of HIV-1 cell-associated RNA.

406 Measuring HIV Latency Over Time: Reservoir Stability and Assessing Interventions

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Background: The quantitative viral outgrowth assay (QVOA) is the gold standard for measuring the latent reservoir of HIV infection, yielding precise measurement of the reservoir of resting CD4+ T cell infection (RCI). But variability of RCI over time on ART, relevant to assess potential effects of anti-latency interventions, has not been fully described. We report an analysis of 160 QVOAs.

Methodology: HIV+ male participants, stably HIV RNA <50 c/ml on ART, donated resting CD4+ T cells via leukapheresis. Acute HIV infection (AHI) patients (plasma HIV RNA detected and HIV Western blot negative) were identified via the North Carolina STAT program, and initiated ART within 45 days of the estimated diagnosis (range 7-45, median 19 days); one patient initiating ART 6 months after infection (early infection) was also studied. Once HIV RNA was <50 copies/ml for 6 months, leukapheresis was performed and RCI quantitated. QVOA was performed using 30-225 million resting CD4+ T cells in 24-96 replicate cultures in limiting-dilution format. RCI was similarly measured for patients initiating ART during chronic infection (CHI). Random effects regression evaluated RCI decay and estimated sources of variability, restricting to RCI measures obtained ≥12 months after ART.

Results: 17 AHI and 20 CHI were studied (ages 19-66 years), including a total of 160 independent QVOA measures (median 4 per patient at median 3 months intervals; median 1.2 years RCI follow-up). Median ART duration at first RCI was 21 months AHI, 78 months CHI. CD4 count at first RCI was 744 cells AHI, 584 CHI. RCI significantly declined over time ($p<0.001$) with estimated mean (95% CI) half-life = 3.6 (2.3-8.1) years. There was no evidence of more rapid decay for AHI vs. CHI ($p=0.99$) after ≥12 months of ART. From the model, the estimated SD for the change in log10 RCI for a patient = 0.38, implying that a >2.5 fold RCI decrease over 2 months would have likelihood 0.16 (16%) under stable ART. A >6 fold RCI decrease would have likelihood 0.023 (2.3%). Empirically evaluating the 123 pairs of consecutive RCI measures, 81 (66%) had <2 fold increase or decrease; 21 (17%) had >2.5 fold decreases and 3 (2.4%) had >6 fold decreases.

Conclusions: Consistent with prior studies, RCI decayed with a half-life of 3.6 years (43 months). Based on using large numbers of cells obtained via leukapheresis, RCI was reliably estimated with longitudinal measurements generally showing <2 fold variation from the previous measure. RCI decreases >6 fold were rare on stable suppressive ART, suggesting a potential threshold to identify effects of anti-latency therapeutics on RCI.

Session P-F5 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

What and Where Is the Reservoir?

407LB The Role of HIV Integration Sites in Extensive Clonal Expansion of Infected Cells in Patients

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Background: Despite successful suppression of HIV by combination antiretroviral therapy (cART), infected cells persist for many years in patients. Long-term control of viremia by cART reveals clonal viral genomes in the blood of most patients, implying clonal expansion of some HIV infected cells. The mechanisms driving clonal expansion are unknown, but are central to HIV persistence. To address this issue, we determined the distribution of proviral integration sites in 5 patients on successful cART using a specific and highly sensitive amplification strategy that yields large numbers of virus-host junctions, identifies their exact location, and measures the relative degree of clonal expansion.

Methodology: DNA was prepared from PBMCs from 5 patients, randomly sheared, and linker-mediated PCR was used to selectively amplify both the 5' and 3'-LTR integration site junctions, whose sequences, as well as those of the sheared breakpoints in the host DNA, were determined by Illumina paired-end sequencing. Clonal expansion of infected cells was demonstrated by the presence of DNA fragments with exactly the same integration site and different host DNA breakpoints.

Results: Analysis of integration site libraries comprising >2000 independent integration events revealed clonal expansion of HIV infected cells in all patients studied. In one patient, about half of the infected PBMCs were derived from a single infected cell. Infected clones persisted in patients for at least 11 years. Integrations in the same orientation in a specific intron of two different genes (MKL2 and BACH2), were seen in independent clones from more than one patient. In one patient, we detected 669 unique sites, of which 14 were in different expanded clones derived from independent integration events in a single 3.5 kb intron of MKL2, and 12 were in a single intron of BACH2. These data show that the expression of these genes must have been affected by these integrations in ways that made a critical contribution to the clonal expansion and/or persistence of the infected cells. Both these genes have been linked to the control of cell growth and human cancers. Other genes associated with cell growth (e.g., PAK2, STAT5B, and CYTH1) in which HIV DNA integration may have contributed to clonal expansion and persistence, were also identified in more than one patient.

Conclusions: Extensive expansion of HIV infected cell clones, some persisting for >11 years, demonstrates that the reservoir of infected cells in patients is maintained, at least in part, by cell division. Although the HIV provirus may serve as a passive marker of clonal expansion, our results show that the HIV integration site can also make an important contribution to the expansion and/or persistence of infected cell clones.

408 Identification of a New Th17 Subset That Contributes To HIV-1 Persistence in ART-Treated Subjects

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Background: Th17 cells play a critical role in mucosal immunity against bacterial pathogens. Th17 cells are depleted from the gut-associated lymphoid tissues of HIV-infected individuals and their functional restoration under antiretroviral therapy (ART) is only partial. We previously reported that Th17 cells exhibiting a CXCR3-CCR4+CCR6+ phenotype (CCR4+CCR6+ Th17) are permissive to HIV infection and their frequency is diminished in chronically HIV-infected subjects receiving viral-suppressive ART (CI on ART). We recently identified a new subset of Th17 cells with a CXCR3-CCR4-CCR6+ phenotype (double negative, DN CCR6+) that expressed RORC mRNA. Here, we investigated the relative contribution of DN CCR6+ and CCR4+CCR6+ Th17 cells to immunity and HIV pathogenesis.

Methodology: Leukapheresis from CI on ART subjects (n=24; CD4 counts >318 cells/μL, plasma viral load <50 HIV-RNA copies/ml) and uninfected controls (n=21) were available for these studies. Highly pure memory Th17 subsets were sorted by flow cytometry and stimulated via CD3/CD28. Lineage-specific cytokines and transcription factors were quantified by ELISA and RT-PCR, respectively. Antigenic-specificity and polarization profiles were determined by flow cytometry analysis of T-cell proliferation (CFSE dilution assay) and cytokine expression (intracellular staining), respectively. HIV replication and integration was measured by ELISA and real-time PCR, respectively.

Results: Similar to CCR4+CCR6+ Th17, DN CCR6+ cells produced IL-17A, and proliferated in response to Candida albicans (a Th17 antigen) but not Cytomegalovirus (a Th1 antigen). The stability of the Th17 profile in DN CCR6+ and CCR4+CCR6+ Th17 cells was proved upon long-term culture under Th17 or Th1 conditions in vitro. DN CCR6+ distinguished from CCR4+CCR6+ Th17 cells in their ability to produce high levels of IL-17F and low levels of IFN-γ. As opposed to CCR4+CCR6+ Th17, the frequency of the DN CCR6+ cells was preserved in HIV-infected subjects. Finally, DN CCR6+ cells were permissive to R5 HIV infection in vitro and levels of integrated HIV-DNA were similarly high in DN CCR6+ and CCR4+CCR6+ Th17 cells isolated from CI on ART HIV-infected subjects.

Conclusions: Our results reveal the existence of a new previously uncharacterized subset of Th17 cells with a DN CCR6+ phenotype. Because they are preserved in frequency during HIV infection and carry integrated HIV-DNA in CI on ART subjects, DN CCR6+ Th17 cells may particularly contribute to HIV persistence under ART. These studies provide a new understanding of Th17 heterogeneity in the context of HIV pathogenesis. Mechanisms by which HIV-infected DN CCR6+ Th17 cells avoid killing by CD8+ T-cells and/or NK cells thus persisting in HIV-infected subjects remain to be investigated.

409 Identifying Defective and Identical Viral Genomes in HIV Reservoirs During Effective HIV Therapy

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Background: A thorough understanding of the distribution of replication-competent virus will be needed to design future HIV eradication therapies. We studied the distribution of replication defective viral genomes in memory T cell subsets in blood and lymph nodes of long-term treated subjects. We also examined the distribution of clonal sequences in order to define the role of homeostatic proliferation as a cause of persistence.

Methodology: Using single-proviral sequencing we isolated intracellular HIV-1 genomes derived from defined subsets of CD4+ T cells (naïve, central (CM)-, transitional (TM)-, and effector (EM)-memory) from peripheral blood and lymph node tissue. Samples were collected from 8 subjects on suppressive therapy (4-12 years): 5 who initiated therapy during early infection and 3 during chronic infection. G-to-A hypermutants were identified using the Hypermut program within the Los Alamos HIV Database. Levels of APOBEC 3F and 3G (A3F and A3G) were measured in T cells (CM, TM and EM) from blood and lymph node tissue using a gene expression sybr green method. Additional defective viral genomes were determined by stop codons or large deletions. Identical sequences were identified by phylogenetic analysis.

Results: The percent of cells infected with hypermutants was estimated to be 31% lower in CM cells than it was in EM cells (p=0.54), and it was estimated to be 35% higher in TM cells than in EM cells (p=0.51) but the percent of cells infected with other defective viral genomes tended to be higher

for EM than CM (38-fold, p=0.0024) and TM (11-fold, p=0.0028). In both blood and lymph node tissue the gene expression of A3G and 3F was highest in EM T cells (EM>TM>CM). The estimated proportion of viral genomes that were hypermutants in subjects treated during early versus chronic infection was similar for all three cell types (<1.6-fold differences), but in EM cells the proportion of all viruses that had other defects was estimated to be >20-fold higher for chronic than early (p=0.018). Phylogenetic analyses showed expansions of identical HIV-1 sequences in all subjects treated during chronic infection; these expansions were predominantly found in EM T cells.

Conclusions: We found that the estimated proportion of HIV genomes during long-term ART that were hypermutants was similar in cells from subjects treated during early and chronic infection, suggesting that these genomes are established soon after infection. We also found >10-fold higher rates of non-hypermutant defective viral genomes in EM cells than either CM or TM cells in blood. These defective genomes and identical HIV-1 sequences predominated in EM T cells of specific subjects, suggesting that they were maintained by clonal expansion of T cells as they differentiated into more terminal cell populations.

410 Healthy HIV-Infected Subjects Harbor HIV in Alveolar Macrophages, Which Can Impair Lung Function

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Background: Alveolar macrophages are specialized innate immune cells that reside in the alveolus, a site with different concentrations of some medications compared to the blood compartment. Alveolar macrophages can be infected by HIV-1 as they express CXCR4 and CCR5, and HIV reverse transcriptase has been detected in alveolar macrophages from humans. The half-life of alveolar macrophages is significantly longer than that of an activated lymphocyte (months/years versus hours/days). However, reports quantifying the burden of HIV in alveolar macrophages are conflicting, and it is unclear what impact the infection has on alveolar macrophage function. We hypothesize that the alveolar macrophage is an important reservoir for HIV, contributing to cell-cell spread of the virus within the lung and exhibiting abnormal function, which contributes to the increase risk of severe lung infections.

Methodology: We conducted a pilot study on healthy HIV-infected subjects who did not have major medical co-morbidities or smoke cigarettes. All subjects underwent bronchoscopy and bronchoalveolar lavage with 180mL of normal saline. Alveolar macrophages were isolated and HIV-1 RNA was quantified in the cells using the Abbott RealTime HIV-1 Assay (Abbott Molecular Inc. Des Plaines, IL), an in vitro reverse transcription-polymerase chain reaction assay. Proviral DNA was qualitatively measured using a modified version of the above-mentioned HIV-1 RNA viral load assay. To measure phagocytic function, alveolar macrophages were isolated and incubated for 1 hour with FITC-labeled S. aureus in a 10:1 ratio. FITC-labeled bacteria containing cells were measured by flow cytometry. Phagocytic index was calculated as follows: (% positive cells x mean channel fluorescence)/100.

Results: We enrolled 22 otherwise healthy HIV-infected subjects (median CD4 count=409/µl, 82% with undetectable plasma viral load). HIV-1 proviral DNA and/or quantitative RNA were detected in 82% of the alveolar macrophages; 78% of this group had an undetectable plasma viral load and 94% were on anti-retroviral therapy. HIV-1 RNA levels ranged from 48 to 2305 copies/mL. Further, HIV-infected subjects with proviral DNA present had decreased alveolar macrophage phagocytosis of FITC-labeled S. Aureus compared to subjects without proviral DNA present [16.6 (IQR 6-45.2) vs. 33.1 (IQR12.2-172.1)].

Conclusions: Alveolar macrophages harbor HIV even in otherwise healthy subjects with undetectable plasma viral loads, representing a potential reservoir for the virus. In addition, HIV viral replication within the macrophage may impair phagocytosis and other immune functions in the lung, leading to an increased risk for lung infection.

411 Quantitative and Phylogenetic Analyses of Persistent HIV in Blood and GALT During Long-Term cART

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Background: HIV infection results in profound effects on gut associated lymphoid tissue (GALT), and combination antiretroviral therapy (cART) only partly reverses HIV-induced destruction. The role of GALT in ongoing HIV persistence remains uncertain. Previous studies have analyzed HIV sequences obtained from pools of multiple pinch biopsies; the degree of sampling variation in individual biopsies is unknown, but pooling may introduce significant bias in estimating the size and structure of HIV populations. To quantify the distribution of infected cells, and determine the phylogeny of local HIV populations within the gut mucosa, we analyzed endoscopy-derived material as individual or small pools of biopsies. We compared viral populations in gut to those obtained from contemporaneous and pre-therapy plasma and peripheral blood mononuclear cells (PBMC)

Methodology: Eight HIV infected patients on suppressive cART for 2-10 years were enrolled. Plasma and PBMC were obtained prior to cART and at time of colonoscopy; small jaws forceps were used to obtain random biopsies from colon and from ileum, when possible. Biopsies were collected as individual snips or pooled in groups of 2-8 snips. Ultrasensitive qPCR assay targeting *gag* was performed to quantify HIV-DNA and RNA copy number; total cell number was determined by qPCR of CCR5 gene. Single genome sequences (SGS) from plasma RNA, PBMC-derived DNA, and gut-derived DNA and RNA were obtained and underwent phylogenetic analysis (MEGA).

Results: We obtained 6-12 individual pinches from colon in each subject and 6-12 pinches from ileum in 5/8 patients. Single copy detection revealed HIV DNA in all pinch biopsies, with a relatively stable DNA copy number (mean 291 cps/10^6 cells, range 83-741, overall patients). In contrast, HIV RNA levels were more variable and ranged <12-220 HIV RNA cps/10^6 cells. No evidence of compartmentalization was detected, either between gut and peripheral

blood or among pinches. Clones of identical sequences were detected in plasma and PBMC and were also present in gut DNA and RNA. Clonal HIV sequences were identified from multiple snips, suggesting that clones were not anatomically restricted. No genetic divergence from pre-therapy HIV was detected in gut or blood-derived HIV, even after >10y of cART.

Conclusions: HIV proviruses are extensively and uniformly distributed throughout the GALT with an estimated 100 million infected cells present in colonic mucosa despite prolonged cART; HIV RNA production varied considerably among pinches. Clonally expanded populations present in gut mucosa were not anatomically restricted, and were not divergent from pre-therapy HIV. Detection of the same identical sequences in gut derived DNA, RNA, and plasma suggests that GALT can be a source of persistent viremia on ART.

412 The Immune Checkpoint Blockers PD-1, LAG-3 and TIGIT Are Associated With HIV Persistence During ART

Remi Fromentin[1], Sandrina DaFonseca[1], Wendy Bakeman[1], Gabriela Khoury[2], Elizabeth Sinclair[3], Frederick Hecht[3], Steven G. Deeks[3], Sharon R. Lewin[2, 4], Rafick P. Sekaly[1], Nicolas Chomont[1]

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Background: The persistence of HIV in a small pool of long-lived latently infected resting CD4 T cells is a major barrier to viral eradication. Interfering with the immunological mechanisms that maintain latency in these cells may lead to novel therapeutic strategies to cure HIV infection. Several immune checkpoint blockers (ICBs) have been shown to actively reduce T cell activation, proliferation and cytokine production in CD4 T cells. We hypothesized that expression of one or several of these ICBs contribute to HIV persistence by continuously and actively promoting HIV latency in infected CD4 T cells.

Methodology: Expression of PD-1, CTLA-4, LAG-3, TIGIT, TIM-3, BTLA, 2B4 and CD160 were measured by flow cytometry on PBMCs from 48 subjects on ART for >3 years with HIV viral load inferior to 50 cop./mL and a CD4 count > 350 cells/µL. The frequencies of CD4 T cells harboring integrated HIV DNA, total HIV DNA, 2-LTR circles and cell associated unspliced (CA-US) HIV RNA were determined by qPCR. Integrated HIV DNA was also measured in sorted memory CD4 T cell subsets expressing some of these ICBs. More specifically, the impact of PD-1 engagement on HIV latency was evaluated in CD4 T cells isolated from virally suppressed subjects using beads coated with anti-CD3, anti-CD28, PD-L1 or the appropriate control.

Results: Absolute CD4 T cell counts were negatively correlated with the expression of PD-1, LAG-3 and TIGIT in CD4 T cells ($r=-0.53$ $p<0.0001$, $r=-0.51$ $p=0.0002$, $r=-0.40$ $p=0.005$, respectively). Interestingly, the frequency of CD4 T cells harboring integrated HIV DNA was positively correlated with the expression of these markers ($r=0.29$ $p=0.06$, $r=0.31$ $p=0.04$ and $r=0.46$ $p=0.002$, for PD-1, LAG-3 and TIGIT, respectively). With the exception of TIGIT with 2-LTR circles ($r=0.39$ $p=0.009$), no statistically significant associations were found between these markers and total HIV DNA, 2-LTR circles or CA-US HIV RNA. Memory CD4 T cells expressing high levels of PD-1 or LAG-3 were enriched for HIV integrated DNA when compared to their negative counterparts. Engagement of PD-1 with its ligand PD-L1 inhibited viral production induced by TCR stimulation in latently infected cells (mean=94.8 % of inhibition), suggesting a functional role for this receptor in the maintenance of HIV latency.

Conclusions: We identified PD-1, LAG-3 and TIGIT as markers associated with incomplete CD4 T cell restoration and HIV persistence during ART. Our data further demonstrate that PD-1 and LAG-3 identify cells carrying integrated HIV DNA in virally suppressed subjects. Collectively, these data suggest that a limited number of specific ICBs may actively promote HIV persistence during ART. Interfering with PD-1 and LAG-3 signaling may disrupt HIV latency and paves the way for the development of novel curative strategies.

413 Distinct Patterns of TLR-Mediated HIV Reactivation in Latently-Infected Microglia vs Monocytes

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Background: Toll-like receptors (TLRs) recognize molecules derived from microbes and play a key role in mediating innate immune responses. Multiple TLRs are typically expressed in cells of the monocytic lineage, including microglia. Microglial cells constitute the major reservoir for HIV infections in the brain, where inflammatory conditions in the central nervous system (CNS) are believed to induce HIV-associated neurocognitive disorders (HAND).

Methodology: Microglial cells pseudo-infection and culture, treatment with TLR agonists and cytokines, flow cytometry, and fluorescence microscopy.

Results: Using HIV-latently infected microglial cell lines, we investigated whether TLR stimulation can induce HIV transcription. Treatment with a panel of TLR ligands, including Mycobacterium tuberculosis (Mtb)-derived molecules, we found that, unlike in monocytic cells, reactivation of HIV by TLR ligands was significantly restricted in microglia. Flagellin (TLR5 agonist) and, to a lesser extent, lipopolysaccharide (LPS; TLR4 agonist) were able to reactivate HIV in hTERT-immortalized glial (hT-Hμglia/HIV) and in SV40-immortalized (CHME-5/HIV) human fetal microglial cells. In the presence of IL-1β, a cytokine over-expressed in HAND patients, Pam3CSK4 (TLR1/2 agonist) can also reactivate HIV. By contrast, agonists for TLR1, 2, 4, 5, 6, or 8 (but not for TLR3, 7, or 9), potently reactivated HIV in THP-1/HIV cells and, to a lesser extent, in U937/HIV and SC/HIV monocytic cells in an NF-κB-dependent manner. Mtb-derived molecules PIM6 and LprG, which are potent TLR2 agonists, reactivated HIV in THP-1/HIV, but not in U937/HIV or SC/HIV cells which, unlike THP-1/HIV, showed no significant expression of TLR2.

Conclusions: We conclude that TLR signaling probably plays a minor role in activating HIV replication in the CNS that can be potentiated in the context of brain inflammation, but can potentially drive replication in peripheral monocytic cells.

414 CXCR3 and CCR5 Expression Are Associated With 2LTR Circles in Patients On Antiretroviral Therapy

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Background: Identifying a subset of T-cells that are enriched for HIV infection in patients on suppressive antiretroviral therapy (ART) will be critical to developing new curative strategies. This study aimed to assess how the expression of inflammatory (CCR5, CXCR3, CCR6, CXCR5) and homeostatic (CCR7) chemokine receptors (CKR) and their ligands correlate with the size of the latent reservoir in patients receiving suppressive ART.

Methodology: 48 subjects on ART for >3 years with HIV viral load <50 copies/ml were recruited in San Francisco. Using flow cytometry, we quantified the expression of the CKR CCR5, CXCR3, CCR6, CXCR5 and CCR7 on CD4+ T-cells. The corresponding ligands for these chemokine receptors were quantified in plasma (Luminex). Total, integrated and 2LTR circle HIV DNA and cell associated unspliced (CA-US) HIV RNA was quantified in CD4+ T-cells. Spearman correlations and negative binomial regression models were performed to test associations between markers of virus persistence and CKR expression on CD4+ T-cells adjusting for current and nadir CD4 T-cell counts.

Results: Subjects were predominantly male (96%) with a median CD4= 684 (IQR=533-858) cells/μl. There were statistically significant negative correlations between current CD4 count and expression of the inflammatory CKR CCR5 (r=-0.50, p<0.001), CCR6 (r=-0.42, p<0.01) and CXCR3 (r=-0.57, p<0.0001) and a positive correlation with the homeostatic CKR CCR7 (r=0.59, p<0.0001). There was a statistically significant negative correlation between integrated HIV DNA and current CD4 (r=-0.52, p=0.0001) but not nadir CD4. CCR5 was the only CKR that substantially correlated positively with integrated HIV DNA (r=0.29, p=0.045) but this largely disappeared when controlled for current or nadir CD4 count in a negative binomial regression model. 2-LTR circles were negatively correlated with nadir CD4 (r=-0.45, p=0.002) but not current CD4. In a negative binomial regression model, 2LTR circles were positively correlated with CXCR3 expression (p<0.001) and CCR5 expression (p=0.032) and both remained statistically significant after adjusting for nadir or current CD4 count. There was no significant relationship between total HIV DNA, CA-US RNA and CKR expression. There was no statistically significant relationship between virus persistence and any of the chemokines measured in plasma, except for a positive correlation between 2LTR circles and the ligand for CCR7, CCL21 (r=0.30, p=0.045).

Conclusions: The association of 2LTR circles with nadir CD4 and CXCR3 and CCR5 expression on CD4 T-cells raises the possibility of ongoing replication in cells that express these specific inflammatory CKR, such as effector memory T-cells, particularly in individuals who initiate ART at lower CD4 counts.

415 CD4+ and CD8+ T Cell Activation Are Strongly Associated With HIV-1 DNA in Resting CD4+ T Cells

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Background: The association between the host immune environment and the size and between multiple measurements of the reservoir (Eriksson et al, PLoS Path 2013). Here, we explored the association between HIV persistence as defined by these assays and the level of T cell activation and function.

Methodology: We performed multiple simultaneous measurements of HIV persistence and analyzed their association with immune function and T cell activation in 30 antiretroviral-treated adults: 10 who started therapy during acute infection and 20 who initiated treatment during chronic infection. All individuals were on a suppressive antiretroviral regimen for at least 36 months and had > 350 CD4 cells/ul. The following assays were performed on patient samples: viral outgrowth, digital droplet PCR (ddPCR) for HIV-1 DNA and 2-LTR circles in PBMCs and resting CD4+ T cells, Alu PCR for integrated HIV-1, and a single copy assay for plasma virus. Flow cytometry was performed to measure frequencies of activated and HIV-specific T cells in blood. Spearman rank correlation coefficients were calculated.

Results: The most consistent host response associated with HIV persistence was frequency of "activated" (%HLA-DR+ +/- CD38+) CD4+ and CD8+ T cells. CD4+HLA-DR+ T cells were strongly associated with frequency of resting CD4+ cells containing total HIV-1 DNA as measured by ddPCR (ρ = 0.65, P=0.006). There were similar associations with activated CD8+ T cells (% CD4+HLA-DR+CD38+: ρ =0.51, P=0.04). This association was strongest with activation in central memory and effector memory CD4+ T cells. Other markers of activation including PD-1 and the co-expression of all markers (CD38+HLA-DR+CCR5+PD1+) on CD8+ T cells were also correlated with HIV DNA in resting CD4+ T cells (PD-1: ρ = 0.37, P=0.04). HIV-specific CD4+ T cells expressing TNF-α and IL-21 were positively correlated with total HIV DNA in resting cells by ddPCR (TNF-α: ρ = 0.54, P=0.046, IL-21: ρ = 0.72, P=0.004). Similar non-significant trends were observed with HIV specific CD4+ T cells expressing IL-2 and IFN-γ. Non-significant negative associations were observed between HIV-specific CD4+ T cells and the frequency of latently infected cells by co-culture.

Conclusions: The frequency of CD4+ and CD8+ T cells expressing activation markers and the frequency of HIV-specific CD4+ cells are directly associated with the frequency of resting cells harboring HIV DNA. Although defining causation in this study is not possible, one possibility is that T cell activation drives persistence, perhaps as a consequence of cell proliferation. This may have implications for reactivation strategies, as reversal of latency, in the absence of effective killing and complete suppression of viral replication, could lead to an increase in reservoir size.

Session P-F6 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

What Can We Learn From Bone Marrow Transplantation?

416 Targeting SIV Reservoirs via Autologous Hematopoietic Stem Cell Transplant in Rhesus Macaques

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Background: Despite many advances in the field of AIDS research, a treatment that eradicates the infection remains elusive. A key obstacle to the development of a cure for HIV is an incomplete understanding of the cellular and anatomic nature of viral reservoirs in the setting of successful ART. To address this gap in our understanding, we developed a model of autologous hematopoietic stem cell transplantation (aHSCT) in SIV-infected, ART-treated rhesus macaques (RM) to interrogate the origin of the SIV reservoir.

Methodology: This pilot study included three SIV-infected RM who received aHSCT and three SIV-infected control RM. The transplant procedure involved pre-infection G-CSF mobilization of CD34+ HSC followed by leukapheresis and cryopreservation of collected cells. All RM were then infected i.v. with RT-SHIV. Four weeks post-infection a potent ART regimen including PMPA, FTC, Efavirenz and Raltegravir was initiated. The three experimental RM received total body irradiation (TBI) followed by infusion of the HSC collected pre-infection. ART was interrupted 40 to 80 days post-transplant. Immunophenotyping of PBMC and measurements of plasma SIV RNA and PBMC SIV DNA levels were collected throughout the study. Multiple tissues described as potential virus reservoirs were collected at necropsy for virologic analyses.

Results: As expected, the ART regimen reduced plasma SIV RNA levels to below 100 copies/ml in all six SIV-infected RM. TBI was myeloablative as measured by circulating platelet, white blood cell, and lymphocyte counts and, following aHSCT, engraftment was successful in all three transplanted RM. A rapid viral rebound was observed in plasma in the non-transplanted control RM as early as one week post-ART interruption. Despite TBI and transplant with pre-infection HSC, plasma SIV RNA rebound was also observed post-ART interruption in two out of three transplanted RM. In contrast, no SIV RNA was detected in the plasma of one transplanted RM at week two post-ART interruption. Furthermore, no SIV DNA was detected in the PBMC of this transplanted animal. However, despite the lack of viral rebound in plasma in this transplanted RM, further analysis of various tissue sites revealed the presence of SIV DNA in spleen and lymph nodes, but not in the gastrointestinal tract.

Conclusions: To the best of our knowledge, this model of SIV/HSCT has never been attempted before. SIV infection followed by aHSCT in virally-suppressed ART-treated RM allows for critical assessment of hematopoietic and non-hematopoietic HIV/SIV reservoirs. Early evidence from this study suggests that non-hematopoietic reservoirs contribute to HIV/SIV persistence. The results of this work may be translated into novel HIV cure strategies.

417 Dynamics of HSPC Repopulation in Non-Human Primates Revealed by a Decade-Long Clonal Tracking

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Background: Hematopoietic stem cell and progenitor cell (HSPC)-based genetic therapy to treat HIV or other previously incurable diseases is becoming increasingly realistic. To date, however, our understanding of the regenerative potentials of primate HSPCs lags far behind the level desired for current and future uses of these cells for therapeutic purposes.

Methodology: We report detailed behavior patterns of repopulating HSPCs in four rhesus macaques transplanted for up to 12 years with autologous CD34+ HSPCs engineered with control lentivirus vectors expressing a fluorescence marker (EGFP) or therapeutic vectors expressing shRNA against the HIV-1 co-receptor, C-C chemokine receptor type 5 (CCR5-shRNA). All animals showed normal hematopoietic recovery and maintained stable EGFP marking in all tested blood lineages. In order to study in vivo HSPC behaviors at the single cell level, vector marked clones in serially collected blood were analyzed by large-scale vector integration site (VIS) sequencing and bioinformatics analysis of genomic VIS sequences.

Results: Our long-term clonal tracking study revealed novel mechanistic insights into complex polyclonal hematopoietic reconstitution in primates, not seen in traditional population-based studies. Analysis revealed thousands of HSPC clones successfully engrafted and expanded sequentially over time in each animal, clustered into groups with different kinetics of repopulation, maintaining the total marked blood cells at a relatively stable level over the years. Consistent with recent discoveries in murine HSC studies, the long-term repopulating clones were distinctively grouped into “myeloid-biased”, “lymphoid-biased”, and “balanced” subtypes based on their unique lineage output potentials. Interestingly, clones with more balanced lineage potentials, accounted for only 4 – 10% of the identified clones, yet predominated, contributing up to 25 – 71 % of total repopulating cells in test animals. No notable effect of CCR5-shRNA expression upon clonal repopulation was observed.

Conclusions: This study is the first system level description of the detailed in vivo behavior patterns of primate HSPCs, providing new insights into primate repopulation and a potential frame of reference for future HSPC-based gene-therapies.

418 Impact of Systemic Cytotoxic Chemotherapy for Malignancies On HIV-1 Reservoir Persistence

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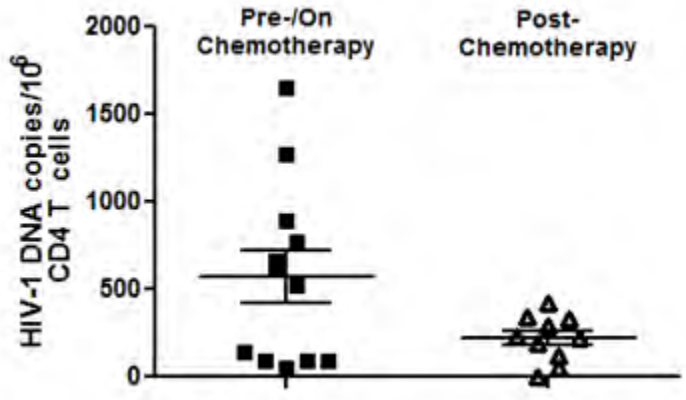
Background: The effects of cytotoxic chemotherapeutic agents on viral reservoir size are not well understood. Therefore, we studied the longitudinal effect of combination chemotherapy for hematologic malignancies and single-agent chemotherapy for Kaposi Sarcoma (KS) on HIV-1 reservoir size.

Methodology: HIV-infected individuals with a diagnosis of malignancy, including hematologic malignancies, KS and Multicentric Castleman's Disease (MCD) requiring systemic chemotherapy were enrolled. Large volume peripheral blood collections were performed at time points before, during, and post-chemotherapy. Flow cytometric characterizations of T lymphocyte subsets were performed and viral DNA and RNA were extracted and quantified from purified CD4+ T cells using sensitive real-time PCR assays. Residual plasma viremia was also quantified using a single-copy RNA assay.

Results: We obtained 28 samples from 15 patients (KS/MCD = 4, Hodgkin = 2, non-Hodgkin lymphoma = 9). In an analysis of all participants, a non-significant decrease in CD4+ T cell-associated HIV-1 DNA was observed between the pre- or earliest on chemotherapy time-points and the first post-chemotherapy time-point (median 576 and 228 copies/10^6 CD4+ T cells, P=0.26 from paired analysis; see Figure). A non-significant decrease in DNA was also observed in a subset of patients on stable antiretroviral therapy with all viral loads <1000 copies/mL (N=13, median 523 and 213 copies/10^6 CD4+ cells, P=0.39). No significant changes in CD4+ T cell-associated RNA were observed, and the frequency and amplitude of residual viremia were similar across time-points. One patient with both angioblastic T-cell lymphoma and B-cell lymphoma had undetectable HIV-1 DNA and RNA from purified CD4 T cells and no detectable viremia by Cobas Taqman PCR viral load assay after 8 cycles of salvage chemotherapy with brentuximab and high-dose methotrexate. The patient died from recurrent CNS disease pending allogeneic stem cell transplantation.



Conclusions: Peripheral blood HIV-1 reservoirs persist after cytotoxic chemotherapy, although one patient had undetectable cell-associated DNA and RNA on salvage chemotherapy for T cell lymphoma. These findings suggest that cytotoxic chemotherapy may have an impact on viral reservoir size, but this effect may vary depending on specific oncologic, chemotherapeutic and viral disease factors. Further investigation of immune function, inflammation and activation in this cohort is warranted.

419 Modeling Functional Cure of HIV in Nonhuman Primates Using Gene-Modified Hematopoietic Stem Cells

Hans-Peter Kiem[1], Christopher W. Peterson[1], Patrick M. Younan[1], Shiu-Lok Hu[2], Patricia Polacino[2], Michael Holmes[3], Philip Gregory[3], Jianbin Wang[3]
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Background: Following hematopoietic stem cell (HSC) transplantation and withdrawal of combination antiretroviral therapy (cART), three previously HIV$^+$ patients remain free of measurable replication-competent virus. These results suggest that HSC transplantation represents a promising strategy to induce a functional cure. To better understand the mechanism of HSC-driven HIV control, and apply this therapy to a greater number of patients, we are developing a model of 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*.

Methodology: 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 transgenic expression of the anti-fusion peptide mC46. Engraftment, persistence, and SHIV response of these autologous stem cells, and stem cell-derived lymphoid and myeloid cells, are measured *in vivo*.

Results: SHIV infection in the pigtailed macaque model results in sustained viremia with consequent reduction in CD4$^+$ T cells. Moreover, administration of three-drug cART to SHIV-infected animals 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. Transplant of mC46-modified HSCs followed by SHIV infection drives positive selection for mC46-modified cell progeny in peripheral blood and secondary lymphoid tissues, resulting in increased CD4$^+$ T-cell counts and an enhanced SHIV-specific immune response against the challenge virus.

Conclusions: Our pigtailed macaque model of HIV infection and cART represents a promising platform for modeling functional cure strategies, including allogeneic transplant. Here we show that expression of mC46 (one strategy for inhibiting HIV infection) protects T-cells from SHIV-dependent depletion by enabling host immune cells to antagonize spreading infection. These data demonstrate that our pigtailed macaque model is suitable for the pre-clinical evaluation of other functional cure strategies including the knockout of CCR5 by zinc finger nucleases. In addition, this 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.

Session P-F7 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Effect of ART On Persistence

420 Patterns of Persistent Viremia After 10 Years of Suppressive ART: ACTG A5276s

Sharon A. Riddler[1], Evgenia Aga[2], Ronald Bosch[2], Joseph J. Eron[3], Rajesh Gandhi[4], Barbara Bastow[5], Margaret Bedison[1], David Vagratian[1], John W. Mellors[1], A5276s Protocol Team

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Background: There is limited information on decay of persistent viremia in patients on long-term ART with HIV-1 RNA < 50 copies(c)/mL. We evaluated patterns of persistent viremia and evidence for ongoing decay in a large cohort of patients on suppressive ART for >10 years.

Methodology: Plasma samples obtained at approximately 4, 7, 10, and 12 years after ART initiation from subjects enrolled in the ACTG ALLRT cohort (A5001) were tested for HIV-1 RNA with a single copy assay (SCA) targeting HIV-1 gag. Selected subjects were ART-naïve at baseline, had HIV-1 RNA <50 c/mL from week 32 of ART forward, with ≥ 3 mL of stored plasma available at each time point. SCA amplification efficiency, compared to the Roche HIV Monitor assay v1.5, was determined from pre-therapy plasma for subjects with SCA < 1 c/mL. The limit of detection of the SCA for 3 mL of plasma was 0.6 c/mL. A decline in the likelihood of HIV-1 RNA being ≥ 1 c/mL during follow-up was assessed using a repeated measures logistic regression model.

Results: Plasma SCA was performed on 4 to 6 samples each from 64 subjects: two measurements were obtained at 4 years of ART (Weeks 192 and 208); and 2-4 measurements were obtained at 2-3 year intervals thereafter. Median duration from ART initiation to last SCA was 11.2 years. Subjects were categorized into 3 groups based on the results at year 4: Persistent viremia (+/+ defined as SCA ≥ 1c/mL at both Weeks 192 and 208; N=17), Intermittent viremia (+/- or -/+; SCA ≥ 1c/mL at 1 of the 2 time points; N=25), or Undetectable (-/-; <1 c/mL at both; N=22). Subject characteristics by group are shown in the Table. Pre-ART HIV-1 RNA levels differed across groups (p=0.027, Kruskal-Wallis) with highest levels in the Persistent viremia group (Table). Subjects with Persistent viremia during year 4 generally had viremia ≥ 1c/mL at years 7 and 10 (65% and 56%, respectively); by contrast, subjects with Undetectable viremia during year 4 rarely had viremia ≥ 1c/mL at years 7 and 10 (14% and 9%, respectively) (Table). In the subset with SCA ≥ 1c/mL at Week 192 (N=27 with total of 111 subsequent SCA measurements) the median SCA at Years 4, 7, and 10 was 1.9, 1.5, and 1.3 c/mL, respectively, and there was no evidence (p=0.55) of a decline in the probability of SCA ≥ 1c/mL over time.

	Total (N=64)	+/+ (N=17)	-/+ or +/- (N=25)	-/- (N=22)
Sex (%) Male	81%	88%	84%	73%
Pre-ART HIV RNA (log_{10} c/mL) Median (1st-3rd quartile)	4.7 (4.4, 5.4)	5.1 (4.6, 5.5)	4.8 (4.4, 5.5)	4.5 (4.2, 4.8)
Pre-ART CD4 (cells/mm^3) Median (1st-3rd quartile)	219 (81, 347)	255 (97, 316)	196 (48, 294)	216 (141, 407)
Duration of ART to last SCA (Years) Median	11.2	10.5	11.0	11.3
SCA ≥1 c/mL (%) ART year 7		65%	32%	14%
ART year 10		56%	36%	9%

Conclusions: The level of residual viremia measured at ~4 years of suppressive ART remained stable for up to 11 years post-ART follow up with no clear evidence for further decay. The mechanisms responsible for stable persistence of different levels of viremia on ART require investigation.

421LB Comparison of Combination ART Regimens for Viral Suppression in SIV-Infected Rhesus Macaques

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Background: Nonhuman primate (NHP) models of human HIV infection, including the most commonly used model involving SIV-infected Indian rhesus macaques, represent an important component of the HIV cure research agenda. Feasible, sustainable combination antiretroviral treatment (cART) regimens to achieve clinically relevant levels of suppression (SIV plasma RNA < 30 copies/ml) are an essential element to enable use of such models in evaluation of experimental HIV cure strategies, but developing such regimens has proven challenging.

Methodology: We compared two different cART regimens (Tenofovir disoproxyl fumarate/Emtricitabine/Dolutegravir; TDF/FTC/DTG vs. Tenofovir disoproxyl fumarate/Emtricitabine/Dolutegravir/Darunavir; TDF/FTC/DTG/DRV), both given as a single, daily, co-formulated subcutaneous injection, in SIVmac239 infected Indian rhesus macaques (n = 3 each), with treatment initiated 2 weeks after intravenous infection. After the initial 4 weeks of treatment, all animals received the TDF/FTC/DTG regimen. We evaluated drug levels, plasma viremia, cell associated SIV RNA and DNA and immune activation.

Results: Both regimens were well tolerated based on clinical and laboratory (CBC and serum chemistry panel) evaluations. Starting from pretreatment plasma viral loads of ~3-4 X 10^7 SIV RNA copies/ml, both regimens provided comparable 4 log declines in plasma viremia over the first 4 weeks of treatment, associated with decreased evidence of SIV infection related immune activation, based on HLA-DR and Ki67 expression. Continued treatment of all animals with TDF/FTC/DTG after the initial 4 weeks of cART produced continued declines in plasma viremia, to < 30 copies/ml in all animals, by 22 weeks post-infection (20 weeks on cART).

Conclusions: Both regimens resulted in prompt, effective suppression of SIVmac239 replication, as reflected by plasma viremia. There was no clear advantage associated with the addition of Darunavir to the regimen during the initial four weeks of treatment, and with continued treatment with TDF/FTC/DTG all animals were suppressed to < 30 copies/ml. TDF/FTC/DTG is an effective suppressive regimen in SIV-infected Indian rhesus macaques, and should facilitate NHP model studies of interventions targeting residual virus in cART suppressed individuals. TDF/FTC/DTG activity was comparable to that of the same regimen using Tenofovir (TFV) instead of TDF evaluated in prior studies; use of TDF instead of TFV in the combination should help minimize potential renal toxicities with long term administration.

422 Impact of RAL/MVC Intensification With or Without HIV-rAd5 Vaccination On HIV DNA: ERAMUNE 02 Study

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Background: HIV eradication may require synergistic interventions that purge latent reservoirs and increase the HIV-specific cellular immune response. DNA prime followed by recombinant adenovirus 5 boost vaccination (HIV-rAd5) has been shown to induce strong CD8+ cytotoxic T lymphocytes responses in HIV-infected and uninfected individuals.

Methodology: Randomized, controlled, non-comparative clinical trial of ART intensification (raltegravir and maraviroc (RAL/MVC)) with or without HIV-rAd5. We included patients having: ≥3 years of HIV-1 RNA ≤500 copies/mL, HIV-1 RNA <40 copies/mL ≥one year, current CD4+ cell count ≥350/mm^3, HIV-1 DNA between 10 and 1,000 copies/10^6 PBMCs and serum Ad5 neutralizing antibody titer ≤ 250. After a lead-in of RAL/MVC intensification for 8 weeks, patients were randomized (1:1) to continue intensification with HIV-rAd5 vaccination [DNA prime at W8-W12-W16 and rAd5 boost at W32 (RAL/MVC/HIV-rAd5 arm)] or continue intensification alone (RAL/MVC arm) for 48 weeks. The primary end-point was >0.5 $\log_{10}$ decrease in HIV-1 DNA at 56 weeks. Secondary end-points included changes in rectal tissue HIV-1 DNA, immunologic changes in peripheral blood, and safety.

Results: We enrolled 28 patients (14 in each arm) on suppressive ART with the following median baseline characteristics: 636 CD4+ cells/mm^3, 672 CD8+ cells/mm^3, 170 HIV-1 DNA copies/10^6 PBMCs, 13 years on ART, and 2.6 years with HIV-1 RNA<40 copies/mL. At week 56, one patient in the RAL/MVC alone arm reached the primary endpoint with a 0.55 $\log_{10}$ decrease in HIV-1 DNA from 156 (W0) to 44 (W56) DNA copies/10^6 PBMCs. Mean PBMC and rectal tissue cell-associated HIV-1 DNA levels did not significantly change after RAL/MVC intensification with or without HIV-rAd5 injections (see table). Peripheral blood CD4+ and CD8+ cell counts did not significantly change from baseline to W56 in either arm (see table). RAL/MVC intensification and HIV-rAd5 vaccination were well tolerated and there were no serious SAEs related to study treatment.

Conclusions: RAL/MVC intensification with HIV-rAd5 vaccination did not reduce the total HIV DNA reservoir in either peripheral blood or rectal tissue. RAL/MVC intensification alone decreased the HIV-1 reservoir by over 0.5 log DNA copies/10^6 PBMCs in one patient.

ERAMUNE 02 Results				
Mean change W0 to W56 in:	**RAL/MVC +HIV-rAd5 (n=14)**	p-value **(W0 vs W56)**	**RAL/MVC (n=14)**	p-value **(W0 vs W56)**
HIV-1 DNA $\log_{10}$ copies/10^6 PBMCs	+0.06	0.46	-0.04	0.73
HIV-1 DNA $\log_{10}$ copies/10^6 rectal cells	+0.06	0.92	+0.14	0.18
CD4+ cells/mm^3	+5	0.97	+50	0.89
CD8+ cells/mm^3	-33	0.60	+35	0.89

423 Impact of Three Different ART Regimens On the GALT: A Randomized Clinical Trial

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Background: Acute HIV infection leads to depletion of the gastrointestinal-associated lymphoid tissue (GALT), driving bacterial translocation, chronic T-cell activation and disease progression. The aim of this study was to evaluate whether ART initiation regimen might determine mucosal recovery, and whether intensification with a fourth drug may achieve better immune reconstitution.

Methodology: In this clinical trial, 33 ART naïve HIV-infected subjects were randomized to three different ART strategies: EFV, MRV or MRV+RAL, each in combination with TDF/FTC. Peripheral blood (PB), rectal biopsies, and duodenal biopsies were obtained at baseline and after 9 months of ART. Tissue was digested into single-cell suspensions for flow cytometry of lymphocyte subsets and activation (HLADR+CD38+) phenotypes.

Results: Twenty-six HIV+ subjects 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] without significant differences between groups. In the EFV, MVC and MVC+RAL arms, median preART CD4 counts were 322, 440 and 453 cell/mm3, (between-group comparisons, P=ns.). All patients achieved complete HIV suppression. Absolute CD4 T-cell counts significantly increased on PB after 9 months of ART by 151 cell/uL [43-386], 239 [128-288] and 281 [120-342], as well as did the %CD4 (delta: 14%, 11%, 17%). The %CD8 significantly declined (delta: 13%, 9%, 17%). However, all between-group comparisons were non-significant, even after adjustment for baseline CD4 T-cell counts. In EFV, MVC and MVC+RAL arms, ART resulted in substantial increases in %CD4 in the GALT, both in duodenal (delta: 10%, 10%, 19%) and rectal mucosa (delta: 21%, 18%, 13%), as well as declines in %CD8 (duodenal delta: -11%, -12%, -20%, and rectal: -21%, -18%, -22%). In the adjusted analysis, the extent of preART %CD4 depletion in duodenal mucosa determined CD4 T-cell recovery, both in PB and GALT (Beta 0.48, P=0.02 and Beta 0.42, P=0.042, respectively), but no effect of treatment was identified.

Peripheral %HLADR+CD38+ CD8+ T-cells significantly decreased in blood at 9 months post ART, the largest decrease was observed in the MVC+RAL arm (delta: -25%, -24%, -34%; between-group comparisons, P=ns). Changes in CD8+ T-cell activation in the GALT were modest compared to those observed in blood [duodenum, delta: -6%, -9%, -29%; colon, delta: -19%, -5%, -5% (between-group comparisons, P=ns)].

Conclusions: Results of this pilot clinical trial in HIV-infected subjects suggest that CD4 depletion at GALT at ART initiation determine CD4 recovery. Overall, initiation with a quadruple ART regimen showed better immunological restoration in blood and GALT, but the differences remained non-significant and larger studies will be needed to confirm this hypothesis.

424 HIV Reservoir Changes in Resting CD4 Subsets in the IL7 Plus ART Intensification Eramune-01 Study

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Background: The ERAMUNE01 trial showed that a year of MVC+RAL intensification alone or with 3 IL7 injections in treated chronic HIV+ patients did not decrease cell associated HIV DNA. IL7 induced a strong transient CD4 T cells increase affecting mainly the CM subset. To further understand the effects of IL7 we evaluated distribution and characteristics of viral reservoir among the distinct resting CD4 T cell subsets.

Methodology: We sorted resting CD25-69-DR-CD4+ N, CM, TM and EM T subsets at D0 and W56 from RAL+MVC and RAL+MVC+IL7 arms (6+6 pts). In each sorted sample: 1) HIV DNA was quantified per 10*6 subset cells, reported to absolute subset count and analysed for subset contribution to total HIV reservoir, using nonparametric tests; 2) HIV inducibility was tested in vitro with or without IL7 or antiCD3+CD28+IL2+IL7 D0 stimulation, amounts of HIV RNA released in supernatants being normalized for HIV DNA content 3) Transcriptome was analysed using the human genome wide microarray Platform 4) Unspliced HIV RNA transcripts from total CD4 were detected using qPCR (GAG gene).

Results: At D0 reservoir distribution did not significantly differ among sorted resting CD4 subsets despite a higher contribution of CM than EM in RAL+MVC+IL7 (p 0.01). At W56 cell HIV DNA did not change in any RAL+MVC subset. At W56 RAL+MVC+IL7 CM reservoir did not significantly increase though CM delta raw (HIV DNA/10*6 CM p 0.02), absolute values (HIV DNA/CM/mL p 0.008) and fold changes (W56-D0/D0 p 0.04) from baseline increased more than in RAL+MVC. Instead RAL+MVC+IL7 TM HIV DNA raw and absolute values increased at W56 (p 0.03) and when compared to RAL+MVC (p 0.01). Thus the RAL+MVC+IL7 reservoir became skewed towards an increase in TM compared to N as raw values (p 0.02) and an increase in CM and TM compared to EM as absolute values (p 0.04). IL7 alone induced HIV production in vitro from both arms (5/8 CM and 7/8 TM tested subsets); antiCD3+CD28+IL2+IL7 stimulation induced HIV in all tested sorted sample (N, CM, TM, EM at D0 and CM at W56). Ex vivo analysis of HIV RNA transcripts showed no IL7 effect 2 to 46 weeks after IL7 infusions. Similarly no transcriptome changes were observed in any resting CD4 T cell subsets between D0 and W56 in both arms.

Conclusions: A year long strategy combining a cycle of IL7 injections plus MVC+RAL intensification did not show major changes in HIV reservoir among resting CD4 T subsets (except an increase in TM cells with intermediate lifespan) despite IL7 ability to trigger HIV production in vitro, to expand "early" (CM) memory and to decrease more differentiated and senescent T cells. A year after IL7 cycle, distribution of reservoir remains however skewed towards TM with a reduced contribution of short-lived EM cells, suggesting those changes do not simply reflect homeostatic proliferation effects of IL7.

425LB Pre-ART HIV-1 RNA as well as On-Treatment CD8 Count and CD4/CD8 Ratio Predict Residual Viremia On ART

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Background: Prior studies have identified pre-ART plasma HIV-1 RNA level as the strongest predictor of residual viremia on ART but analyses have had limited power to identify other associations. We examined pre-therapy and on-treatment predictors of residual viremia in a large, well-characterized ACTG cohort.

Methodology: Plasma samples obtained 192 and 208 weeks after ART initiation from subjects enrolled in the ACTG ALLRT long-term follow-up study (A5001) were tested with a single copy assay (SCA) targeting HIV-1 gag. Selected subjects were ART-naïve, had HIV-1 RNA <50 c/ml from week 32 of ART forward, and had ≥ 3 ml stored plasma available for each SCA. The limit of detection of the SCA was 0.4-1 c/ml. SCA amplification efficiency compared to the Roche HIV Monitor assay v1.5 was determined by testing pre-therapy plasma for subjects with SCA < 1 c/ml at both on-treatment time points. Subjects with samples showing <10% amplification efficiency were excluded. Logistic regression for repeated measures (using GEE) was used to estimate odds ratios (ORs) for each predictor.

Results: A total of 334 subjects had SCA results at weeks 192 and 208 of suppressive ART. The majority of subjects (82%) were male with pre-ART median age of 40 years, median CD4 cell count 248 cells/mm^3, and HIV-1 RNA 4.7 $\log_{10}$ c/ml. Initial ART regimens were NNRTI + NRTIs (61%), PI + NRTIs (28%), and other (11%). The median CD4 cell count after 4 years of ART (average of weeks 192 and 208) was 588 cells/mm^3. The SCA values (n=668) ranged from <0.4 to 41.4 (median <1; IQR <1, 2.5); among those values ≥1 c/ml (n=296), the median was 2.8 (IQR 1.7, 5.2). In univariate analysis, the likelihood of residual viremia ≥ 1 c/ml was predicted by higher pre-ART HIV-1 RNA (OR 1.79 per 1 $\log_{10}$ [95% CI 1.32, 2.42], p<0.001), higher on-treatment CD8 cell count (average of weeks 192 and 208; OR 1.07 per 100 cells/mm^3 [95% CI 1.02, 1.12], p=0.008), and lower on-treatment CD4/CD8 ratio (OR 0.72 per 0.5 [95% CI 0.58, 0.90], p=0.004). The type of initial ART regimen, sex, race/ethnicity, injection drug use, age, pre-ART or on-treatment CD4 cell count, and pre-ART CD8 cell count or CD4/CD8 ratio were not associated with residual viremia (all p> 0.05). After adjusting for pre-ART HIV-1 RNA, the average CD8 cell count and CD4/CD8 ratio at weeks 192 and 208 remained significant predictors of residual viremia (p=0.014 and 0.031, respectively).

Conclusions: In this large, cross-sectional study, the level of residual viremia was predicted by higher pre-ART HIV-1 RNA as well as by higher on-treatment CD8 cell count and lower on-treatment CD4/CD8 ratio. Whether residual viremia is a cause or consequence of these immunologic differences requires further investigation, including interventions that affect residual viremia or T cell reconstitution.

Session P-F8 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Immunology for Cure

426 Eradication of HIV-1 Reservoirs With Antibody Mediated Killing

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Background: To date, there is no effective cure for HIV-1. The 'shock and kill' approach aims to reactivate the reservoir and target its clearance via immune or therapeutic mechanisms. Beyond T cells, purging the reservoir after reactivation with HIV-specific antibodies that recruit the cytotoxic and antiviral activity of the innate immune system has not been assessed. It has been shown that functional antibodies have a protective effect in HIV-disease progression and were induced in the RV144 vaccine trial. Finding epitopes targeted by functional antibodies on reactivated latent cells could lead to the design of new therapeutic approaches to eradicate HIV reservoirs.

Methodology: Latently HIV-1 infected cell lines (ACH2, J89GFP and U1), were treated for 24 hours with PHA or the histone deacetylase inhibitors (HDACi) vorinostat, panobinostat, or romidepsin and incubated with monoclonal antibodies (mAbs) to Env (n=30) for the detection of various epitopes on reactivated cells. Intracellular p24 or GFP and extracellular Env were detected with flow cytometry. An antibody dependent cellular phagocytosis (ADCP) assay was performed on reactivated ACH2 (Panobinostat). A monocytic cell line, THP-1, were stained by cell trace blue, while ACH2 cells were stained by CFSE and cultured for 4 hours in the presence of mAbs. Percentage phagocytosis was calculated as double positive cells over CFSE alone.

Results: The HDACis, romidepsin and panobinostat induced HIV reactivation (p24 or GFP) to the highest levels in ACH2, followed by J89, and then U1 cells. Latency reversal in all cell types led to an upregulation of surface Env. Different epitopes were exressed on the cell surface as seen by the differential ability of the mAbs to recognize the reactived cells, with 2G12 recognizing the largest fraction of reactivated population. Moreover, antibody-coated reactivated ACH2 cells were efficiently phagocytosed by monocytic THP-1 cells. Interestingly, gp41 antibodies showed the most effective recruitment of ADCP, despite a delayed epitope expression. Finally, antibody mediated elimination of latently reactivated cells exhibited glycan dependent killing, with afucosylated antibodies exhibiting the strongest ADCP.

Conclusions: Here we show that HDACi-reactivated latently infected cell lines robustly expressed Env on the cell surface. More critically, a clear hierarchy was observed among tested mAbs in their ability to recognize reactivated cells, and recruit innate effector activities that can promote efficient killing or eradication of the reservoir. These findings provide a critical footprint for epitopes that a therapeutic vaccine or passive transfer antibodies needs to target that could lead to the rapid elimination of the reservoir, providing a path to a functional cure.

427LB Maraviroc Reverts Latent HIV-1 in ART Suppressed Patients Through NFkB Without Viral Load Increase

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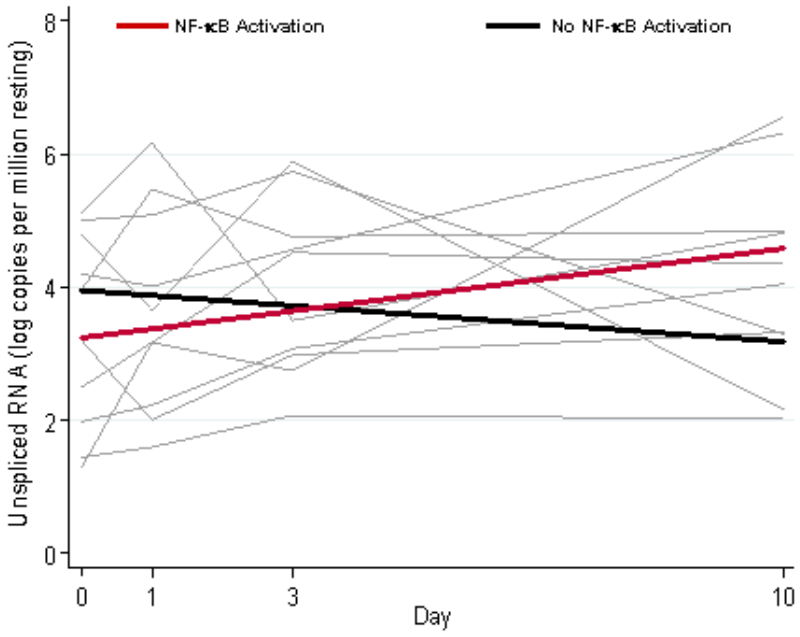
Background: CCR5 intracellular signaling pathways leading to NF-κB, NFAT and AP-1 activation, could promote HIV-1 transcription in resting CD4$^+$ T cells. In previous experiments, we have shown that maraviroc could activate NF-κB and specific target genes in resting CD4$^+$ T cells from viremic and ART

suppressed HIV-1 infected patients. The aim of the current work was to explore HIV-1 transcription, the implicated mechanisms and the effect on HIV-1 viral load.

Methodology: We conducted a clinical trial of 10 days of maraviroc (MVC) intensification in 10 HIV-1 infected adults on suppressive ART (MARAVITRANS; Eudra CT: 2012-003215-66). Blood was collected at baseline, after 1, 3 and 10 days on MVC and 18 days after MVC withdrawal. NF-κB, NFAT and AP-1 activation in resting CD4+ T cells were detected by an ELISA-based kit (Actif Motif). NF-κB activity was estimated measuring target genes' expression by real-time PCR. Cell-associated HIV-1 unspliced RNA (usRNA) was quantified in resting CD4+ T cells by real-time PCR. Viral load was measured by kPCR (Siemens). Significant changes in NF-κB activation respect to usRNA levels were determined using Multilevel Mixed Model analyses.

Results: All patients completed full MVC dosing and follow up. We observed in 8/10 patients an increase in NFκB activation at day 10 and persisted after drug withdrawal in some patients (day 28), including two patients with D/M tropic virus. Upregulation of at least one NF-κB target gene was observed in cases where NF-κB activation was detected.
However, we did not detect activation of NFAT or AP-1 in any patient. The mean log usRNA copies per million resting CD4+ T cells increased across the study (0.3, 0.6, 0.8 and 1.3), but was only significant at day 28 relative to baseline (p=0.014). In the 8 patients in which the presence of MVC was associated with an increase in NF-κB activation, an increase in usRNA was detected in resting CD4+ T cells. Finally, an association between NF-κB activation and usRNA levels could be shown by a Multilevel Mixed Model analysis, which revealed statistical significance at day 10 with respect to baseline (p=0.04) in patients with NF-κB activation (Fig.1). All patients had undetectable plasma viral load at all timepoints, with no blips observed.



Conclusions: Taken together, our data suggest that MVC can activate NF-κB and the subsequent reversion of latent HIV-1 in resting CD4+ T cells from ART suppressed HIV-1-infected patients, without viral load increase.

428 Regulatory B cells Attenuate Anti-HIV CTL Responses After Reactivation of Latent Reservoirs

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Background: To achieve HIV eradication, the mechanisms underlying impaired cytotoxic T lymphocyte function (CTL) during antiretroviral therapy (ART) must be elucidated. In HIV-peptides stimulated samples, IL-10hi programmed-death ligand-1 (PD-L1)hi regulatory B cells (Bregs, CD19+CD24hiCD38hi) attenuate anti-HIV CTL activity. Here we investigate immunoregulatory Breg function in the clinically relevant setting of HIV viral reactivation in vitro using the FDA-approved HDAC inhibitor, suberoylanilide hydroxamic acid (SAHA).

Methodology: We assessed endogenous Breg frequency and phenotype in HIV-infected ART-treated (n=20, HIVART), viremic (n=17, HIVVIR) and uninfected (n=20, HIVNEG) subjects. In SAHA (500nM) treated VPD450 (proliferation dye)-labeled total or Breg-depleted PBMC from HIVART subjects, we evaluated the frequency of CD107a+ and HIV-specific (HIV-Dextramer) CD8+ T cells, CD4+ T cell proliferation, and frequency of p24+CD4+ T cells. We assessed HIV DNA by qRT-PCR and virus in culture supernatant using a TZM-BL binding assay. In Bregs:CD4+ co-cultures, CD4+ T-cell proliferation was determined after IL-10 and PD-L1 blockade.

Results: Compared to HIVNEG subjects Breg-frequency was slightly lower in HIVVIR (p=0.06) and significantly lower in HIVART (p=0.01) subjects. However, Bregs from HIVVIR subjects expressed highest levels of IL-10 (HIVNEG p<0.0001, HIVART p<0.0001). Bregs from HIVART also expressed more IL-10 than those from HIVNEG (p=0.01). Breg PD-L1 levels were comparable in HIVNEG and HIVVIR but about 30% higher in Bregs from HIVART subjects. After SAHA treatment, Breg-depletion led to higher frequencies of CD107a+ (p=0.06) and HIV-specific (HIVgagSL9+, p=0.09) CD8+ T cells. In Breg-depleted samples, enhanced CTL phenotype was associated with 218% more HIV in culture supernatant, a reduction in p24+CD4+ T cells (p=0.02) and integrated HIV DNA (p=0.02). In co-cultures, Bregs significantly inhibited CD4+ T cell proliferation (p=0.03) compared to a non-Breg B-cell subset, and this was partially reversed after antibody blockade of IL-10 receptor and/or PD-1.

Conclusions: Here we present novel data suggesting that during eradication interventions, Bregs attenuate effective CTL responses hindering the clearance of infected cells, hence these cells may represent a barrier to HIV eradication. Bregs via IL-10 and PD-L1 provision, likely modulate critical players required for the generation of effective anti-HIV CTL responses. Our data suggest that, during curative measures, Bregs might be an immunotherapy target to complement reactivation of HIV latent reservoirs.

429 Evaluation of HIV-1 Reservoir Characteristics in a Therapeutic HIV-1 Gag Vaccine Trial

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Background: ACTG A5197 was a placebo-controlled trial of a therapeutic rAd5 HIV-1 gag vaccine in participants on suppressive antiretroviral therapy. The vaccine induced HIV-1 Gag-specific CD4+ interferon-γ-producing cells, which was correlated with lower viral rebound during an analytic treatment interruption (ATI). We investigated the effects of vaccination on HIV-1 reservoir characteristics prior to the ATI.

Methodology: Participants received the vaccine/placebo at study weeks 0, 4, and 26 prior to a 16-week ATI at week 38. Cell-associated HIV-1 RNA and DNA (CA-RNA and CA-DNA) and HIV-1 residual viremia (RV) by a single-copy assay were quantified at weeks 0, 8, and 38. HIV-specific CD4+ and CD8+ activity were assessed by an intracellular cytokine staining assay.

Results: At week 8, after two doses of the vaccine/placebo, modest differences between study arms were noted both in the levels of RV (vaccine [N=65] vs. placebo [N=30]: median 0.7 vs. 1.1 cp/mL, P=0.08) and proportions of individuals with detectable RV (37% vs. 57%, P=0.08). Participants in the vaccine arm with undetectable RV had a significantly higher frequency of both HIV-1 Gag-specific CD4+ interferon-γ-producing cells (undetectable [N=39] vs. detectable [N=24]: 277 vs. 161 cells/106 lymphocytes, P=0.03) and CD8+ interferon-γ-producing cells (undetectable [N=39] vs. detectable [N=24]: 1326 vs. 669 cells/106 lymphocytes, P=0.04). By week 38, however, no significant differences were observed in the numbers of Gag-specific CD4+ or CD8+ interferon-γ-producing cells between those with and without detectable RV in the vaccine arm. Therapeutic vaccination did not induce significant changes in CA-RNA or CA-DNA prior to ATI. At study entry, CA-RNA and CA-DNA levels were correlated with the numbers of HIV-specific CD4+ interferon-γ-producing cells (CA-RNA [N=93]: r = -0.23, P=0.03 and CA-DNA [N=93]: r = -0.28, P<0.01) and CA-RNA was associated with RV (r = 0.23, P=0.04, N=77). These associations weakened after vaccination and were not significant at weeks 8 and 38. Plasma HIV-1 RNA set point during the ATI was significantly associated with pre-ATI week 38 CA-RNA and CA-DNA (CA-RNA [N=90]: Spearman r = 0.51, P<0.01 and CA-DNA [N=93]: r = 0.47, P<0.01).

Conclusions: Early in the vaccination course, higher frequencies of Gag-specific CD4+ and CD8+ cells were associated with lower levels of RV, but this effect waned over time. Higher pre-ATI CA-RNA and CA-DNA levels were associated with higher viral load set point during the ATI, but were not significantly altered by the therapeutic vaccine. In this study, therapeutic HIV vaccination induced HIV-specific T cells, but more potent immune responses may be needed to reduce the latent HIV-1 reservoir.

430LB Engineered TCR-Redirected Clearance of Gag-Positive Reservoir Cells From ART-Treated Subjects

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Background: Combination ART is unable to eradicate HIV infection due to rapid establishment of a reservoir of long-lived latently infected CD4+ T cells. Immunotherapeutic strategies that target viral reservoirs are needed to achieve a functional cure. Immune-mobilising monoclonal T cell receptors (TCRs) have been used successfully to kill cancer cells without the need for ex vivo cellular manipulation. We report on the antiviral efficacy of TCRs that re-direct CD8+ T cells to kill HIV-infected CD4+ T cells (HIV 'ImmTACs').

Methodology: TCRs specific for the immunodominant HIV gag epitope, SLYNTVATL (SL9), and its common escape variants were engineered to achieve picomolar affinity and fused to a humanised CD3-specific single chain antibody fragment (scFv) to create ImmTACs. The potency of these ImmTACs against CD4+ T cells from 10 HLA-A*0201+ patients on ART for >1 year was assessed using CD8+ T cell viral inhibition and killing assays.

Results: Replication of endogenous HIV in CD4+ T cells was significantly reduced by ImmTAC-mediated re-direction of ex vivo autologous CD8+ T cells at CD8+/CD4+ cell ratios of 1:1 and 1:10 (mean, SD: 72%, 14%, p = 0.008; 55%, 15%, p = 0.004 respectively) and at nanomolar ImmTAC concentrations (10-8 - 10-11 M). More profound inhibition (mean, SD: 85%, 8%, p < 0.0001) was achieved using CD8+ T cells from healthy donors, implying a persistent global functional defect in autologous CD8+ T cells from patients despite long-term ART. No significant effect on HIV replication was observed with CD8+ T cells alone or with an irrelevant TCR. ImmTAC-mediated killing was indicated by specific upregulation of caspase-3 in infected CD4+ T cells and by a lack of viral recrudescence after removal of the ImmTAC from cell cultures. Of note, ImmTACs enabled rapid and efficient killing of resting as well as activated CD4+ T cells and their potency was highly correlated with the level of intracellular HIV gag expression (r2 = 0.48, p <0.0001). These data demonstrate that resting CD4+ T cells from patients were susceptible to immune killing. ImmTAC potency was dependent on CD8+ T cell phenotype, with effector memory (CCR7-/CD45RA- and CCR7-/CD45RA+) subsets showing the greatest antiviral efficacy.

Conclusions: HIV ImmTACs can re-direct CD8+ T cells to kill primary CD4+ T cells carrying diverse virus isolates, even when in the resting state. Their potency at low effector/target cell ratios and low epitope densities, coupled with the capacity to harness a large number of effector cells simultaneously, addresses major limitations in adaptive immunity to HIV. ImmTACs have the potential to accelerate clearance of HIV reservoirs.

431 Cross-Clade Inhibition of HIV On Primary Cells by CXCR4 or CCR5 Fused To the C34 Peptide From gp41 HR2

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Background: HIV-1 entry into CD4+ T cells requires binding to CD4 and either the CCR5(R5)or CXCR4 (X4) co-receptor. Thus, strategies that disable productive co-receptor (CoR) engagement should provide potent protection from HIV infection. Previously we described a 34 amino acid peptide from the

C-terminal heptad repeat-2 domain of gp41 (C34) which, when fused to the amino terminus (NT) of either R5 or X4, inhibits HIV-1 infection in transformed cells in vitro. Moreover, our initial studies suggested that C34-R5 or C34-X4 fusions provided trans-dominant resistance to infection irrespective of viral tropism (i.e. either C34-R5 or C34-X4 could inhibit entry of R5, X4 or dual-tropic isolates).

Methodology: Using lentiviral vectors, C34-R5 or C34-X4 fusion constructs were transduced into anti-CD3/CD28-stimulated primary human CD4 T-cells. Controls included GFP alone and C34-conjugated to CD4. Susceptibility to infection by R5, X4, or dual tropic HIV-1 from different clades was assessed by flow cytometry and reverse transcriptase activity (RT). Functionality of the transduced T-cells was determined by evaluating their expansion and intracellular cytokine levels after restimulation with PMA/ionomycin or anti-CD3/CD28 beads.

Results: In CD4 T-cells from multiple donors, when C34-R5 or C34-X4 were expressed, there was almost complete inhibition (>98%) of HIV-1 infection by intracellular p24 levels and RT. GFP-only and C34-CD4 expressing cells were infected at levels similar to untransduced T-cells. C34/CoR expression was >90% on Day 0 and stable during the 14 days of culture. Trans-dominant inhibition by C34-R5 or C34-X4 occurred for X4, R5 and dual-tropic primary isolates from clades B and A/E. Remarkably, when C34-CoR transduced and untransduced cells were titrated (1:4, respectively) and challenged with diverse HIV isolates, a condition that provides a more sustained exposure to HIV, selective enrichment of C34-CoR expressing cells occurred from the expected starting levels of ~25% up to 60% C34-CoR+ cells during viral replication. Lastly, PMA/ionomycin and anti-CD3/CD28 stimulation of C34-R5 and C34-X4 expressing T-cells grew normally and produced levels of intracellular IFNg, MIP-1b, TNFa, and IL-2 that were indistinguishable from untransduced cells.

Conclusions: Engineering primary CD4 T-cells with C34-modified chemokine coreceptors provides potent trans-dominant and heterologous resistance to diverse HIV-1 isolates. This cross-clade protection results in the survival and selective expansion of C34-CoR transduced cells. This novel method of engineering HIV-resistant, functional CD4 T-cells that can be expanded ex vivo and adoptively reinfused represents a promising and innovative approach with the potential to control HIV infection in humans.

Session P-F9 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

Toward A Cure...

432LB Ing-B a Potential PKC Activator for HIV Eradication Is Active in SIVmac251-Infected Macaques

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Background: We here show the potential of a novel PKC activator, a hexanoate derivative of Ingenol (Ing-B) for purging the lentiviral reservoir in SIVmac251-infected macaques. cure. Here we present the preliminary results on a hexanoate derivative of Ingenol (Ing-B) in SIVmac251-infected macaques.

Methodology: In a pilot trial in two SIVmac251-infected macaques, Ing-B was administered in escalating doses (1, 2.5, 5 mg BID) for one week each, alternated with off-treatment weeks. Blood samples were collected at 0, 3, and 7 days post-treatment for for analysis. In another experiment, two SIVmac251-infected macaques were treated with HAART composed by tenofovir, FTC, and raltegravir for 3 months to suppress viral load. After viral suppression, the animals were treated orally with Ing-B (0.2mg/kg BID) for 4 weeks and hematological , toxicological , immunological, and virological parameters were follow up weekly.

Results: In dose escalation trial in non-suppressed animals, Ing-B activated blood leukocytes and transiently increased plasma VL (up to 1 Log) in SIV-infected macaques. Accordingly, plasma viral load and activation markers decreased during the washout periods. Ing-B was less toxic and can be orally administered to animals with no apparent side effects. Env sequencing showed an important turnover of different quasispecies sequences from tissue to plasma in different time points during Ing-B doses. In the second trial on monkeys with suppressed VLs, Ing-B could activate latent virus, resulting in several viral load spikes during 4 weeks on treatment in the presence of HAART. These viremic peaks were preceded by an elevation of CD69+ lymphocytes and monocytes. After removing HAART and Ing-B, the VLs decreased to undetectable levels (<50 copies) in both monkeys and VL control has been maintained for 5 weeks so far. The preliminary results of the ELISpot analysis were in line with the VL trends, displaying anti-Gag immune responses when viral loads became detectable. However, following therapy interruption, cell-mediated responses against Gag decreased and eventually disappeared paralleling the reduction of VL to undetectable levels. Additionally, the CD4+ lymphocytes isolated from the two animals after Ing-B treatment yielded no intracellular vRNA after induction with PMA and ionomycin for 18hs, suggesting its impact on the viral reservoir.

Conclusions: Our data suggest that Ing-B is a viable candidate includable in drug combinations aimed at curing AIDS.

434 SAHA Dampens TCR-Mediated Reactivation of Latently Infected Cells

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Background: Cell activation via T-cell receptor (TCR) stimulation represents a standard step in the analysis of primary cell models of HIV latency. Reactivation from latency using other pharmacological or immunological stimuli is generally benchmarked against the results of TCR signaling. We analyzed the molecular interaction between TCR stimulation and SAHA (a histone deacetylase inhibitor that increases viral transcription) to assess whether these two approaches were synergistic or antagonistic at the molecular level - with the goal of understanding post-transcriptional processing of viral transcripts.

Methodology: We use a CD4+ T_{CM} latency model (Sahu *et al.* 2006, Tyagi *et al.* 2010) that requires sorting of activated and infected cells, followed by reversion to a resting memory phenotype and maintenance of latent cells by co-culture with H80 feeder cells. After 4 weeks of latency, cells were reactivated with anti-CD3/anti-CD28/IL-2 (TCR stimulation), SAHA, or both. Materials were collected at 8h and 24h post-stimulation for viral reporter analysis by FACS and for RNA-seq analysis. RNA data were normalized by added spike-ins, and results are reported under 5% false discovery rate.

Results: In this primary cell model, SAHA was characterized by an increase in viral transcripts at both 8h and 24h post-treatment as compared to DMSO, while increase in viral transcripts upon TCR stimulation was observed mostly at 24 h. Enhancement of virally-encoded GFP translation was observed mainly upon TCR stimulation, regardless of SAHA adjunction. Analysis of variance on transcriptome profiles performed over 14,036 genes revealed that TCR stimulation altered the expression of 8384 genes, enriched for cell metabolism and cell cycle among other pathways, and consistent with the induction of a cellular environment supportive of viral replication. Addition of SAHA dampened the transcriptional response to TCR stimulation: the two responses were anti-correlated ($r=-0.19$, $p<10^{-109}$). In particular, a fraction of TCR regulated genes (n=1064, 13%) showed a significant non-additive response upon SAHA co-administration, which was highly dominated by antagonistic effects (n=953, 90%), suggesting a negative interaction between the two treatments.

Conclusions: The current data suggest that activation of cells treated with SAHA does not improve translation of viral transcripts beyond effects from cellular activation alone. On the contrary, transcriptome analysis indicates that SAHA antagonizes the expression of numerous genes that depend on TCR signaling.

435LB HIV-1 Expression Within Resting CD4 T-Cells Following Multiple Doses of Vorinostat In Vivo

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Background: A single dose of the potent class I histone deacetylase inhibitor (HDACi), vorinostat (VOR) upregulates HIV RNA expression within the resting CD4+ T cells of antiretroviral (ART)-treated, aviremic HIV+ patients. The ability of VOR to repeatedly disrupt latency is unproven, the optimal dosing schema is unknown, and the effect of repeated VOR exposure on host mechanisms that might contribute to viral expression is uncertain.

Methodology: In a Phase I-II single-center study, HIV+ participants maintained suppressive ART, and resting CD4+ T cells were obtained for study via leukapheresis. Following a single VOR 400 mg dose, an increase in resting CD4+ T cell-associated HIV RNA (rc-RNA) was measured in all patients (Archin, Nature 2012), and consenting patients later received VOR 400 mg daily Monday-Wednesday for 4 weekly cycles, followed after a 4-8 week rest period by another 4 weekly cycles. VOR serum concentrations ([VOR]), measurements of histone acetylation within PBMCs, rc-RNA, total cellular HIV DNA, and quantitative viral outgrowth assays (QVOA) from resting CD4+ T cells were obtained. A population PK model was built from all available [VOR] data using nonlinear mixed effects modeling with NONMEM 7.2. The model was used to predict individual [VOR] at the time of leukapheresis and perform exploratory exposure-effect relationships.

Results: In 5 patients VOR was well tolerated with no adverse events > Grade I; mild declines in platelet counts < Grade I were seen at late time points. Repeat dose [VOR] were similar to single dose. However, when measured by leukapheresis after dose 11 (2nd dose of cycle 4) and dose 22 (2nd dose of cycle 8) cellular histone acetylation was little increased from baseline, and measures of rc-RNA only modestly increased in some patients. QVOA and other assays were not significantly affected. [VOR] corresponding to the leukapheresis measurements show an exposure-effect relationship with clock-wise hysteresis, signifying tolerance to VOR over time.

Conclusions: The results of this study suggests that HIV latency is disrupted by an initial VOR dose, but a refractory period of more than 24 hours ensues, which may reduce the responsiveness of the viral promoter to HDACi induction. Attempts to use HDACis to deplete persistent HIV infection will require a detailed understanding of the kinetic effects of HDACis on host cellular functions. Gene expression analysis to understand the complex cascade of events that follow VOR exposure in vivo are ongoing.

436 Autophagy Induction by Histone Deacetylase Inhibitors Inhibits HIV-1 Infection in Macrophages

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Background: Histone deacetylases inhibitors (HDACi) have been shown to induce HIV production from latently infected cells in vitro with the aim to enhance elimination of these cells and achieve a cure. However, the activity of these drugs in non-T-cell reservoirs is unknown. In this study, we investigated the effect of HDACi on the induction of autophagy, and in the replication of HIV within human primary macrophages.

Methodology: Monocyte-derived macrophages (MDM) were treated with HDACi (romidpesin, vorinostat, belinostat, givinostat, or panobinostat) at sub-cytotoxic concentrations and assessed for autophagic flux using the expression and phosphorylation of autophagy proteins and the lipidation of microtubule-associated protein 1 light chain 3B (LC3B) by immunoblotting, qRT-PCR, and fluorescence microscopy. MDM were challenged with 10^5 $TCID_{50}$ HIV-1_{Ba-L} per 5 x 10^5 cells, and replication assessed using HIV p24 antigen release into culture supernatants. The role of autophagy in the HDACi-mediated inhibition of HIV infection was investigated using small molecule inhibitors or by transducing MDM with shRNA for *BECN1* or *ATG5*. Data were analyzed using the Mann-Whitney U test.

Results: HDACi induced autophagic flux in MDM in a dose-dependent manner (belinostat < givinostat < vorinostat < panobinostat < romidepsin) as demonstrated by increased lipidation of LC3B, degradation of sequestosome and increased autophagosome formation ($P < 0.05$) in the absence of increased cell death. We also identified that HDACi induces autophagy through a ULK1 complex-dependent mechanism by suppressing MTOR activity as

indicated by the dephosphorylation of RPS6KB2, EIF4EBP1 and ULK1, the most upstream and essential component of the classical autophagy pathway. HDACi induced autophagy significantly inhibited HIV-1 replication in macrophages over 10 days in a dose-dependent manner that reflected autophagy induction ($P < 0.001$) and was abrogated in the presence of RNAi for autophagy proteins or chemical inhibitors of autophagic flux ($P > 0.05$).

Conclusions: HDACi induces autophagy in human macrophages by releasing the ULK1 complex from inhibition by MTOR-mediated phosphorylation possibly as a prosurvival mechanism to counteract their cytotoxic effects. If HDACi are to form part of a multi-pronged strategy to eliminate latently infected cells with the ultimate goal of a functional or sterilizing cure for HIV, careful consideration of toxicity as well as activity in non-T-cell reservoirs is essential. These data support an important role for autophagy in the control of HIV infection, and provide new insights into novel approaches to inhibit HIV-1 replication and potentially eradicate the virus from infected cells.

437 An In Vitro Compound Screen for Selective Apoptosis Induction in HIV-1 Infected Resting CD4+ T Cells

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Background: Despite the ability of antiretroviral therapy to suppress viral replication, proviral HIV-1 persists in resting memory CD4+ T cells. These cells, termed the latent reservoir, represent a major barrier to HIV-1 eradication. One strategy to purge this reservoir, termed "shock and kill", aims to induce proviral transcription without inducing cellular activation (the "shock") with subsequent elimination of these cells via viral cytopathic effect or immune system targeting (the "kill"). While a number of promising candidate "shock" compounds have been identified, ongoing research suggests that "shocked" T cells do not undergo cell death. Novel strategies to eliminate these cells may be necessary for the "shock and kill" approach to deplete the latent reservoir. We hypothesize that resting central memory CD4+ T cells (Tcm) expressing HIV-1 genes are phenotypically distinct from their uninfected and latently infected counterparts and can be selectively targeted for apoptosis.

Methodology: We designed an in vitro screening assay to evaluate for selective apoptosis induction among Tcm actively expressing HIV-1 genes. Naïve CD4+ T cells from healthy donors were activated by T cell receptor stimulation and progressed to a quiescent state determined by morphology and loss of activation markers. 10 days post-activation they were infected with eGFP-pseudotyped HIV-1. Screening was performed with a chemical compound library containing 160 cell-permeable protein kinase inhibitors. Apoptosis among infected (GFP+) and uninfected (GFP-) cells was detected by flow cytometry. Screening hits were defined as compounds that induced apoptosis among GFP+ cells greater than three standard deviations (SD) above the apoptosis mean from negative control wells. Compounds inducing apoptosis >3SD above baseline in both GFP+ and GFP- cells were excluded as non-specific.

Results: We identified two kinase inhibitors, HA1077 and kenpaullone, that reproducibly and selectively target HIV-1 infected resting Tcm for apoptosis in independent experiments using cells from multiple donors. HA1077 is a Rho kinase inhibitor and kenpaullone is an inhibitor of multiple cyclin-dependent kinases and glycogen synthase kinase 3α and β. These compounds appear to be non-toxic and trigger minimal bystander cell apoptosis.

Conclusions: We have developed a novel primary cell screening assay to identify compounds that selectively induce apoptosis in HIV-1 infected resting Tcm. Using a commercial kinase inhibitor library we have identified two reproducible compound hits to date. These compounds, and the mechanisms by which they selectively induce apoptosis in HIV-1 infected cells, merit further exploration. These results may help to further ongoing HIV-1 eradication strategies.

438LB Panobinostat Induces HIV Transcription and Plasma Viremia in HIV Patients on Suppressive cART

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Background: Reactivating HIV-transcription is currently investigated as a strategy to eliminate latently infected cells. We aimed to evaluate the ability of the potent histone deacetylase inhibitor (HDACi) panobinostat to reverse HIV latency. panobinostat to reverse HIV latency.

Methodology: In a phase I/II clinical trial, HIV-infected adults received oral panobinostat 20 mg 3 times/week every other week for 8 weeks while maintaining combination antiretroviral therapy (cART). The primary endpoint of cell-associated unspliced HIV-RNA (CA-US RNA) was analyzed in total CD4+ T cells using semi-nested qPCR. Secondary endpoints included safety, plasma HIV-RNA, as well as total and integrated HIV-DNA. Changes from baseline were analyzed using repeated measurement analysis of variance and paired t-test or Wilcoxon signed-rank test. Binary outcomes were analyzed using a logistic model with a random effect for each patient.

Results: Fifteen patients were included and all completed full panobinostat dosing and follow up. Levels of CA-US RNA increased significantly during panobinostat treatment ($p<0.0001$) with significant increases on time points on-treatment as compared to baseline. The median maximal fold-increase in CA-US RNA was 3.5 (range 2.1-14.4). Levels of CA-US RNA remained elevated 4 weeks post-panobinostat (fold-increase 1.60; 95% CI: 1.17-2.19; $P=0.003$). Using a transcription mediated amplification-based semi-quantitative assay (Procleix Ultrio Plus, 59 % analytic sensitivity of 3.6 copies/mL), HIV-RNA in plasma was detected more frequently during panobinostat administration with an odds ratio of 10.5 (95% CI: 2.2-50.3) for a positive test on-treatment compared to baseline. Sixteen adverse events (AEs) were presumed related to panobinostat; these occurred in 10 patients and were all grade 1 AEs. Fatigue was the most frequently reported drug-related AE. CD4+ T cell counts were unaffected by panobinostat treatment. The level of total HIV DNA/106 CD4+ T cells decreased transiently from baseline to day 14 ($P=0.040$), but returned to baseline level at subsequent time points in most patients. There was no change from baseline in integrated HIV DNA.

Conclusions: Eight weeks of cyclic therapy with panobinostat was safe and well tolerated. Panobinostat treatment caused a significant increase in CA-US HIV-RNA levels, increased detection of plasma HIV RNA as well as a transient decrease in total HIV DNA. Our results show that Panobinostat efficiently induces HIV transcription and is a promising candidate for future combination strategies to reactivate and eliminate the latent HIV reservoir.

439 Failure of HIV-1 To Replicate in Human T Cells Expressing a Tat Mutant

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Background: Our research indicates that Nullbasic[1] is possibly the strongest anti-HIV protein tested. Nullbasic inhibits HIV replication at 3 distinct steps of the viral life cycle: transcriptional activation by Tat, Rev-mediate RNA transport and HIV reverse transcription[1-3]. As Nullbasic opposes transactivation by Tat, a key step in the activation of latently infected T cells, we hypothesized that Nullbasic might enforce latency in infected cells. Previously we showed that Jurkat and primary human cells[3] expressing Nullbasic were strongly protected from HIV replication. Recently Nullbasic expression was improved by using new lentiviral vectors. Our results showed that Nullbasic is stably expressed by T cell lines. Hence we performed in vitro and animal experiments to determine the effectiveness of Nullbasic to protect cells from HIV and to oppose activation of HIV in latently infected T cells.

Methodology: A gene encoding Nullbasic-FLAG-ZsGreen1 or ZsGreen1 was inserted into a modified lentiviral vector. VLPs were used to transduce Jurkat T cells and primary human CD4+ cells. Transduced cells were incubated with HIV and virus infectivity and replication assays were performed. Analysis of viral cDNA synthesis and proviral DNA integration was undertaken. Total cellular mRNA profiling of Jurkat cells expressing Nullbasic was performed. Analysis of HIV latency and activation of HIV-1 using PMA, SAHA, TNF-alpha and prostratin in latency model T cell lines expressing Nullbasic was undertaken. HIV replication and the stability of the transduced primary human cells were investigated in humanized Rag2-/- γc-/- mice.

Results: In repeated experiments, results showed that Jurkat cells expressing Nullbasic completely inhibited HIV replication for months. Similar results were observed using primary CD4+ human lymphocytes. Nullbasic can strongly inhibit HIV activation in ACH2 and U1 models of viral latency. J-Lat cells were protected to a much smaller degree if stimulated with TNF-alpha and prostratin. Differential Illumina™ mRNA expression analysis of Jurkat-Nullbasic and control Jurkat cells revealed that only one gene, STAT3, had a statistically significant but weak (0.5 fold) increase in expression in Nullbasic expressing cells. CD4+ cells expressing Nullbasic did not support HIV-1 replication in humanized Rag2-/- γc-/- mice.

Conclusions: Here we confirm that Nullbasic is an excellent candidate for a gene therapy approach to protect human cells from HIV infection. Nullbasic appears to exhibit no cellular toxicities unlike the HIV Tat protein from which it is derived. Our data suggest that Nullbasic can protect cells from infection as well as suppress the activation of latent HIV.

1. PLoS ONE 4: e7769, 2009
2. PLoS ONE 7: e51466, 2012
3. Human Gene Therapy 24:270, 2013

440 Hepatitis C Therapy Reduces CD4 T-Cell-Associated HIV-1 DNA in HIV-1/HCV Coinfected Patients

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Background: Hepatitis C therapy with Interferon-α (IFN-α) and Ribavirin (RBV) can effectively cure HCV infection in a significant proportion of patients, but effects of this regimen on cellular reservoirs for HIV-1 are unknown. This study aimed at elucidating the effects of combined therapy with IFN-α and Ribavirin against HIV-1 infected cells in HIV-1/HCV co-infected patients receiving suppressive antiretroviral therapy.

Methodology: CD4 T cells were isolated from a cohort of HIV-1/HCV co-infected patients who received suppressive HAART and HCV treatment with IFN-α and Ribavirin (n=12). CD4 T cells collected from time intervals immediately before or after therapy with IFN-α/RBV were used for comparison. Cell-associated HIV-1 DNA was measured using established PCR protocols. *In vitro* HIV-1 reactivation assays were performed using PBMCs from HAART-treated HIV-1 infected patients. Wilcoxon paired rank test was used to test for statistical differences.

Results: CD4 T cell-associated HIV-1 DNA remained stable during time periods prior to IFN-α/RBV therapy. During exposure to IFN-α/RBV, a moderate, but significant ($p<0.02$) and sustained decline of HIV-1 DNA was observed in CD4 T cells. This decline of HIV-1 DNA was inversely correlated to IFN-α-associated CD4 T cell losses. However, *in vitro* experiments failed to demonstrate an effect of pharmacological doses of IFN-α on HIV-1 reactivation, suggesting that the reduction of HIV-1 DNA during treatment with IFN-α or IFN-α/RBV is not due to direct effects of IFN-α or IFN-α/RBV on HIV-1 reactivation from latency.

Conclusions: These data demonstrate that Hepatitis C treatment with IFN-α/RBV can moderately reduce the reservoir of HIV-1 infected CD4 T cells that persists despite suppressive antiretroviral therapy in HIV-1/HCV co-infected patients. Exploring the mechanisms underlying the reduction in HIV-1 DNA during IFN-α/RBV therapy may be helpful for designing improved clinical strategies for HIV-1 eradication.

441 HIV-1 Nef Inhibits Autophagy in Macrophages Through Transcription Factor EB Sequestration

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Background: Transcription factor EB (TFEB) is a master gene expression regulator of the classical autophagy-lysosome pathway. Under basal conditions, TFEB is phosphorlyated by MTORC1, resulting in the cytoplasmic retention of TFEB through interactions with 14-3-3 proteins. When MTORC1 is inhibited, TFEB is dephosphorylated, prompting its translocation to the nucleus where it increases the expression of genes encoding lysosomal proteins. HIV-1 Nef

acts as an anti-autophagic maturation factor through interaction with beclin-1, an essential autophagy and tumor suppressor protein. In this study, we investigated the role of Nef and TFEB in the modulation of autophagy during HIV-1-infection of human macrophages.

Methodology: Monocyte-derived macrophages (MDM) were challenged with 10^5 $TCID_{50}$ $HIV\text{-}1_{Ba\text{-}L}$ or $HIV\text{-}1\Delta_{Nef}$ per 5 x 10^5 cells. Autophagy and the role of TFEB was assessed using the expression, localization and phosphorylation of autophagy proteins combined with the lipidation of microtubule-associated protein 1 light chain 3B (LC3B) by immunoblotting, qRT-PCR, and fluorescence microscopy or by transducing MDM with shRNA for *TFEB*. Data were analyzed using the Mann-Whitney U test.

Results: Following exposure of macrophages to $HIV\text{-}1_{Ba\text{-}L}$ or heat-inactivated HIV-1, TFEB is dephosphorylated and translocated to the nucleus. This correlated with an increase in autophagy as evidenced by increased lipidation of LC3B, degradation of sequestosome and increased autophagosome formation ($P < 0.01$) and was attenuated by TFEB silencing ($P < 0.05$). In the presence of productive infection, TFEB phosphorylation and cytoplasmic sequestration started to increase and autophagy markers decrease by 5 days post-infection and by 7 days, levels were similar to the uninfected controls ($P > 0.05$). $HIV\text{-}1\Delta_{Nef}$ similarly induced the dephosphorylation and nuclear localization of TFEB that corresponded to an increase in autophagy during initial infection. Conversely, at 7 days post-infection nuclear accumulation of dephosphorylated TFEB and autophagy markers remained elevated ($P < 0.02$).

Conclusions: These results support a model whereby, during initial infection, the interaction between virion surface proteins and host receptors serve as a signal for autophagy initiation that is dependent upon the dephosphorylation and nuclear translocation of TFEB mediated by the inhibition of MTORC1. Once HIV-1 establishes a productive infection, Nef down regulates autophagy through the phosphorylation and cytosolic sequestration of TFEB. These findings help to explain how HIV-1 modulates autophagy to promote its own replication and cell survival, and further suggests that disrupting the autophagic balance within the infected cell can inhibit HIV-1 and potentially eliminate the infected cell.

Session P-G1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

CNS Viral Escape and Neuroinflammation On ART

442 HIV-1 RNA Detection in CSF in ART-Treated Subjects With Incomplete Viral Suppression in Plasma

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Background: It has been proposed that HIV replication may continue in sanctuary sites such as the brain due to suboptimal antiretroviral drug penetration or activity. The aims of this study were to investigate HIV-1 RNA levels in cerebrospinal fluid (CSF) of subjects on ART and relate the findings to HIV-1 RNA detection in plasma.

Methodology: The UK PARTITION study obtained paired CSF and plasma samples from two groups; group A - undergoing investigation for possible neurological disease; group B - unexplained intermittent or persistent HIV-1 RNA detection >50 copies/mL within the previous 12 months in the absence of neurological disease. HIV-1 RNA levels were measured by a modified Abbott RealTime assay, achieving a sensitivity of detection of 1-3 copies/mL. CSF/plasma discordance was defined as HIV-1 RNA levels differing by >0.5 log10 copies/ml. Residual plasma HIV-1 RNA detection was defined as a level between 1 and 49 copies/ml. ART concentrations were determined in CSF and plasma by tandem mass spectrometry.

Results: 152 subjects were recruited; 114 in group A and 38 in group B. In the total study population, median HIV-1 RNA levels were 10 copies/ml (IQR 5-103) in plasma and 5 copies/ml (IQR 3-186) in CSF (p=.032). Among 64 subjects with plasma HIV-1 RNA <50 copies/mL, 47 had residual plasma HIV-1 RNA detection. In these 47 patients, HIV-1 RNA levels in CSF were median 5 copies/ml (IQR 3-15), including 10 subjects (group A n=6), with CSF/plasma discordance and median CSF levels of 208 copies/ml (IQR 114-1274). Of the 17 subjects with no residual HIV-1 RNA detection in plasma, none had detectable HIV-1 RNA in CSF (p=.037).

Overall, 8/38 subjects in group B (21%) had CSF/plasma discordance, with median HIV-1 RNA levels of 911 copies/mL (IQR 156-2330) in CSF and 42 copies/mL (IQR 12-81) in plasma.

CSF/plasma discordance was not was not associated with CNS penetration effectiveness score. No correlation between CSF concentrations of darunavir, raltegravir, efavirenz and atazanavir and HIV-1 RNA detection in CSF were observed.

Three discordant CSF samples were sequenced to determine the drug resistance profile; two samples from patients on emtricitabine showed the reverse transcriptase (RT) mutation M184I; the third sample from a heavily pre-treated patient showed multiple RT mutations comprising TAMs (D67N, K70R, T215Y, K219E), L74V and M184V for NRTIs, and L100I and K103N for NNRTIs.

Conclusions: The CNS may be the source of ongoing HIV-1 replication in a proportion of patients that fail to suppress below 50 copies/mL in plasma, as well as those with residual plasma HIV-1 RNA detection between 1-49 copies/mL. This has implications for the management of low-grade viraemia and 'blips', both in terms of stratifying lumbar punctures and tailoring treatment for effective suppression in the CNS.

443 CSF Viral Escape in Patients Without Neurological Disorders: Prevalence and Associated Factors

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Background: CSF viral escape (CVE) is an emerging issue in the HIV setting and has been associated with neurologic symptoms and neurocognitive impairment. Few studies have estimated CVE prevalence and factors associated.

Methodology: Single-center retrospective study on CSF/plasma paired samples obtained from HIV-patients undergoing spinal tap because of neurological signs/symptoms or CNS stage of systemic diseases. Patients with diagnosis of CNS disorders were excluded. Repeated CSF/plasma samples obtained from the same patient were included if collected while receiving different cARTs. CVE was defined: a) detectable CSF HIV-RNA with concurrent plasma levels <50 copies/mL; b) CSF HIV-RNA >1.0 log higher than concomitant plasma RNA level. Adjusted ORs of CVE were calculated by fitting a logistic multivariate regression model.

Results: 303 CSF/plasma pairs collected from 115 patients were included: 88% male, median age 48 (IQR 41-52), HIV acquisition heterosexual in 43%, MSM in 21%, IDU in 27%. CD4 count was <200 cells/mm3 in 48% and >350 in 25%; 31% were CDC stage C. CSF was collected in 14% during 1994-2004, in 48% during 2004-2008, in 37% during 2009-2013. At the time of collection, 50% were on cART with TDF/FTC, 12% with ABV/3TC, 9% with ZDV/3TC, 33% with EFV, 33% with LPV/r, 12% with ATV/r. CVE was detected in 32/303 samples (10.6%). At multivariable analysis, male gender (OR 0.23; 95%CI 0.07-0.76), CD4 >350 (0.22; 0.06-0.73) and 2009-2013 period (0.05; 0.00-0.25) were all independently associated to a decreased risk of CVE. Fitting a separate logistic model including ARVs and using TDF/FTC as reference, both ABV/3TC (OR 8.20; 1.61-41.65) and ZDV/3TC (OR 11.12; 1.62-76.35) were related to an increased CVE risk. In the same model, having EFV as reference, ATV/r (OR 5.67; 0.98-32.72) was related to a higher risk of CVE. Age, duration of cART and 2010 CPE score were not associated with CVE. A sensitivity analysis including only 151 patients with plasma HIV-RNA <50 copies/mL, found 22 CVE (12.5%). At logistic regression, the protective effect of male gender, CD4 >350, 2009-2013 period was confirmed. Among ARVs, only the increased risk associated with ABV/3TC use when compared to TDF/FTC remained significant.

Conclusions: In this large record of CSF/plasma paired samples from patients without CNS disorders, CVE occurred in about 10% of cases, with a reduced frequency in recent years. Male gender and higher CD4 count had a protective role. Though channeling bias in this cross-sectional study cannot be ruled out, the lack of correlation of CVE and CPE score, and the protective role of TDF/FTC (versus ABV/3TC or ZDV/3TC) and of EFV (versus ATV/r) suggest that effective viral suppression in plasma more than neuropenetrative effectiveness of ARVs may drive the control of HIV replication in CSF.

444 Early Monocyte Inflammation Among Treatment-Naïve Acute HIV-Infected Thai Subjects

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Background: Monocytes (MO) are a heterogeneous population of myeloid cells defined into 3 distinct subsets based on CD14 and CD16 expression as classical (CD14highCD16-), non-classical (CD14lowCD16++) and an intermediate (CD14highCD16+) subset. It is suggested that CD16 expressing MO subsets patrol the periphery, migrate into tissues and display pro-inflammatory features. Our previous work identified CD16 expressing MO harboring HIV DNA appear to serve as a correlate to HIV-associated neurocognitive disorders (HAND) in chronic HIV infection. MO changes that occur in the earliest stages of HIV infection may be mechanistically relevant to the persistence of cognitive complications in patients despite suppressive antiretroviral therapy (ARV).

Methodology: We characterized MO inflammatory phenotype and functional responses (IL-6, IL-1β and TNF-α) by a novel multiparametric flow cytometric technology in a prospective study of 17 ART-naïve acute HIV-infected (AHI) individuals, captured during a hyper-acute window during Fiebig stage I (RNA+/HIV IgM-, n=10) and III (HIV IgM+/IgG-, n=7) before appreciable antibody response can be measured and correlated to clinical parameters of disease progression (eg: plasma HIV Viral load). Wilcoxon rank sum tests were conducted to compare the differences between Fiebig stages.

Results: We observed that subjects captured in Fiebig I had lower plasma HIV viral load compared to subjects in Fiebig III: median (Interquartile range) = 4.3 log10 copies/ml (3.6,5.4) vs 5.5 log10 copies/ml (5.4,7.5); p=0.01). Cross-sectionally, Fiebig I subjects had a greater frequency of only non-classical MO compared to Fiebig III (18.2% (8.7,26.9) vs 7.4 %(4.4,12.1); p=0.03). Lipopolysaccharide (LPS) stimulated IL-6+ MO responses were greater in Fiebig I compared to Fiebig III (14.5% (7.7,17.7) vs 5.3% (4.9,9.3); p=0.04). No differences in either basal or LPS stimulated IL-1β or TNF-α MO responses was seen between Fiebig stages. Plasma HIV viral load was inversely associated with both basal (r=-0.603;p=0.008) and LPS (r=-0.562; p=0.015) stimulated IL-6+ MO responses.

Conclusions: These results indicate that the presence of HIV soon after infection differentially alters the inflammatory profile of various MO subsets and precedes peak viremia in AHI. Tracking MO inflammation after early institution of ARV therapy in AHI may have significant implications in reducing HAND.

445 Cerebrospinal Fluid Viral Blips and Persistent Escape in HIV-Infected Patients On ART

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Background: Cerebrospinal fluid (CSF) viral escape, where HIV-1 RNA is increased in CSF while suppressed in plasma, has previously been shown to occur infrequently in subjects responding well to antiretroviral therapy (ART). It is unclear if CSF viral escape represents a continuous low-grade CNS infection in some patients, and may constitute a risk for future neuronal damage. The light subunit of the neurofilament protein (NFL) is a component of myelinated axons, and elevated concentrations in CSF are a sensitive marker of ongoing axonal injury in HIV-associated dementia (HAD). To investigate the frequency of CSF viral escape in relation to neuronal damage, we analyzed NFL in a longitudinal cohort of subjects responding well to ART.

Methodology: Subjects on effective ART ≥6 months with plasma HIV-1 RNA <50 c/ml at inclusion, followed with ≥2 lumbar punctures for CSF analysis were identified from a longitudinal study. Subjects with CNS opportunistic infections or other significant CNS disease were excluded from the analysis. Transient low increases in plasma viral load ("blips") during the study period were allowed. HIV-1 RNA was analyzed with real-time PCR (Cobas TaqMan, Roche). CSF concentrations of NFL were measured by an enzymatic 2-site quantitative immunoassay (UmanDiagnostics, Umea, Sweden). CSF neopterin was measured by ELISA. The relationship between CSF NFL levels and age were analyzed with a linear mixed effects model. Mann Whitney U-test was used for group wise comparison.

Results: Seventy-five (52 male, 23 female) patients with multiple CSF analyses (median 5, range 2-14) were included in the analysis. 26 (35%) had CSF RNA above quantification limit (20 c/ml) on at least one time point (median 50; IQR 32-78 c/ml); 6 (8%) subjects had increased CSF RNA in consecutive samples. 40 (53%) patients had ≥1 (range 0-6) transient plasma HIV-1 RNA >20 c/ml (median 44; IQR 29-71 c/ml). In 8 samples, RNA was >20 c/ml in both CSF and plasma. Of all 373 tested samples, 38 (10%) and 74 (20%) were >20 c/ml in CSF and plasma, respectively. CSF neopterin was higher in samples with increased (median 7.3, IQR 6.4-11 nmol/l) than with undetectable (median 6.4, IQR 5.1-7.7 nmol/l) CSF HIV-1 RNA ($p<0.05$). No similar difference was found in CSF NFL.

Conclusions: In this longitudinal analysis we found that occasional increased CSF HIV-1 RNA was not uncommon in patients on effective ART, although less frequent than in plasma. A minority of subjects had persistently increased CSF virus which may represent CSF viral escape. Increased CSF HIV-1 RNA was related to a higher level of intrathecal immune activation. However, we found no correlation between CSF HIV-1 RNA and NFL, suggesting that increased CSF virus and immune activation does not result in CNS axonal injury in patients on ART, at least not in the short term.

446 Mitochondrial DNA Is Associated With Inflammation and Neurocognitive Deficits in HIV Infection

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Background: HIV enters the central nervous system (CNS) early in infection leading to persistent inflammation and often resulting in HIV associated neurocognitive disorders (HAND). Cells in the CSF tend to be activated and inflammatory factors may increase cell death, releasing mitochondrial DNA (mtDNA) into the cerebrospinal fluid (CSF). MtDNA itself can induce a potent inflammatory response and may contribute to the persistent inflammation in the CNS. We hypothesized that higher levels of free mtDNA in CSF would be associated with higher levels of immune activation, pro-inflammatory cytokines, and chemokines, as well as with worse neurocognitive performance.

Methodology: We performed a retrospective evaluation of CSF supernatant samples collected from 31 HIV infected individuals enrolled in an NIMH-funded cohort, 16 of whom had available longitudinal assessments. Neurocognitive performance, summarized by the global deficit score (GDS), sociodemographic and clinical data were collected for each participant. Neurocognitive impairment (NCI) was defined as a GDS ≥ 0.5. We quantified mtDNA load (ML) in CSF using the highly sensitive droplet digital PCR platform. Biomarkers of immune activation (sCD14 and sCD163), pro-inflammatory cytokines (TNF-α, IL-6), and chemokines (MCP-1, IP-10) were measured using immunoassays. Statistical analyses were performed using R software.

Results: Using mixed effects regression analysis and all samples available, a higher ML in CSF was associated with greater neurocognitive dysfunction (GDS, $p=0.002$), higher levels of the CNS inflammatory chemokine IP-10 ($p=0.03$) and sCD14 ($p=0.01$). In cross-sectional analysis, the association of ML with CNS inflammation was more prominent in the subgroup of patients with a detectable CSF HIV VL (IP-10, $r=0.7$, $p=0.001$), and the subgroup of patient with a CD4 count <350 (IP-10, $r=0.68$, $p=0.03$). In this latter subset, ML also correlated with CD4 nadir ($r=0.71$, $p=0.03$). When NCI was present, a higher ML in CSF correlated with greater neurocognitive dysfunction (GDS, $r=0.78$, $p=0.001$), increased CNS levels of the inflammatory chemokine IP-10 ($r=0.7$, $p=0.001$), and increased plasma levels of the inflammatory chemokine MCP-1 ($r=0.67$, $p=0.01$). However, there was no association between CSF VL and GDS, and IP-10 was only weakly associated with GDS ($r=0.53$, $p=0.06$).

Conclusions: Extracellular mtDNA may represent a novel biomarker of neurologic damage that not only is easily measurable in CSF, but also may associate better with neurocognitive dysfunction than other biomarkers. Additionally, mtDNA may contribute to persistent inflammation of the CNS seen in HIV infection. A better understanding the role of mtDNA in the CNS inflammation could lead to improved therapies for HAND.

447 CNS Outcomes of cART vs. cART plus Maraviroc and Raltegravir Intensification During Acute HIV

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Background: Within weeks of HIV infection, HIV RNA is found in cerebrospinal fluid (CSF) with accompanying changes in brain parenchyma by magnetic resonance spectroscopy (MRS) supporting theories of early CNS seeding with virus. Intensification of cART with CCR5 and integrase inhibitors is strategized to limit HIV reservoirs when instituted early after HIV infection. The impact of cART intensification on CNS outcomes, when instituted during the earliest stages of infection is not known. We investigated change in inflammatory markers using MRS and CSF cytokines among subjects randomized to cART (efavirenz (EFV), tenofovir (TFV), emtricitabine (FTC), n=25) vs. cART+ (cART + raltegravir (RAL) and maraviroc (MVC)).

Methodology: 62 acute HIV subjects (31 cART and 31 cART+) underwent MRS for N-acetyl aspartate (NAA), choline (CHO), myoinositol (MI), and glutamate/glutamine (Glx) at basal ganglia (BG), parietal gray matter (PG), frontal white matter (FW), and frontal gray matter (FG) during acute HIV (Fiebig stage I-IV) then at 12 and 24 weeks after cART vs. cART+ randomization. Subjects intolerant to EFV (n=3) or with resistance (n-=1) in the cART arm were switched to RAL whereas EFV was discontinued for those intolerant (n=5) or resistant (n=1) in the cART+ arm. CSF was sampled for HIV RNA, IL-6, IP-10, MCP-1 and neopterin at baseline and 24 weeks after randomization. Comparisons employed regression models across visits for MRS and comparison of baseline to last sampling for MRS and log10 transformed cytokines.

Results: Enrollment occurred a mean (range) of 17 (4-40) days after estimated HIV exposure. Mean (SD) age was 29 (7.3) years and 94% were male with no differences by arm. 50 cases underwent MRS at baseline (25 cART and 20 cART+) and 43 at week 24 (25 cART and 18 cART+). 31 had baseline CSF sampling (14 cART and 17 cART+) and 27 at week 24 (13 cART and 14 cART+). Increased NAA in PG (p=.03), FW (p=.005), and FG (p=.04) was observed over 24 weeks and decreased CHO in BG (p=.0005), but no differences were observed by arm. Mean cytokine levels declined in nearly all subjects. Baseline cytokine levels were associated with degree of change in each measure; however, treatment arm was not.

Conclusions: Intensification of cART with CCR5 and integrase inhibitors was not associated with differences in CSF cytokines or MRS markers of inflammation during acute HIV. Improved CNS markers of increased NAA, decreased tCHO and decreased inflammatory cytokines were noted in both groups, regardless of intensification.

Session P-G2 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

HAND in Aging Populations

448 The Effects of Age and Study Cohort On Brain Structure Among Men With HIV Disease

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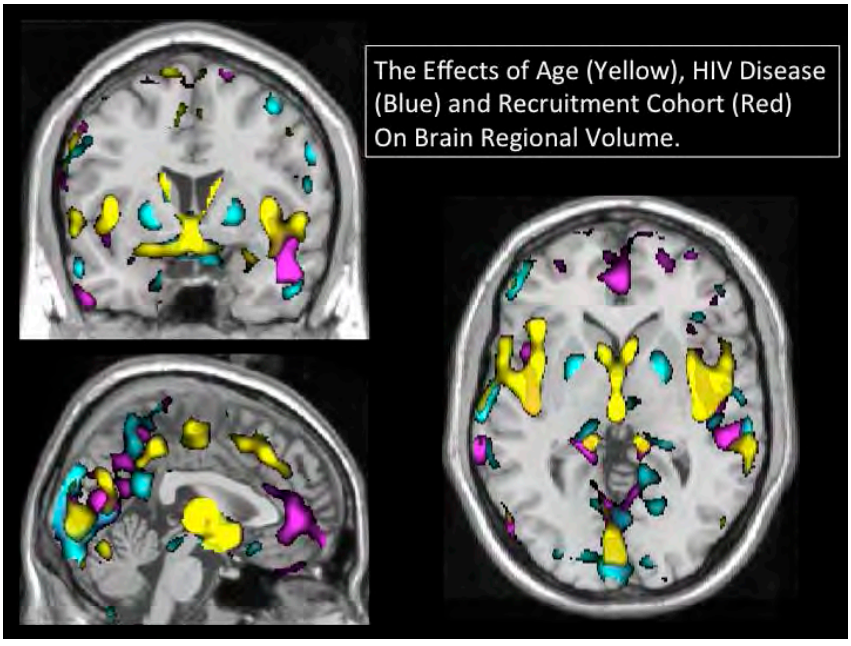
Background: Chronic HIV infection and advancing age are associated with decreased brain volume. However, as the HIV epidemic has changed since the introduction of combination antiretroviral therapy (CART), it is important to evaluate the effects of calendar period cohort recruitment on these relationships.

Methodology: 328 men (age: 50-75) enrolled in the MRI study of the Multicenter AIDS Cohort Study (MACS) underwent high resolution anatomical brain imaging (MP-RAGE at 3T field strength). The brain images from 281 met QC standards and were processed using a non-parametric correction of intensity non-uniformity (N3). Standard voxel-based morphometry (VBM) methods were run using Statistical Parametric Mapping (SPM5). Brains were segmented into grey matter, white matter and CSF compartments. The voxel-level analysis controlled for total intracranial volume and for MACS site.



Results: At the whole brain level, the HIV-infected men had significantly lower grey matter volumes (adjusted for intra-cranial volume) compared to the uninfected men (beta= -.16). Age was significantly associated with decreased grey matter volume (beta= -.20); there was no HIV-by-Age interaction. Figure 1 shows the VBM results projected onto the standard Colin27 template. The significant brain regions are shown with the t-statistics, thresholded at a False Discovery Rate of p<.05 (100 voxel extent threshold). Age was significantly associated with decreased brain volume across both cortical and subcortical regions (yellow areas in Fig. 1), including the caudate nucleus, ventral putamen, and the insular cortex. HIV disease was associated with atrophy in the basal ganglia, especially the putamen (marked in blue). The men who enrolled in the MACS in 2001/2003 had decreased brain volume in the anterior cingulate gyrus (red) relative to men who enrolled in the mid-late 1980s. There was no interaction between HIV Disease and cohort, and there was no interaction between Age and HIV Disease.

Conclusions: Although there are significant differences in brain volumes based on calendar period recruitment cohort, these effects did not interact with HIV serostatus. Within this study sample, the effects of age on brain volumes are more extensive than those associated with HIV Disease, suggesting that with survival to older age, more attention needs to be paid among infected individuals to age-associated risks for brain tissue loss.

449 FMRI Reveals Asymptomatic Deficits Among HIV+ Older Adults On cART When Compared To HIV- Controls

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Background: Despite increased use of combination antiretroviral therapy (cART), HIV-associated neurocognitive disorders (HAND) remain prevalent among HIV+ persons, resulting in deficits among high-level executive function. The purpose of this study was to characterize neural bases of cognitive control deficits among older virally suppressed HIV+ cases vs. HIV- controls, using functional magnetic resonance imaging (fMRI). Findings will inform whether HAND processes continue in the presence of successful cART treatment and in the absence of clinical manifestations.

Methodology: HIV+ adults receiving cART with an undetectable viral load were compared with controls. Subjects were $\geq$ 50, with no illicit drug use or contraindications to fMRI, and MMSE $\geq$ 25. High-level executive functions were assessed with Trail Making Tests and Wisconsin Card Sorting Test. fMRI data were collected with a face-gender or word-semantic task on overlapping face and word stimuli, and a task switching paradigm where subjects were cued to respond to faces while ignoring words, or vice versa, in an unpredictable order. The cost of task switching was measured as the difference between the switch trials (first trials after task switching cue) and the repeated trials (after switch).

Results: 15 subjects completed fMRI (10 HIV+; 5 HIV-). While there were weak trends in behavior decrement among HIV+ (p>0.2), no significant differences were found between groups for demographic, behavioral, or neurocognitive characteristics. Whole brain fMRI analysis revealed an increase in activity associated with task switching in a dorsal-anterior cluster (anterior cingulate cortex, ACC) in HIV+ (cluster size=795, q_{FDR} <0.05), suggesting an increase in switching cost. Regions of interest (ROI) analysis confirmed the difference in bilateral ACC (p<0.01, but neither middle nor posterior cingulate, p>0.2), and revealed stronger neural responses to task-irrelevant stimuli at corresponding sensory cortices in HIV+ (p<0.04), suggesting an impairment in inhibition.

Conclusions: In HIV+ subjects without cognitive control deficits at a behavioral level, fMRI revealed significant increases in activity at executive circuits due to task switching relative to HIV- controls and impairment in inhibiting task-irrelevant information at posterior sensory cortex. Findings were present despite viral suppression, suggesting an early pathological change at a neuronal level, which may be the root of cognitive control deficits related to subsequent HAND. This pilot study informs use of fMRI as a means of predicting HAND, suggesting that viral suppression may not be sufficient to prevent HAND.

450 Longitudinal Progression of Cortical Atrophy in HIV-Patients On Stable Treatment

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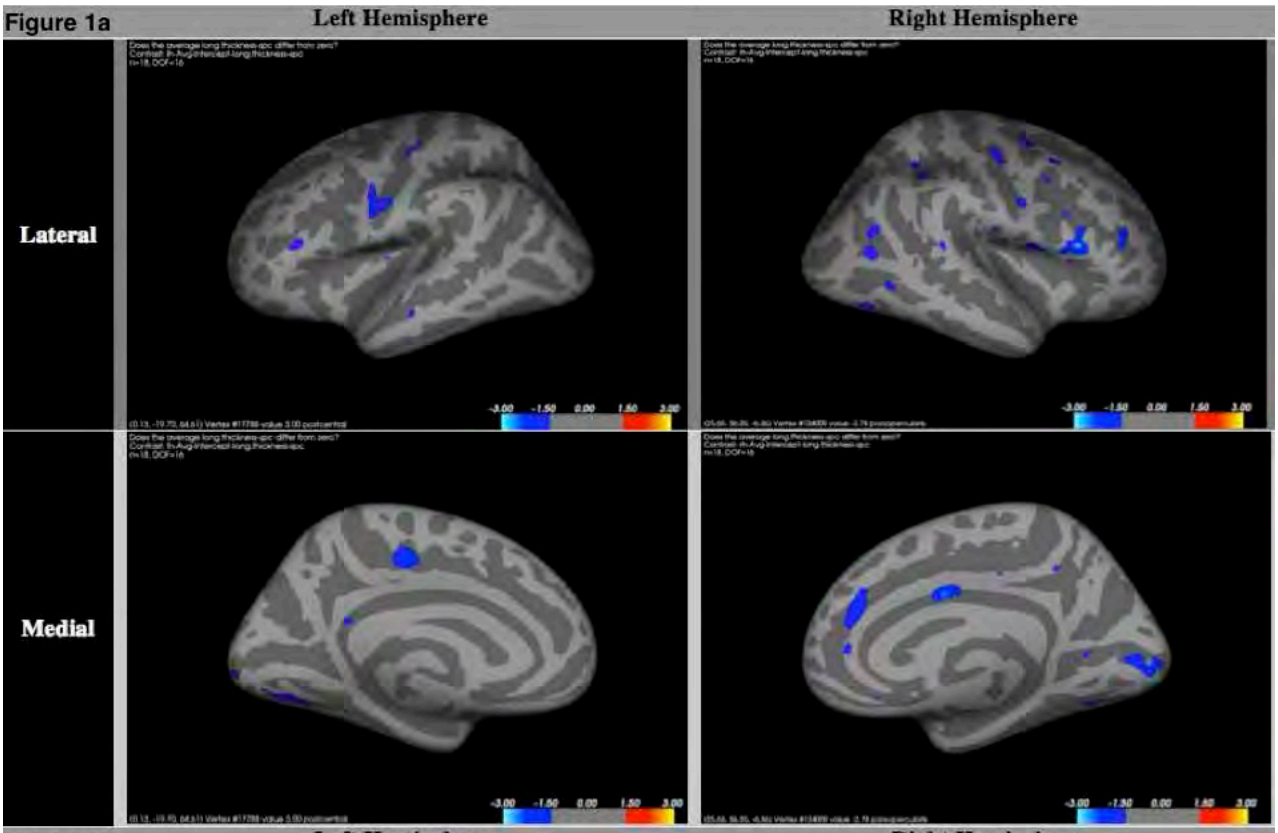
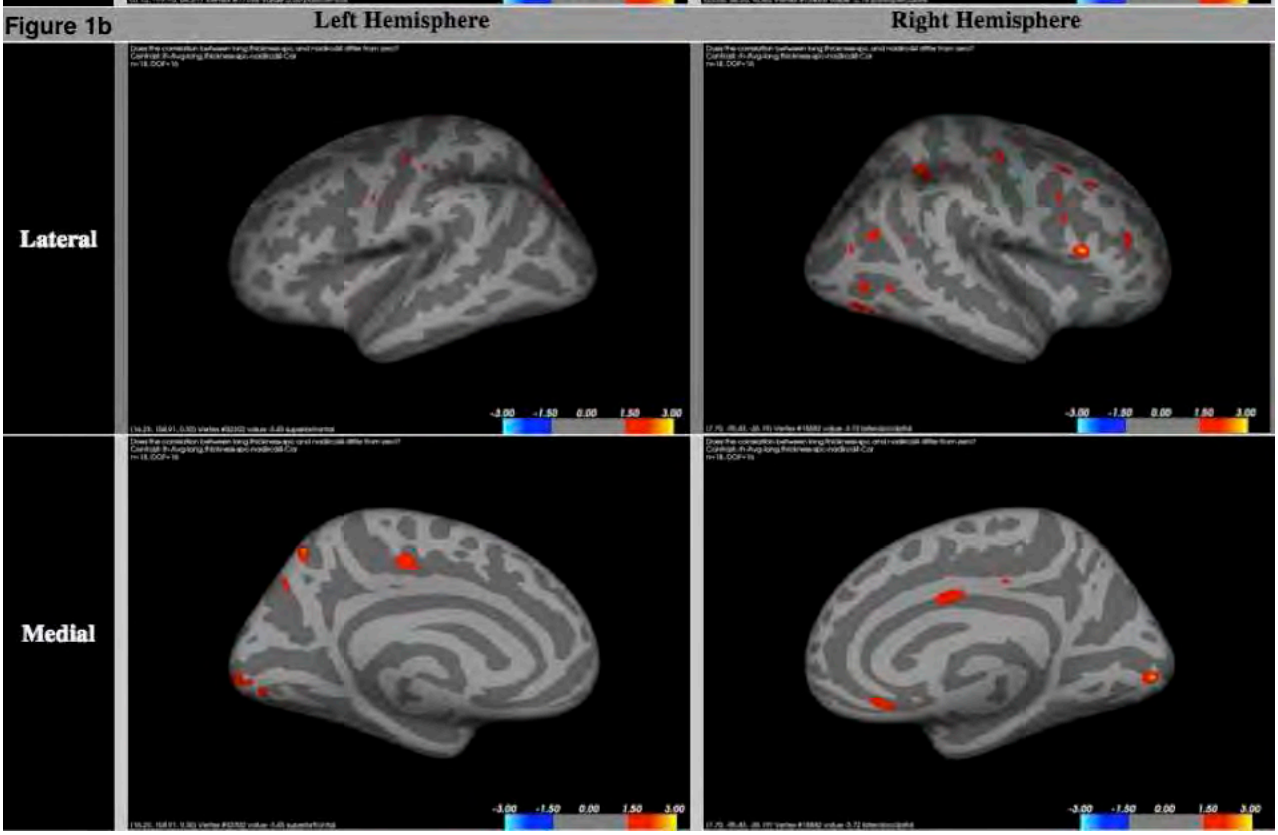
Background: Emerging evidence largely based on cross sectional studies show that chronically infected HIV patients on effective combined antiretroviral therapy are susceptible to neuronal damage, which can lead to cognitive dysfunction. A low nadir CD4 has been shown to be an important predictor. This study examines the longitudinal progression of cortical atrophy in a representative cohort of HIV-positive patients on stable medication regimens.

Methodology: Magnetic resonance imaging (MRI) data and relevant clinical variables were obtained from the NIH-funded HIV Neuroimaging Consortium (HIVNC) cohort, for a small subsample of 18 HIV-infected patients, across three time-points (initial scan, six-month, one-year). To extract cortical thickness values evaluations, MRI data was processed using the longitudinal stream in FreeSurfer v.5.1.1 (Martinos Institute, Boston, MA). Parametric heat maps indicating clusters of significant change were calculated and used to visualize the relationship between cortical change and key baseline clinical variables.

Results: The means (SD) were: age, 48.4 (6.41) years; nadir cd4 count, 32.8 (24.62) cells/mm3; baseline cd4 levels, 319.8 (179.55) cells/mm3; duration HIV, 11.6 (7.72) years; and all on stable cART. Statistically significant (P < 0.05) regions of cortical thinning were found over time (fig 1a), which was strongly correlated with nadir CD4 concentrations (fig 1b). Cortical thinning spans a variety of brain regions corresponding to functional systems and appears to be more focused in the primary cortical rather than association regions.

Conclusions: This is among the first studies to show that stably treated HIV-infected patients show progressive cortical atrophy, in part related to the nadir CD4 count. Further analysis is underway to assess the generalizability and functional relevance of these findings and determine the factors that contribute to brain tissue loss in the setting of stable and chronic disease.





451 FMRI Evidence for HIV-Induced Acceleration of Aging in Middle-Aged Women

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Background: Studies have shown that HIV-associated neurocognitive disorders (HAND) are more severe in older people with HIV disease than their younger counterparts, and it has been suggested that the increased vulnerability might be due to HIV-induced accelerated aging. However, the experimental evidence for the accelerated aging theory remains elusive.

It has been proposed that aging-related cognitive decline might be due to decreases in neural specificity, which precede the onset of significant behavioral changes, as shown in recent functional magnetic resonance imaging (fMRI) studies of aging. In the present study, using two advanced fMRI techniques - fMRI rapid adaptation (fMRI-RA) and local regional heterogeneity (Hcorr) - both capable of measuring neural specificity more directly than conventional fMRI techniques, we test the hypothesis that HAND involves changes at the neural level similar to those found in cognitive aging, i.e., a decrease in neural specificity.

Methodology: Twenty-nine middle-aged (43-59 years old, mean 50.5±0.8) women with no major psychiatric disorders or other confounding health problems (16 HIV-seropositive receiving HAART, 13 HIV-seronegative) recruited from the Washington DC site of the Women's Interagency HIV Study participated in this study. The two groups were matched in age ($p>0.7$), education ($p>0.9$), and general cognitive function ($p>0.8$, Mini Mental Status Examination). Behavioral performances in face discrimination, verbal fluency, and episodic memory were assessed using standard tests. Neural specificity was estimated in the fusiform face area (FFA, a region central for face processing), the visual word form area (VWFA, a key region for reading), and hippocampus (a critical region for episodic memory), using fMRI-RA (FFA) and/or Hcorr (FFA, VWFA, and hippocampus).

Results: Statistical analyses were conducted on behavioral and fMRI data using repeated measures ANOVA or t-test. No differences were found in behavioral performance between controls and HIV+ subjects (at least $p>0.2$), nor in conventional fMRI data (at least $p>0.3$). By contrast, significant decreases in neural specificity were found in the HIV+ group, in FFA ($p<0.01$, fMRI-RA; $p<0.005$, Hcorr), VWFA ($p<0.01$, Hcorr), and hippocampus ($p<0.04$, Hcorr).

Conclusions: Advanced neuroimaging techniques revealed significant decreases in neural specificity in middle-aged HIV-positive subjects, similar to those found in cognitive aging, even in the absence of changes at the behavioral level. These results strongly support the accelerated aging theory of HAND, and suggest fMRI-RA and Hcorr a promising tool to detect early neuronal dysfunction and to evaluate therapeutic effects in asymptomatic patients, when behavioral assessments cannot detect differences.

452 Factors Related To Brain Atrophy in a Cohort of HIV Infected Patients: ANRS CO3 Aquitaine Cohort

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Background: Neuroimaging studies in HIV-infected patients have suggested that volume loss in cerebral white (WM) and grey matter (GM) could be associated with cognitive deficits and motor function impairment. Factors that could contribute to such structural brain abnormalities have rarely been investigated, especially in the setting of combination antiretroviral therapy (cART). In this study, we examined if HIV infection characteristics, comorbidities, cardiovascular (CV) risk factors and socio-demographic variables were independently associated with markers of cerebral atrophy in a large cohort of HIV-infected patients.

Methodology: The ANRS CO3 Aquitaine Cohort recruits patients with HIV-1 infection through a hospital-based information system in southwestern France. Between 2007 and 2009, 180 participants were included in the COGLOC substudy and had a cerebral Magnetic Resonance Imaging examination in the Bordeaux University Hospital. A Voxel-Based Morphometry procedure was used to extract GM and WM volumes for each subject. Markers of cerebral atrophy were GM volumes and brain parenchymal fraction (BPF=[GM+WM]/Total Intracranial Volume). The independent association between each of the atrophy markers and age, gender, level of education, HIV characteristics, comorbidities, and CV risk factors were analyzed by covariance models.

Results: Participants' mean age was 48.7 years, and 86% were male. Older age, longer time since HIV diagnosis, neuroAIDS condition, HIV transmission by intravenous drug use, and hypertension were independently associated with larger brain atrophy i.e reduced BPF and GM volume (Table). Neither CD4 count nor HIV RNA level was associated with cerebral atrophy severity. The results were consistent across brain atrophy markers, except for level of education: higher education being associated with larger GM, but not with BPF.

Conclusions: In HIV-infected patients, like in the general population, age is an important correlate of brain atrophy level. In addition, time since HIV diagnosis, HIV transmission by intravenous drug use, neuroAIDS stage and hypertension independently affected brain atrophy level. Future studies are needed including both longitudinal MRI and neurocognitive assessment firstly to explore whether some structural brain MRI changes are transient and secondly to investigate the mechanisms underlying brain changes in HIV infection and their functional consequences.

Multivariable analysis of factors associated with brain MRI atrophy markers						
Variables	Categories	N	Brain Parenchymal fraction (%)	P value	Grey Volume in ml	p value
			Mean (SE)		Mean (SE)	
Age	≤50 years old >50 years old	105 75	65.2(1.8) 62.7(1.7)	<0.01	634 (17) 597 (17)	<0.001
Higher education	No Yes	83 97	63.6(1.7) 64.3(1.7)	NS	617 (22) 634 (22)	<0.05
Time since HIV diagnosis	< 12 years ≥ 12 years	97 83	65.2 (1.7) 63.2 (1.8)	<0.05	632 (22) 607 (23)	<0.05
AIDS stage	No Aids Stage AIDS stage Neuro AIDS	134 36 10	65.6 (1.6) 64.4 (1.8) 61.9 (2.1)	<0.05	637 (15) 625 (18) 584 (23)	<0.05
HIV transmission group	Intravenous drug use Homosexual Heterosexual/others	21 98 61	61.8 (2.1) 65.0 (1.8) 65.2 (1.8)	<0.05	577 (20) 623 (16) 628 (17)	<0.05
CD4+ lymphocytes count	<200 200-350[[350-500[≥500	8 39 38 95	61.7 (2.5) 64.3 (1.9) 64.7 (1.9) 64.6 (1.9)	NS	618 (32) 634 (24) 634 (25) 635 (24)	NS
HIV RNA	No Yes	25 155	63.8 (2.0) 63.8 (1.8)	NS	634 (25) 627 (23)	NS
Hypertension	No Yes	135 45	64.8 (1.7) 63.1 (1.8)	<0.05	625 (16) 606 (18)	<0.05
Smoking status	Never smoker Former smoker Current Smoker	42 53 83	63.8 (1.7) 64.0 (1.8) 64.1 (1.8)	NS	627 (18) 606 (18) 614 (18)	NS

453 Hyperphosphorylated Tau in Cerebrospinal Fluid: A Biomarker for Neurological Aging in HIV-1?

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Background: With widespread use of combined antiretroviral treatment (cART), overt HIV-1 associated dementia (HAD) is rarely seen. However, milder forms of HIV-associated neurocognitive disorders have frequently been reported also in patients on cART. Hyperphosphorylated tau in CSF (p-tau) is an established biomarker in diagnosis of Alzheimer disease. It increases with age also in healthy subjects and is not influenced by neuroinflammation. In this study we decided to assess whether p-tau can be used as a marker of neurological aging in HIV patients.

Methodology: In a cross-sectional retrospective study, CSF concentrations of p-tau (phosphorylated at threonine 181) were measured with an enzyme-linked immunoassay in HIV-1 infected neuroasymptomatic patients without treatment (n=172), in HIV-infected patients on cART and plasma HIV-RNA <50 copies/ml (n=68), in HAD (n=33) and in HIV-negative controls (n=291). For statistical measures, correlations and linear regression were used.

Results: The cART group and HIV-negative controls showed significant positive correlations of p-tau and age ($p<0.01$ and $p<0.001$ respectively), whereas no significant correlations were found in the NA and HAD groups. When looking at the HIV-positive population as a whole, a significant difference was seen in slope compared to controls ($p<0.001$).

Conclusions: HIV-negative controls and HIV-infected on cART show significant increases of p-tau with age. No such connection could be found in untreated neuroasymptomatics and HAD. Patients with HAD do not have higher p-tau levels than asymptomatic subjects. Several younger untreated HIV-infected subjects, both asymptomatic and with HAD, had high p-tau while this is not the case in older individuals. The mechanism behind this skewness remains to be explained.

Session P-G3 Poster Session
Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**
Neuropathogenesis

454 Efavirenz Produces a Differential Bioenergetic Response in Neurons and Glial Cells

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Background: CNS side effects are the main adverse events of Efavirez (EFV), but the mechanisms responsible are unknown although recent evidence shows that this drug undermines mitochondrial function. Neurological pathogenesis is often associated with mitochondrial dysfunction and it is known that glia cells overcome the damaging effects of mitochondrial inhibition by rapidly up-regulating AMP-kinase (AMPK)-mediated glycolysis and maintaining ATP levels, which is crucial for cell homeostasis and viability. In contrast, neurons lack this defence mechanism, which makes them more vulnerable to bioenergetic challenge. We have analysed if EFV interferes with the mitochondria of neurons and glia cells and assessed its influence on cellular bioenergetics. Since there is a substrate of CNS inflammation during HIV-related cognitive disorders, we have also evaluated if EFV effects are exacerbated by nitric oxide (NO), a mediator of inflammation and inhibitor of mitochondrial respiration.

Methodology: Human cell lines (glioma and neuroblastoma) and rat primary cultures of astrocytes and neurons were treated with clinically relevant concentrations of EFV. Exogenous NO was applied by addition of its donor DETA-NO. Parameters of mitochondrial function and bioenergetics were studied using standard cell biology techniques. Data (mean±S.E.M, n=3-5) were expressed as % (of untreated cells, considered 100%) and analysed by Student's t-test, significance vs. vehicle.

Results: EFV (10 and 25 μM) inhibited mitochondrial respiration, enhanced ROS generation, undermined $\Delta\psi_m$ and reduced ATP levels in a significant and concentration-dependent fashion in both neurons and glia. However, AMPK was activated only in glia, leading to an up-regulation of glycolysis (enhanced lactate production and increased intracellular ATP), whereas in neurons there was a decrease in ATP concentration. The combination of EFV+NO potentiated the effects of either one on mitochondrial parameters in both neurons and glia, but ATP generation and lactate production were again enhanced only in the latter. EFV+NO did not deplete the number of glia (Veh=103.1±1.831; EFV10=103.3±2.078; DETA-NO=74.43±1.645***; DETA-NO+EFV10=69.86±2.703***), but substantially aggravated the effect of EFV (10μM) on neurons (Veh=103.2±1.372; EFV10=96.38±2.761*; DETA-NO=65.00±4.359***; DETA-NO+EFV10=27.80±3.666***) (% of untreated cells).

Conclusions: Our results suggest that EFV exerts a direct and specific effect on the energetic balance and viability of neurons and glia through a mechanism involving acute mitochondrial inhibition, an action that could be exacerbated in neuroinflammatory conditions like those often present in HIV-patients, or when the brain-blood-barrier is disrupted.

455 Corneal Sensory Nerve Fiber Loss in SIV-Infected Macaques: Tracking HIV PNS Damage

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Background: Human immunodeficiency virus-associated peripheral neuropathy (HIV-PN) is currently the most frequent neurologic complication of HIV infection, affecting most individuals living with HIV. HIV-PN is a length-dependent small sensory fiber neuropathy typified by bilateral numbness, tingling, and burning sensations in the lower legs. Because electrophysiology is insensitive to changes in small unmeylinated fibers, microscopic evaluation of epidermal nerve fiber density in skin biopsies has become the standard for diagnosis of HIV-PN. However, longitudinal assessment is limited by the invasiveness and technical demands of this technique. While noninvasive assessment of corneal sensory nerves has proven clinically useful in diagnosing and monitoring other peripheral neuropathic conditions, such as diabetic neuropathy, corneal nerve alterations in HIV have yet to be characterized

Methodology: To determine whether corneal nerve alterations developed in an SIV model of HIV-PN, we established a βIII tubulin immunostaining protocol for detecting nerves in corneal whole mount specimens harvested at terminal timepoints, and then developed novel manual and automated counting methods to measure corneal nerve density.

Results: Manual and automated counting methods each demonstrated significantly lower subbasal corneal nerve fiber counts among SIV-infected animals that rapidly progressed to AIDS as compared to slow progressors. Concomitant with decreased corneal nerve fiber density, rapid progressors had increased levels of SIV RNA, CD68-positive macrophages, and GFAP expression by glial satellite cells in the trigeminal ganglia ($P<0.05$, Mann-Whitney).

Conclusions: These findings demonstrate that corneal nerve assessment has great potential to diagnose and monitor HIV-induced peripheral neuropathy. In particular, noninvasive techniques such as in vivo corneal confocal microscopy may be valuable to identify and track PNS damage in the HIV clinical setting.

456 HIV-Tat Protein in Inflammatory Infiltrates of CNS-IRIS and in CSF of Patients On ART

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Background: Persistent low level inflammation is found in most patients with chronic human immunodeficiency virus (HIV) infection despite virological control on antiretroviral therapy (ART). Some of these individuals develop immune reconstitution inflammatory syndrome of the central nervous system (CNS-IRIS), the pathophysiology of which is poorly understood.

Methodology: We immunostained brain biopsy and autopsy tissue and from HIV infected individuals on ART with CNS-IRIS, from virologically controlled HIV infected without IRIS as well as from patients with HIV encephalitis (HIVE). Tissue was stained for the HIV-proteins transactivator of transcription (Tat) and p24 antigen as well as for T cell markers. We established an ELISA for the detection of Tat and examined in the cerebrospinal fluid (CSF) of HIV patients on ART (n=65).

Results: Brains from patients with CNS-IRIS showed monocytic infiltrates which strongly stained for Tat while p24 immunostaining was negative. Tat was also present in 2/7 HIV patients on ART without evidence of p24. HIVE brain tissue demonstrated Tat and p24 expressing macrophages in microglial nodules and perivascular regions. In the CNS-IRIS patients, infiltrates consisted of CD3+ T-cells which were predominantly CD8+ with few CD4+ cells and occasional IL-17+ cells. In 32/65 CSF samples of HIV-infected individuals on ART, Tat was detected by ELISA. In a subset of CSF samples the presence of Tat was confirmed by Western blot analysis.

Conclusions: HIV-Tat protein may drive inflammation in the form of acute CNS-IRIS or chronic inflammation in the CSF of individuals controlled on ART. While ART controls HIV replication it fails to impact Tat production. The prevention of Tat production is therefore an important therapeutic target.

457 Central Nervous System Demyelination in Pediatric SIV Infection

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Background: Pediatric HIV infection remains a global health crisis with an estimated 1,500 children under the age of 15 years becoming infected with HIV-1 each day in the developing world. Children are much more susceptible to HIV-1 neurological impairments than adults. Imaging studies have shown reduced radial diffusivity, suggesting demyelination may be a prominent feature in pediatric HIV infection that is associated with diminished executive function. A major obstacle in pediatric HIV research is sample access. The proposed studies take advantage of ongoing pediatric SIV pathogenesis and vaccine studies to test the hypothesis that pediatric SIV infection diminishes myelinated fibers in the frontal and motor cortices as well as the hippocampus.

Methodology: Newborn rhesus macaques (Macaca mulatta) that received oral inoculation with a repeated-exposure of SIVmac251 (n=4) or vehicle (control n=4) were recruited for this study. After a 6-18 week survival time, the animals were sacrificed and the brains prepared for quantitative histopathological analysis. Matched sections from the frontal cortex, motor cortex and hippocampus were stained with gold chloride, a putative marker for myelin.

Results: We report here a significant reduction in myelination and myelinated fibers in the frontal cortex, motor cortex, and hippocampus.

Conclusions: Previously reported from this model ha shown significant loss of hippocampal neurons and neurogenic capacity that may contribute to the rapid neurocognitive decline associated with pediatric HIV infection. Data presented here that neuronal loss maybe exacerbated by loss of central nervous system myelination. These data provide a neuroanatomical substrate for reduced radial diffusivity as well as reported multiple sclerosis-like signs in HIV-1 infected children. Support: U.S. PHS grants S06GM08016 (MBRS-SCORE, NIGMS/NIH) to TH; Leadership Alliance Fellow to MR; District of Columbia Developmental Center for AIDS Research (P30AI087714) to MB; and 1R01DE019064 (NIH/NIDCR) and 2P30 AI050410 to KA.

458 Brain Iron Transport Is Associated With Neurocognitive Performance in HIV/AIDS

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Background: Iron dysregulation in the brain is a consistent and poorly understood feature of neurocognitive disorders, and functional neuronal iron deficiency has been implicated in certain dementias. We hypothesized that HIV-Associated Neurocognitive Disorder (HAND) pathophysiology involves brain iron deficiency, reflected by increased transferrin receptor (TFR) RNA expression in brain.

Methodology: Subjects who died of HIV/AIDS and participated in the National NeuroAIDS Tissue Consortium (NNTC) Study underwent uniform autopsy/neuropathology protocols and comprehensive neurocognitive assessments within 6 months pre-mortem. HAND was defined according to the Frascati criteria. Total RNA was extracted and purified from frozen brain tissue (frontal neocortex at Brodmann Area 9); TFR messenger RNA was quantified by RT-PCR. Associations of TFR RNA expression with HAND and standardized, neurocognitive domain scores were assessed by multivariable-adjusted regression analysis to estimate β-coefficients (β) or odds ratios (OR) and their 95% confidence intervals (CI).

Results: Among 287 evaluated decedents from the NNTC Brain Bank (mean age 44, median CD4 cell count 109/mm^3, 31% pre-HAART era), HAND was present in 243 (85%), including asymptomatic neurocognitive impairment (N=76), mild neurocognitive disorder (N=72), and dementia (N=95). TFR RNA expression levels, available in 274 subjects (91%), were unrelated to brain viral burden. TFR RNA expression in neocortex was associated with HAND (crude OR 2.3, $p<0.05$ for all diagnoses combined; OR 2.9, $p<0.01$ for association with dementia) in unadjusted analyses; TFR RNA levels were 15.4%

higher in HAND cases than controls [median 0.90 *vs.* 0.78, respectively (p=0.05)]. These associations persisted after adjustment for age at neurocognitive testing, race/ethnicity, plasma CD4 cell count, total RNA, post-mortem interval, hepatitis C co-infection, and current/past alcohol abuse [OR 5.2 (95% CI 1.5-18.1, p<0.05) for all HAND; OR 5.9 (95% CI 1.6-22.3, p<0.05) for asymptomatic and mild neurocognitive impairment combined; OR 7.7 (95% CI 1.3-45.6, p<0.05) for dementia]. Speed of information processing, attention working memory, and global T-scores were or tended to be negatively associated with TFR RNA expression [adjusted β= -3.4 and -3.0 for speed of information processing and attention working memory, respectively (both p<0.05); adjusted β= -2.6 for global T-score (p=0.07)].

Conclusions: TFR RNA expression in the frontal neocortex is independently associated with both milder and more severe forms of HAND and with performance on neurocognitive testing among individuals dying of HIV/AIDS, suggesting a role for brain iron deficiency in HAND etiology and/or progression.

461 Cognitive and Brain Microstructure Abnormalities in HIV-1 Infected Humanized Mice

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Background: We reported modest neuropathological change that follows progressive HIV-1 infection of humanized mice. Whether such changes are relevant to human disease including cognition and behavior are not known. To these ends, we applied time-dependent behavioral and advanced neuroimaging tests to infected animals to assess relationships between immune and cognitive function, viral replication and brain metabolites to HIV-1-associated neuropathology.

Methodology: Humanized NOD/scid-IL-2Rgcnull mice transplanted at birth with human CD34+ hematopoietic stem cells were infected with HIV-1ADA at 22 weeks of age. Infection was followed for 16 weeks. Mice were bled at 0, 4, 8 12 and 16 weeks post-infection (wpi) for human immune cell analysis by flow cytometry and viral load (VL) measurements. Animals were subjected to serial volume selective proton magnetic resonance spectroscopy (1H MRS) and diffusion tensor imaging (DTI) at pre- and 4, 8, 12 and 16 wpi to measure brain metabolites and changes in tissue architecture, respectively. Total RNA from cortex was isolated at the study end from both infected and control mice groups and HIV-1gag was quantified using real-time quantitative PCR to look at the brain viral RNA level. Animals were evaluated one week prior to and 4 and 8 weeks following viral infection by open field activity (OFA) test as a measure of habituation in new environments, motor function and field exploratory behavior. At the study end, brains were analyzed immunohistochemically for neuronal, oligodendrocytes and glial inflammatory markers.

Results: Mice showed sustained plasma viremia with concomitant reductions in CD4+ T lymphocytes. Behavioral abnormalities included failure to habituate to a new environment and increased anxiety with HIV-1 infection. Systemic viral loads were associated with selective cortical N-acetyl aspartate, creatine and choline reductions. Diffusion tensor imaging (DTI) abnormalities were detected in white matter fiber structure and in cortical gray matter in HIV-1 infected animals compared to uninfected controls. Post-mortem multispectral imaging microscopic analysis of brain tissue showed reduction in synaptophysin, neurofilament and glial antigens, those are reflective of DTI and metabolite changes.

Conclusions: These results demonstrate, for the first time, notable relationships between viral load, imaging abnormalities and brain region-specific neurodegeneration in a mouse model demonstrating neurocognitive deficits. These findings are clearly reflective of human disease and can be applied to future therapeutic interventions for neuroAIDS.

462 SIV Dynamics in the CD8-Depleted vs Non-CD8-Depleted Rhesus Macaque Model for NeuroAIDS

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Background: Appropriate animal models are required to understand why neurological disease due to HIV infection persists in the era of cART. The CD8-depleted and SIV-infected macaque is frequently used to study the pathogenesis of HIV because it results in the rapid onset of SIV-associated encephalitis, which ensures the collection of a large amount of data for researchers in a short period of time, while reducing animal suffering and maintenance costs. Of interest is how CD8 depletion may generate a biological environment that may or may not impact viral evolution in nature.

Methodology: Two groups of macaques were inoculated with the SIVmac251 viral swarm. One group of six macaques, was CD8-depleted, while another group of 12 macaques, was allowed to progress naturally with SIV. At three weeks post infection, SIV envelope sequences were generated from tissues (plasma, CD14, and bronchial lavage) from all macaques. Two hundred viral swarm sequences were generated for comparison to the macaque data. Evolutionary analyses, including clustering, phylogeny, recombination, selection and signature pattern analysis were performed for the 3-week sequence data. Virus was also quantitated from tissues at the time of euthanization, including brain, for all CD8-depleted macaques and 7 of the non-depleted macaques (at this time five macaques have not been euthanized).

Results: Viral diversity in both groups of macaques was similar and significantly increased when compared to the viral swarm. Clustering analysis showed considerable overlap between the CD8-depleted and non-CD8-depleted macaque sequences; however, potentially macrophage tropic SIV, with signatures associated with brain were found only in the CD8-depleted macaques. Positively selected sites between the two groups of macaques were also similar and frequently mapped to putative recombination breakpoints. At end-stage disease, virus was isolated from all tissues in the CD8-depleted macaques; however, 5 out 7 of the non-depleted macaques did not have any amplifiable SIV RNA or DNA in brain and bone marrow tissue samples while maintaining high viral loads in CD14+ and CD3+ cells until death.

Conclusions: In terms of sequence evolution, the primary difference between the two groups of macaques was the emergence of a small number of potentially neurotropic virus in the CD8 depleted animals, which is interesting since all CD8-depleted macaques developed neuroAIDS, while only 1 in 12 non-depleted macaques have developed neuroAIDS at this time. The finding that low viral load levels in bone marrow and brain coincide with the lack of encephalopathy may implicate bone marrow as the source of brain virus. The study supports research using the CD8-depleted, rapidly-progressing macaque model for the study of neuroAIDS.

463 Vascular Endothelium and Neurological Performance During Primary HIV Infection

Sebastian Urday[1], Kevin Robertson[2], Fang-yong Li[1], Felicia C. Chow[3], Julia Peterson[3], Elaine M. Nitta[3], Richard W. Price[3], Priscilla Y. Hsue[3], Serena Spudich[1]
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Background: HIV-infected individuals with well-controlled infection have increased rates of premature cardiovascular (CV) disease and neurocognitive dysfunction. In longstanding HIV infection, vascular disease and neurological dysfunction may associate, connected through a common pathogenetic pathway of inflammation, which persists even in the setting of optimal antiretroviral therapy (ART). We tested whether measures of CV and neurologic function correlate during the early stages of HIV infection.

Methodology: 15 individuals with primary HIV infection (PHI, < 1 year since HIV transmission) underwent both CV and neurologic testing in San Francisco, USA. Vascular measures included: (1) carotid artery intima-media thickness (IMT) in the common carotid, bifurcation region and internal carotid artery; (2) brachial artery flow-mediated dilation (FMD); (3) hyperemic velocity; and (4) asymmetric dimethylarginine (ADMA), a plasma marker of endothelial dysfunction and atherosclerotic potential. Neuropsychological performance was measured as total z-score (based on normed performance on 11 tests) and brief NPZ-4 (based on a subset of four tests). We examined correlations between CV and neurologic measures weighted by the number of repeated visits per each subject with the use of the Pearson correlation coefficient.

Results: At baseline, PHI subjects had a median age of 37 (IQR 32, 47) years, CD4 count of 474 (361, 656) cells/μL, plasma HIV RNA of 4.59 log10 copies/ml (3.64, 4.94), and CSF HIV RNA of 2.58 log10 copies/ml (1.69, 3.33). Subjects were enrolled at median 93 (77, 153) days post infection and 100% were ART naïve. The interval between CV and neurologic testing was 31 (16, 75) days. Duration of follow-up was 364 (0, 641) days. Higher ADMA correlated with worse neuropsychological performance, assessed by NPZ-4 ($r = -0.81$, $P = 0.05$). Unexpectedly, greater IMT in the left internal carotid artery and overall mean IMT correlated with better NPZ-4 ($r = 0.73$, $P = 0.02$; $r = 0.64$, $P = 0.04$, respectively). No associations were found between FMD or hyperemic velocity and neurologic measures.

Conclusions: In an exploratory analysis, higher ADMA levels, suggestive of more severe endothelial dysfunction, inversely correlated with neuropsychological performance during early HIV infection. A seemingly paradoxical association between increased IMT, another surrogate marker of atherosclerosis, and better neuropsychological performance warrants further study.

Session P-G4 Poster Session
Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**
Host Genetics in HAND

464 Heme Oxygenase-1 Polymorphism and Protein Deficiency Associated With Neurological Disease in HIV

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Background: Neuroprotective therapies that target the pathological processes persisting in ART-treated individuals are needed. Heme oxygenase-1 (HO-1) has anti-inflammatory and neuroprotective roles and was recently proposed to modulate the association between inflammation and HIV replication in HIV-infected individuals. 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 have now investigated the role of HO-1 in neuroinflammation and neurocognitive impairment in HIV-infected individuals.

Methodology: Protein and RNA expression were analyzed by Western blot and qPCR, respectively, in prefrontal cortex lysates from HIV-, HIV+, and HIV encephalitis (HIVE) brains (n=156) from clinically characterized subjects from the National NeuroAIDS Tissue Consortium. HO-1 promoter regions were genotyped by PCR with capillary electrophoresis. Statistical analysis was performed by ANOVA with a Holm-Sidak post-test and multivariate linear regression.

Results: HO-1 protein levels were deficient in the prefrontal cortex of HIV+ subjects compared to HIV- controls ($p<0.01$), with more severe HO-1 deficiency observed in HIVE subjects ($p<0.001$). HO-1 deficiency correlated with CNS viral load and with brain parenchymal markers of macrophage and innate immune activation (CD163, ISG15, MX1). HO-1 deficiency correlated with neurocognitive impairment in executive and speed of processing domains in the Caucasian subpopulation ($p<0.01$). Prefrontal cortex HO-1 RNA was elevated in HIVE subjects ($p<0.01$), suggesting a post-transcriptionally mediated deficiency. Shorter variants of a HO-1 promoter region GT(n) microsatellite polymorphism, previously shown to associate with enhanced HO-1 transcription, correlated with increased HO-1 protein expression and decreased mRNA expression of markers of macrophage activation (CD163, CD68) in the prefrontal cortex. Moreover, shorter HO-1 promoter variants were associated with a significantly lower prevalence of HIVE among HIV+ subjects ($p<0.05$).

Conclusions: HIV infection reduces CNS HO-1 protein expression post-transcriptionally and this deficiency may play a role in neuroinflammation and neurocognitive impairment in HAND patients. Variations in a HO-1 promoter region microsatellite polymorphism may be a genetic determinate of brain HO-1 protein production and subsequent HIV neurological disease progression. HO-1 is a potentially targetable neuroprotective host factor that modulates macrophage-mediated neurodegeneration in HIV infection. Therapeutic inducers of HO-1 need to be examined for the potential clinical efficacy in reducing the prevalence of HAND in ART-treated individuals.

465 Mitochondrial DNA Haplogroups and Neurocognitive Impairment in the CHARTER Cohort

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Background: Neurocognitive impairment (NCI) remains an important complication of HIV infection in the combination antiretroviral therapy (CART) era. Mitochondrial DNA (mtDNA) haplogroups are ancestry-related patterns of single nucleotide polymorphisms that have been associated with neurodegenerative diseases in HIV-uninfected populations, and with HIV- and CART-associated outcomes. We hypothesized that mtDNA haplogroups are associated with NCI in HIV-infected adults, and examined these associations in CHARTER.

Methodology: CHARTER is a U.S.-based observational study of ambulatory HIV-infected adults who underwent standardized neurologic assessments. Primary outcomes were the global deficit score (GDS; both as a continuous measure and impairment defined as GDS≥0.5) and HIV-associated neurocognitive disorder (HAND; defined using Frascati Criteria). Haplogroups were assigned using mtDNA sequence from whole blood and HaploGrep; analyses were race/ethnicity stratified. Multivariable regression of associations between haplogroups and GDS or HAND were performed adjusting for comorbidity status (incidental vs. contributing), current CART status (yes vs. no), plasma HIV RNA, CHARTER site, wide-range achievement test score, and CD4 T cell nadir.

Results: Haplogroups were available from 1068 persons without confounding comorbidities; median age was 43 years, CD4 nadir was 180 cells/mm^3, 763 (71%) were on CART, and 492 (46%) had HAND at baseline. In cross-sectional univariable analyses, Hispanics (N=104; 9.7%) had a greater likelihood of both GDS impairment and HAND ($p<0.001$ for both). Among Hispanics, those belonging to haplogroup B (N=18; 17%) had a lower median GDS (0.21 vs. 0.63; $p=0.004$), and lower likelihood of HAND of any severity (OR 0.30; 95% CI 0.11-0.87) and GDS impairment (OR 0.19; 0.06-0.62). These relationships persisted in stratified analyses of subgroups on CART, with detectable plasma HIV RNA, or with incidental comorbidities. There were no statistically significant differences by haplogroup among non-Hispanics. In adjusted models, haplogroup B tended to be associated with a lower GDS ($\beta=-0.26$; $p=0.06$) and remained significantly associated with reduced risk of GDS impairment (adjusted OR 0.12; 0.02-0.67; $p=0.02$), independent of CD4 nadir and other factors listed above.

Conclusions: In this cohort of predominantly CART-treated subjects, a common Hispanic mtDNA haplogroup was associated with lower prevalence of NCI. Mitochondrial genetic variation may be an ancestry-specific host factor contributing to risk of NCI in chronically HIV-infected persons. Future studies could explore targeted genetic testing for risk stratification and personalized preventive and/or therapeutic interventions.

466 MBL2 Promoter Polymorphism rs7096206 Predicts Brain Metabolite Anomalies in HIV-Infected Adults

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Background: Mannose binding lectin, coded by *MBL2* gene, recognizes high-mannose N-linked glycans on HIV-1 gp120 and activates complement pathway leading to HIV-1 opsonization and phagocytosis; however its role in HIV-related neuropathogenesis is unclear. We hypothesized that the presence of *MBL2* promoter polymorphism rs7096206 (-221-G/C or *MBL2*-Y/X), linked to lower expression, impaired complement activation, and inflammatory cytokines response, will predict neuroinflammation and brain damage in HIV-infected adults.

Methodology: 244 subjects from the CHARTER (CNS HIV AntiRetroviral Therapy Effects Research) cohort were evaluated with single voxel magnetic resonance spectroscopy (svMRS) to assess levels of 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 (BG) using LC Model. GWAS *MBL2-rs7096206* genotype associations with brain structural MR imaging (sMRI) volumes and svMRS were cross-sectionally examined by multi-variable linear regression. All analyses controlled for scanner and either cranial vault volume (for sMRI) or proportion of tissue in voxel (svMRS). Adjusted analyses included comorbidity, current CD4>=200, nadir CD4>=200, detectable plasma and CSF VL, and HCV co-infection. A Holm-Bonferroni correction for multiple comparisons was used.

Results: Of the 244 subjects studied, 81% were male; 53% White and 43% Black. *MBL2*-rs7096206 wild type Y/Y, heterozygote Y/X and homozygote variant X/X genotypes were present in 64%, 32% and 4% individuals respectively. 76% of 244 were on HAART and 11% were ARV naïve. Presence of the variant *MBL2*-X allele was associated with higher CHO in FWM (8.2% [2.3%, 14.4%], $p=0.057$) and BG (8.6% [3.5%, 14%], $p=0.001$) in the whole cohort; this was also true in the on-HAART only group (FWM: 10.9% [3.4%, 18.9%], $p=0.043$; BG: 9.8% [3.5%, 16.4%], $p=0.025$). The X allele also was associated with higher CR in FWM (8.2% [3.2%, 13.4%], $p=0.011$)) in the whole cohort; this effect remained significant in the on-HAART group in the FWM (9.1% [2.8%, 15.8%], $p=0.043$).

Conclusions: Higher levels of CHO in the presence of the *MBL2-X* allele suggest greater inflammation in the HIV-1 infected brain. Higher CR may suggest increased energy metabolism in the brain to counteract HIV-1 mediated inflammation. Presence of *MBL2-X* allele results in lower MBL levels, impaired innate immune response and complement activation leading to the deposition of MBL-gp120 complexes and inflammatory cytokine response resulting in neuroinflammation and brain damage. These findings suggest that *MBL2* genotype is a potential predictive biomarker for HIV-related neuroinflammation and brain damage.

Session P-G5 Poster Session
Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

PML and Other CNS Infections

467 Pathogenesis of JC Virus Reactivation During Natalizumab Treatment

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Background: Progressive multifocal leukoencephalopathy (PML), caused by JC virus (JCV), is an opportunistic infection in immunocompromised hosts and its pathogenesis remains elusive. Recently, PML affects multiple sclerosis (MS) patients treated with natalizumab, a monoclonal antibody against alpha-4 integrins which prevents entry of inflammatory cells in the central nervous system. We sought to uncover the site and prevalence of JCV reactivation and determine JCV-specific cellular response during prolonged exposure to the drug.

Methodology: We enrolled 39 JCV-seropositive MS patients, including 32 on natalizumab monotherapy for 18-20 months (n=14), 22-25 months (n=7) and >36 months (n=11), 2 on interferon-beta monotherapy >36 months and 5 untreated MS patients as controls. We performed QPCR in CSF, blood and urine for JCV DNA and we determined JCV specific T-cell responses using enzyme-linked immunospot (ELISpot) and intracellular cytokine staining (ICS) essays, ex vivo and after in vitro stimulation with JCV peptides

Results: JCV DNA was detected in the CSF of 3/35 (8.6%) subjects tested (1 in 18-20 and 2 in >36 months on natalizumab), who had no symptoms or MRI lesions consistent with PML. JCV DNA was detected in peripheral blood mononuclear cells (PBMC) of 10/39 (25.6%) subjects but not in plasma. JCV DNA load was higher in $CD34^+$ cells compared to B Cells (p=0.0064), T cells (p=0.0035) and polymorphonuclear (PMN) cells (p=0.0043) and in monocytes compared to T cells (p=0.0048) and PMN (p=0.008). Viruria was detected in 8/39 (20.5%) patients. JCV-specific $CD4^+$ T-cells were detected ex vivo more frequently in subjects with JCV DNA in PBMC (p=0.027). JCV-specific T cells were detected more frequently by ICS than ELISpot ex vivo [26/39 (66.7%) vs 6/39 (15.3%);p<0.001] and after in vitro stimulation [39/39 (100%) vs 33/38 tested (86.8%);p=0.03]. Both assays were significantly more frequently positive after in vitro stimulation than ex vivo (p<0.001). JCV-specific $CD4^+$ T-cells were more frequently detected than $CD8^+$ T-cells after in vitro stimulation [39/39(100%) vs 34/39(87.2%); p=0.05].

Conclusions: Asymptomatic JCV reactivation may occur in CSF of MS patients on prolonged natalizumab treatment. JCV is associated with multiple leukocyte subpopulations and viral load may be higher in $CD34^+$ cells and monocytes compared to other cells. JCV detection in plasma or urine may not be adequate markers for viral reactivation. Presence of the virus in the bloodstream may trigger a $CD4^+$ mediated immune response. JCV-specific cellular response is highly prevalent in MS patients and its detection may be enhanced after in vitro stimulation with JCV peptides.

468 Impaired *T. pallidum* Opsonic Antibody Function in HIV-Infected Patients With Neurosyphilis

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Background: Compared to HIV-uninfected (HIV-) patients, HIV-infected (HIV+) patients may be at increased risk of neurosyphilis (NS). *T. pallidum*, the bacterium that causes syphilis, is cleared from sites of infection by activated macrophages that ingest and kill opsonized organisms. We hypothesized that HIV+ individuals might have a defect in opsonic antibody production or function that could impair bacterial clearance and predispose them to NS.

Methodology: Monocyte derived macrophages (MDMs) were derived from peripheral blood mononuclear cells in culture with 1 ng/ml macrophage colony stimulating factor. MDMs were incubated with Nichols strain *T. pallidum* at a bacterium to cell ratio of 25:1 with 17% patient sera for 4 hrs. at 37C in 5% CO_2, fixed and stained by immunofluorescence for *T. pallidum*. Opsonic capacity of sera was determined as % MDMs ingesting opsonized *T. pallidum* and was normalized to the result of a pool of sera from 55 HIV+ and HIV- patients with syphilis (RPR titer 1:64). Normal human AB sera served as the negative control. Mann-Whitney U test was used to compare continuous variables between groups and linear regression was used for multivariable analysis.

Results: Serum opsonic capacity was determined in quadruplicate for 53 HIV+ and 24 HIV- patients with syphilis. Median serum RPR titer (IQR) was significantly higher in HIV+ compared to HIV- (1:128 [1:64-1:256] vs. 1:64 [1:32-1:128], p=0.001). 21 HIV+ and 10 HIV- had NS (reactive cerebrospinal fluid (CSF)-Venereal Disease Research Laboratory test or CSF white blood cells >20/ul). Serum opsonic capacity was higher in patients whose RPR titers were ≥1:32 compared to those with <1:32 (0.54 [0.37-0.84] vs. 0.40 [0.26-0.53], p=0.02) and in HIV- compared to HIV+ (0.62 [0.40-1.20] vs. 0.43 [0.29-0.64], p=0.01). Opsonic capacity remained significantly higher in HIV- patients after taking into account serum RPR titer (p=0.003). Among the HIV+, opsonic capacity was lower in patients with NS compared to those without NS (0.38 [0.28-0.55] vs. 0.47 [0.30-0.67], p=0.11); when serum RPR titer was taken into account, this difference was significant (p=0.047). Opsonic capacity did not differ by CD4 count or ARV use.

Conclusions: Despite having lower RPR titers, sera from HIV- patients with syphilis had significantly greater opsonic capacity than sera from HIV+ individuals with syphilis. Among the HIV+, those with NS had significantly lower serum opsonic capacity compared to those without NS. These results suggest that HIV+ syphilis patients may be at increased risk of NS because of impaired opsonic antibody production or function.

469 Significance of Plasma JCV-DNA in HIV Progressive Multifocal Leukoencephalopathy (PML)

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Background: PML, caused by polyomavirus JC (JCV), remains a severe opportunistic disease in HIV-infected patients. Detection of JCV-DNA in plasma and peripheral leukocytes has been reported in immunocompromised subjects, with or without PML, but it was neither regarded as a sensitive and specific diagnostic marker of PML. Moreover, it is not known whether it can be considered as a marker of more aggressive PML course. The aim of this study was to assess the diagnostic and prognostic significance of JCV-DNA levels in plasma at PML onset on clinical outcome.

Methodology: This is a cross-sectional, retrospective, multicentre study of 79 patients with HIV-related PML and 49HIV positive controls whose plasma samples were collected within 90 days from onset of symptoms and available for virological analysis. Patients were enrolled in Italy between 1993 and 2012. PML diagnosis was confirmed by JCV-DNA detection in CSF in 68 cases, at autopsy in 2 cases, or based on typical clinical and radiological features in 9 cases. Associations between categorical measures were assessed by the Fisher's exact test. The effect of a number of factors on time from onset of symptoms to the end of follow-up due to progressive disease or death was assessed by Kaplan-Meier and Cox proportional-hazard models.

Results: Sixteen/79 patients (20.3%) were female and 63 (79.7%) male, median (IQR) age was 38 years (34-43.5), CD4+ were 80 (38-220) cells/μL, plasma HIV-RNA was 3.87 (1.69-4.98) log10 copies/mL at the time of PML and 59/79 (74%) were exposed to combined antiretroviral treatment (cART). Fifteen patients showed contrast enhancement at magnetic resonance imaging, 12 experienced immune reconstitution inflammatory syndrome (IRIS), and 10 received high-dose steroids. JCV-DNA was detected in plasma of 4/49 (0.1%) control subjects and of29/79 (36%) PML patients. The sensitivity and specificity of the presence of JCV-DNA in plasma was36.7% and 91.8%, respectively. The only independent factor associated with JCV-DNAdetection in plasma was JCV-DNA in CSF. The occurrence of IRIS was associated with more favourable clinical outcome. cART therapy was associated with an 8-fold reduction in the hazard of progression or death among patients without JCV-DNA in the plasma ($p=0.003$) but only a 3-fold reduction among patients with JCV-DNA in plasma ($p=0.005$) and patients with JCV-DNA in CSF ($p=0.012$).

Conclusions: Detection of JCV-DNA in plasma has low sensitivity but high specificity in PML diagnosis. Presence of JCV-DNA in plasma is associated with a less favorable clinical outcome in patients with PML. Although cART is associated with dramatic reductions in the hazard of progression or death from PML, its effect is attenuated when JCV-DNA is not suppressed in plasma.

Session P-G6 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

CNS Viral Genetics

470 CD4-Independent Infection in the CNS of R5 SHIV+ Macaques Is Associated With Severe Neuropathology

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Background: HIV infection of mononuclear phagocytes in the CNS is the main driving force of HIV-associated encephalitis (HIVE). Neurotropism is primarily determined by the env gene, which seems to evolve independently in this anatomic region. The emergence of highly macrophage-tropic viral strains that engage CD4 and CCR5 receptors differently or require little or no CD4 for entry has been reported in HIV and SIV infection of the brain, and appears to be the main selective pressure in this compartment. Here we aimed to characterize Env variants within the brain of R5 SHIV-infected macaques with giant cell encephalitis (SHIVE) to determine the phenotypes associated with neurologic disease spectrum.

Methodology: Samples from the CSF, blood and brain were collected at the time of necropsy from five encephalitic animals infected with R5 SHIV-B and two encephalitic animals infected with SHIV-C. Full-length envelope glycoprotein gp160 (env) was obtained by single genome amplification (SGA) or bulk PCR. Phylogenetic analyses were performed to genotypically characterize the variants, and single round replication competent viruses were generated and assessed for infection of CD4low cells and CD4negative cells. Moreover, brain tissue sections were pathologically analyzed using in situ hybridization and immunohistochemical techniques.

Results: Phylogenetic analysis of env gp120 V3-V5 sequences obtained from the CSF and plasma of the SHIVE animals showed a correlation between lack of viral compartmentalization and severity of neuropathology. Furthermore, Envs isolated from animals with the most severe lesions showed an increased ability to infect primary macrophages and CD4low cells. Histologic examination showed that compared to animals presenting milder forms of CNS pathology, animals with severe and extensive lesions had the most pronounced macrophage/microglial activation and the strongest SIV in situ labeling in resident microglia and astrocytes. In agreement with these findings, the ability of viral infection in the absence of CD4 was more readily detected in the brain and CSF compartments of the animals with severe encephalitis.

Conclusions: The severity of neuropathological changes is associated with macrophage tropism of Envs from the CNS, and further evolution to CD4-independence and infection of resident microglia and astrocytes. The R5 subtype B and C SHIVE macaques on which this study was based provide a new and robust model to further our understanding the role of the HIV envelope in neuropathology and residual virus in the CNS, providing information that should guide efforts toward eradicating HIV from the body.

471 HIV-Associated Neurocognitive Disorder Is Associated With HIV-1 Dual Infection

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Background: HIV-1 dual infection (DI) has been associated with decreased CD4 T-cell counts and increased viral loads. The same markers are also associated with the development of HIV-associated neurocognitive disorder (HAND), which continues to be a prevalent and debilitating problem among HIV-infected individuals in the era of antiretroviral therapy (ART). Despite this, the neurological sequelae of DI are poorly characterized. We used next-generation sequencing (NGS) to measure the prevalence of DI among ART-suppressed CHARTER cohort participants, and examine the relationship between HAND and DI.

Methodology: CHARTER cohort participants were selected who had > 4 years of follow-up and were suppressed on ART (N=34). NGS (454 FLX Titanium, Roche) was performed on PBMC-derived HIV-1 DNA populations using four PCR-amplified coding regions (env C2-V3, gag p24, pol RT, and pol PR). Samples were classified as DI when (i) maximal genetic diversity exceeded previously optimized thresholds, (ii) phylogenetic reconstruction showed two divergent populations supported with bootstrap values >95%, and (iii) local BLAST ruled out contamination with in-house strains. All study participants underwent neurocognitive, substance use, and neuromedical measurements at each study visit. A global deficit score indicative of HAND was derived from a comprehensive battery of neuropsychological tests adjusted for demographics and corrected for practice effect over time. Participants with comorbidities confounding HAND were excluded.

Results: Of 34 participants, 21 (62%) remained neurocognitively normal throughout the study period and 13 (38%) showed varied degrees of impairment. In univariate analyses, timepoints with HAND were associated with lower CD4 T-cell counts and with a shorter estimated duration of infection ($p < 0.05$). Despite ART, 27 participants had detectable HIV viral loads, but these levels were not significantly different between the normal and impaired groups ($p = 0.866$). Nine study participants had evidence of DI in at least one HIV coding region [prevalence of 26.5%, 95%CI 13.8%-43.1%]. Among the 13 participants with HAND, 7 (54%) had DI in at least one timepoint, while 2 out of 21 (9.5%) neurocognitively normal participants had evidence of DI ($p < 0.05$).

Conclusions: Using NGS, we identified a high (26.5%) prevalence of DI in a population of virally suppressed HIV-infected individuals. The presence of neurocognitive impairment was associated with DI, lower CD4 counts and with shorter duration of infection. These data suggest that DI may play an important role in the development of HAND among at-risk infected individuals, perhaps due to increased viral diversity, although the elucidation of proximate causes will require further investigation.

472 Single Genome Analysis Reveals Genetic Characteristics of Neuroadaptation Across HIV-1 Envelope

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Background: The prevalence of HIV-1 associated neurocognitive disorders (HANDs) has been estimated to be 45-50% in the CHARTER study. In the cART era, this disease burden is largely represented by asymptomatic and mild neurocognitive disease (ANI and MND). We hypothesized that detailed analyses of full-length HIV-1 *env* (>2.5Kb) would allow for the identification of genetic characteristics associated with the presence of viral variants in the CNS.

Methodology: We used single genome amplification to generate full-length HIV-1 *env* clade B variants from the paired CSF and plasma samples of 15 chronically infected HIV+ subjects from CHARTER with no neurocognitive impairment (NCI) (N=6), ANI (N=7) and MND (N=2). Subjects were viremic and either treatment nave (N=8) or experienced (N=7). We used phylogenetic analyses to determine viral compartmentalization, potential N-linked glycosylation sites (PNLGS) and genetic diversity. We identified patterns of compartmentalization with the Viral Epidemiology Signature Pattern Analysis software and the CorMut package was used to detect correlated mutations.

Results: We analyzed 717 confirmed single genome sequences (SGS) and found that various degrees of compartmentalization exist across disease states and histories of cART utilization. In individuals with compartmentalized virus, mean HIV-1 *env* diversity was lower in CSF- than in plasma-derived variants (p=0.04). Mean V1V2 loop length was shorter and the mean number of PNLGS was lower in CSF-derived variants compared to their paired plasma counterparts (p=0.01 and p=0.04). The correlation between V1V2 loop length and number of PNLGS in CSF variants was significant (p=0.02, r^2=0.34). Mean viral diversity (CSF + plasma) and V1V2 length (CSF) did not differ significantly between individuals without NCI and those with ANI or MND (p>0.05 for all comparisons). In individual phylogenies, we identified HIV-1 *env* positions where the dominant amino-acid differs significantly between CSF and plasma quasispecies in both variable and constant regions of gp120 as well as in gp41 (Bonferroni corrected $p<2\text{-}7\text{x}10^{-4}$). Comparing positions across individuals, we identified 25 compartmentalization hotspots across the *env* gene. These include the previously identified HXB2 gp160 position 308 (V3 13), as well novel positions at 463 (V5 4) and 641 (gp41 130). Correlated mutation analyses reveal that a subset of the amino-acid residues in these positions form a network of significant correlations, with mutual information scores > 0.1.

Conclusions: Detailed analyses of SGS-derived full length *env* from subjects with the most common HAND diagnoses in the cART era allowed us to confirm and extend current knowledge of the genetic characteristics associated with HIV-1 *env* neuroadaptation.

Session P-G7 Poster Session
Thursday March 6, 2014, 2:30 PM–4:00 PM Exhibit Hall A
ART Effects On HAND and CNS Reservoirs

473 HIV-1 Replication in Central Nervous System Increases Over Time On Protease Inhibitor Only Therapy

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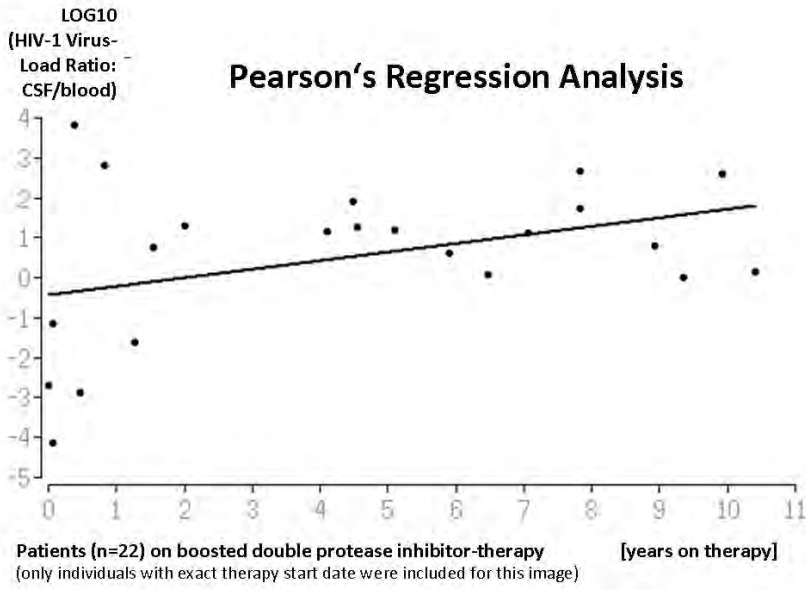
Background: Class sparing antiretroviral therapy with only protease inhibitors (PI) had been associated with central nervous system (CNS)-replication of HIV-1, probably due to impaired CNS penetration-effectiveness, but clinical confirmation is scarce.

Objective was to evaluate risk factors for CNS replication of HIV-1 in patients on only boosted PI, versus nucleoside reverse transcriptase inhibitor (NRTI)-containing triple therapy.

Methodology: Retrospective case-control study (1:5-ratio), with patients from a large German HIV-treatment unit, data were collected from 2005-2013. All patients with available data on antiretroviral therapy, clinical and demographic characteristics, and paired results from simultaneous HIV-1 load-assessments in cerebrospinal fluid (CSF) and blood plasma, were eligible. CSF was collected for various reasons, patients were both neurologically symptomatic, or asymptomatic. A virus-load (VL)-ratio for CSF/blood-quotient was built, and patients were evaluated according to treatment with either only boosted PI (cases), or NRTI-containing triple therapy (controls). Univariate group statistics and Pearson's regression analysis for time-dependent results for PI-patients were generated.

Results: 155 patients were evaluated: 24 cases and 131 controls. All cases used boosted double PI-regimens, consisting of saquinavir (21), lopinavir (20), atazanavir (4), fosamprenavir (2) and indinavir (1), respectively. At time of CSF collection, the mean age was 47 years (y), 22% were female, time from first HIV-diagnosis was 10.2y (cases 15.7 vs controls 9.2, $p<0.001$), the mean number of regimens was 7.39 for cases and 4.24 for controls ($p=0.002$), and median CD4 count were 186/mm3, or 162/mm3 (n.s.). The proportion of patients with undetectable HIV-1 in CSF was 25% for cases and 49.6% for controls ($p=0.026$) whereas in blood 46% vs. 41% (n.s.). Median CSF-VL was 600 cop/mL for cases, and 50 cop/mL in controls ($p=0.027$); median VL from blood was 115cop/mL, or 173cop/mL (n.s.). Mean VL-ratio was 342.91 for cases and 54.48 for controls ($p=0.002$). Pearson's regression analysis showed an increasing trend for VL-ratio over time for cases (see figure).



Conclusions: In this unselected cohort, HIV-1 replication in CSF was higher for patients on only PI, than for those on NRTI-containing triple therapy, supporting a worse CNS-penetration effectiveness for used PI. Patients' over time rise in CNS-viral replication suggests that this effect was time-dependent.

474 Low Prevalence of Neurocognitive Impairment in a Swedish Cohort of HIV-1 Infected Individuals

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Background: Prevalence of HIV-associated neurocognitive disease (HAND) is not clear and cross-sectional studies report rates from 19 to > 50%. CogState is a validated computerized neurocognitive (NC) test where measures of processing speed, attention, working memory and learning show strong correlations with conventional neuropsychological tests. CogState has been validated in patients with AIDS and ADC and in HIV patients without dementia.

Methodology: This is a cross-sectional study of 91 HIV-infected patients who performed a LP and CogState test between Jan 2011 and July 2013. Mean age was 46 yrs, 74% men. Transmission route was: heterosexual 64 %, homosexual 32 %, IVDU 2%, bloodtransfusion 1% and MTCT in 1%. 58 (64 %) were on ART. 2% had an ongoing substance abuse. 8% had previous or ongoing CNS symptoms. CogState Brief Battery include 4 tests: detection (psychomotor function/attention), identification (speed of information processing/attention), one card learning (learning) and one back test (working memory). Questions were asked: "Do you feel depressed?", "Do you experience memory or concentration difficulties?" and "Do you have problems performing your work or in your daily activities such as shopping, paying bills or home maintenance?". CSF was analyzed for WBC, HIV RNA, neurofilament light protein (NFL), β2-microglobulin, neopterin and IgG-index. Plasma was analyzed for CD4-cell count (cc) and HIV RNA.

Results: 88% of patients on ART had plasma HIV RNA <50 cop/mL and 93% had CSF HIV RNA <50 cop/mL. 8 (9%) performed <1 SD on two or more NC tests. 5/8 (6%) reported memory or concentration difficulties, and 3(3%) had difficulties in ADL, classified as HIV-1 associated mild neurocognitive disorder (MND). 75% of all performed within 1 SD in all 4 tests. 26 (29%) had memory or concentration difficulties and they had lower mean CD4 cc (336 cells/μL) than asymptomatic patients (496 cells/μL) ($p<0.05$), lower nadir CD4 cc (116 cells/ μL vs 201 cells/ μL, $p< 0.01$) more problems in ADL ($p<0.01$) and symptoms of depression ($p<0.0001$). No differences were found between groups in CogState tests or CSF variables. All results remained adjusting for ART. There were no differences between patients on ART and naïve patients regarding NC performance, memory or concentration difficulties, symptoms of depression or ADL problems.

Conclusions: This study indicates a low prevalence of HAND in a well treated cohort with low prevalence of confounding factors. The majority (75%) performed normally in all four tests which exclude the classifications of ANI, MND or HAD even if one more cognitive domain was assessed. Memory and concentration difficulties was not associated with CSF variables, but with symptoms of depression and low CD4-cell count.

475 Novel Method for More Reliably Estimating the Burden of Cognitive Impairment in HIV

Tanja Su[1], **Judith Schouten[2,3]**, Gert J. Geurtsen[2], Ferdinand W. Wit[3,4], Ineke G. Stolte[5], Peter Portegies[2,6], Matthan W. A. Caan[1], Peter Reiss[3,4], Charles B. Majoie[1], Ben A. Schmand[2,7], on behalf of the AGEhIV Cohort Study Group

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Background: The commonly used published Frascati criteria likely overestimate HIV-associated neurocognitive disorder (HAND) prevalence. Modified criteria proposed by Gisslèn attempt to reduce sensitivity while retaining specificity. Multivariate normative comparison (MNC), specifically designed to control for false-positive rate while retaining sensitivity, is a novel and potentially more accurate technique for evaluating cognitive impairment (CI).

Methodology: 103 HIV-infected men with suppressed viraemia on cART for ≥12 months and 75 uninfected male controls (comparable regarding age, ethnicity, IQ and education), all aged ≥45 and participating in the AGEhIV cohort study, underwent neuropsychological assessment (covering fluency, attention, information processing speed, executive function, memory and fine motor function). Frascati and Gisslèn criteria were applied to detect HAND. Next, MNC was used to compare all test scores of each HIV-positive individual against the distribution of test scores of the total control group. MNC uses Hotelling's T2 to statistically compare multiple characteristics of an individual against the distributions of the same characteristics in a control group taking the covariance between all characteristics into account. The false positive rate (alpha, which is selectable at any percentage) was set at 5% one-tailed, providing a specificity of at least 95%.

Results: HIV-positive men as a group performed worse compared to uninfected controls on all domains tested, although differences were not statistically significant.

Applying Frascati criteria, HAND was present in 49 HIV-positive (48%) but also in 31 uninfected men (41%) ($p=0.41$), and by Gisslèn's criteria in 15 HIV-positive (15%) and 7 uninfected men (9%) ($p=0.30$). Using MNC, CI was detected in 32 HIV-positive men (31%) (Table).

Conclusions: Cognitive impairment by Frascati criteria was highly prevalent in HIV-positive but nearly equally so in uninfected men, confirming low specificity of this method. Although HAND prevalence was reduced applying Gisslèn's criteria, it remained nearly as prevalent among uninfected controls, indicating improved sensitivity but continued low specificity. Applying MNC with its low false-positive rate provided a more accurate estimate of HIV-associated cognitive impairment of approximately 30 percent in HIV-infected men with suppressed viraemia on cART.

Table 1

	Cognitive impairment								
	Frascati			Gisslèn			MNC		
	HIV+	HIV-	p-value	HIV+	HIV-	p-value	HIV+	HIV-	p-value
HAND diagnoses (no, %)	49(48%)	31(41%)	0.41	15(15%)	7(9%)	0.30	32(31%)	<5%*	-
Asymptomatic neurocognitive Impairment (ANI) (no, %)	30(29%)	13(17%)	-	3(3%)	1(1%)	-	No subclassification		
Mild neurocognitive disorder (MND) (no, %)	14(14%)	17(23%)	-	11(11%)	5(7%)	-			
HIV-associated dementia (HAD) (no, %)	5(5%)	1(1%)	-	1(1%)	1(1%)	-			

* The false positive rate (alpha) was set at 5% one-tailed, thus the specificity was at least 95%.

476 Improvement of Depression and Anxiety After Discontinuation of Long-Term Efavirenz Treatment

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Background: Efavirenz is part of first-line antiretroviral therapy guidelines of WHO since 2002. The side effects of efavirenz are mainly neuropsychiatric and generally considered to be mild and transient. Recent studies indicate however that discontinuation of chronic efavirenz treatment can be observed in up to 50% of cases, possibly related to long term neuropsychiatric side-effects. The aim of this study was to 1) assess neuropsychiatric symptoms in HIV-infected patients on long-term efavirenz therapy and 2) study the effect of a switch to non-efavirenz containing anti-retroviral treatment on neuropsychiatric symptoms.

Methodology: In an observational clinical trial, 47 HIV-infected participants on long-term efavirenz treatment were included with suppressed viral loads and high CD4 cell counts. 23 reported signs and symptoms (mainly neuropsychiatric symptoms or physical complaints) and 24 asymptomatic patients were included as controls. All participants completed three self-report questionnaires on neuropsychiatric symptoms.

All symptomatic patients were switched to a non-efavirenz containing regimen and were retested 2 week and 3 months after switching. The depression-anxiety-stress-scale (DASS) was used to assess anxiety, depression and stress, the symptom-checklist (SCL-90) to assess a variety of neuropsychiatric symptoms and the outcome-questionnaire (OQ-45) to assess daily life functioning. Data were analyzed using multivariate ANOVA for baseline group comparisons and repeated measures ANOVA to analyze any change in the group of switchers over time. Linear regression was used to analyze prediction of symptom change after switching.

Results: Neuropsychiatric symptoms were common among HIV-infected patients on long-term efavirenz therapy, mainly being depression, anxiety, stress, insufficiency in thinking and paranoia. After switching, these symptoms improved significantly to near normal levels. These effects were most prominent for depression, anxiety and stress symptoms (using DASS and SCL-90). Improvement in neuropsychiatric symptoms was best predicted by high baseline symptoms, using the SCL-90.

Conclusions: Neuropsychiatric symptoms are common among HIV-infected subjects and may be caused by different factors/agents, including long-term efavirenz use. Neuropsychiatric assessment, the SCL-90 in particular, could identify those that may benefit most from the discontinuation of efavirenz.

477 New Advanced EEG Technique To Monitor Early Brain Damage in Naïve HIV and Its Recovery During ART

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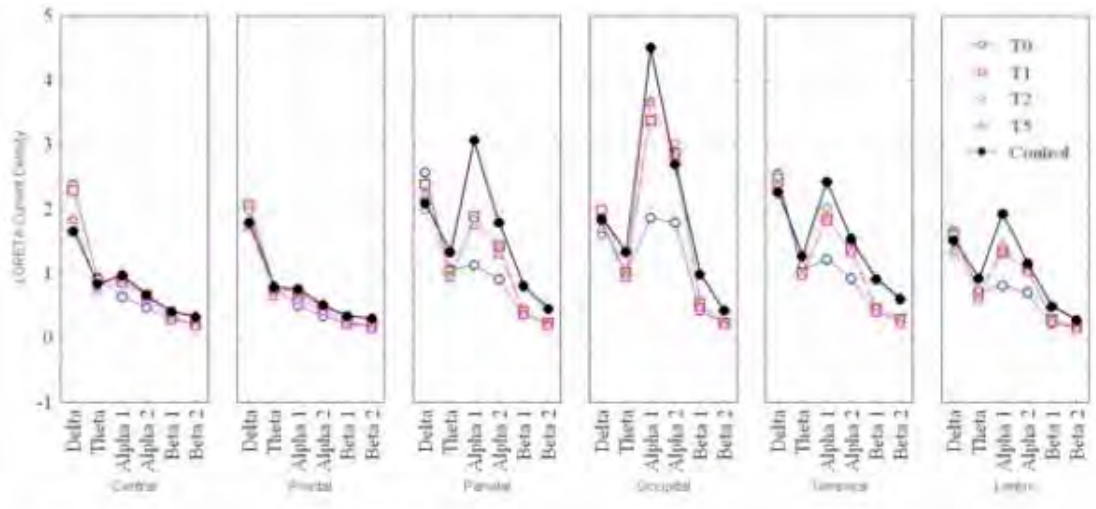
Background: HIV patients may show a wide spectrum of cognitive deficits from mild forms up to dementia demostrable with neuropsychological tests; however earlier deficits can be hidden for years by brain neuroplasticity and these result in an absence of symptoms. Cognitive impairment is typically accompanied by a pathological increase of EEG rhythms at frequencies <4 Hz (delta) and by a decrease of dominant rhythms at 8-12 Hz (alpha). We demonstrate that these EEG rhythms are abnormal in asymptomatic naïve HIV subjects and show recovery under antiretroviral therapy.



EEG rhythms improvement during ART.
T0: baseline; T1: after 4 weeks of ART; T2: after 8 weeks of ART; T5: after 20 weeks of ART.

Methodology: Resting state eyes-closed EEG rhythms were recorded in 38 HIV subjects asymptomatic for neurocognitive deficits before and after twenty weeks of ART and in a control group of HIV-negative subjects. EEG data were recorded in eyes closed resting state subjects according to a 10-20 system. EEG rhythms of interest were delta (2-4 Hz), theta (4-8 Hz), alpha1 (8-10 Hz), alpha2 (10-12 Hz), beta1 (13-20 Hz) and beta2 (20-30 Hz). To spatially enhance the recorded data, cortical EEG sources were estimated by low resolution electromagnetic tomography (LORETA - a freely downloadable software). ANOVA was used for statistical analysis.

Results: Central and parietal delta sources showed a higher amplitude in the HIV group at baseline than in the control healthy group ($p<0.001$). The opposite was true for alpha sources ($p<0.05$ to 0.000005). Furthermore theta, alpha1, alpha2, beta1 and beta2 sources were lower in amplitude in the treated subjects than in the control ($p<0.05$ to 0.00001). Compared to the baseline, the treated subjects were characterized by a recovery of the EEG rhythms in lower central and parietal delta sources ($p<0.05$) and higher parietal, occipital and temporal alpha1 sources ($p<0.05$). (Picture)

Conclusions: Advanced EEG techniques developed by LORETA unveil abnormalities of the resting state rhythms in asymptomatic naïve subjects, but also their recovery in just a five months period of ART. These EEG markers reflect both HIV progression and ART neuroprotective effects in HIV subjects, toward a simple and cheap clinical application up to a therapeutic optimization. Furthermore LORETA can represent in the future a sensitive and specific method of evaluation of HIV infection in the CNS since also able to detect virological blip.

478 HIV-Replication Control Rates Needed To Prevent Neurocognitive Performance (NP) Decline

Ignacio Pérez-Valero[1], Robert Heaton[2], Donald Franklin[3], Scott Letendre[2], Reena Deutsch[2], Bernard Gelman[4], David Simpson[5], Ann Collier[6], Igor Grant[2], and the CHARTER Group

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Background: There are controversies regarding the level of HIV-suppression needed to prevent neurocognitive performance (NP) decline and the capacity of different ART types to prevent NP decline in HIV-suppressed patients.

Methodology: Prospective comparison of NP decline rates in non-HIV controls (HIV-) and HIV-infected volunteers (HIV+) with $\geq$2 years of follow up presenting 1 of these 3 patterns of HIV virological control: Always suppressed (AS) on ART (HIV RNA <50cop/mL); Sometimes suppressed on ART (SS); And always detectable despite ART (AD). Patients were selected from CHARTER and HNRP cohorts. A comparison between HIV+ AS treated with PI+2NRTIs vs. NNRTI+2NRTIs was also performance. NP decline was defined using regression-based norms for NP change that corrected for all known factors that may influence test-retest differences in normals (Cysique et al. J Clin Exp Neuropsychol 2011; 33:505-22).

Results: 93 HIV- and 346 HIV+ (AS: 103, SS: 112 and AD: 131 patients) were analyzed. Overall, HIV+ were more frequently ($p=0.004$) males (80.6% vs. 66.7%) of older age (mean: 43.8 vs. 36.1 years; $p=0.001$) than HIV-. Proportions of NP decline were, after a median time of follow up of 2.5 years: HIV- 15%, AS 18.5%, SS 22.3% and AD 26%). Comparing to HIV-, only HIV+ AD presented higher rates of NP decline ($p=0.046$), after adjusting for significant cofactors: Neurological comorbidities ($p=0.031$) and history previous ART regimens ($p=0.004$). In the HIV+ AS group, 37 volunteers received NNRTI+2NRTIs and 43 PI+2NRTIs. Comparing both ART groups, HIV+ AS on PI+2NRTIs had similar baseline characteristics than NNRTI+2NRTIs except for a lower CD4 nadir (median: 93 vs. 180 cells; $p=0.041$) and a lower CPE score vs. 2.0 (median: 7 vs. 8; $p=0.045$). NP decline of HIV+ AS on PI+2NRTIs was 7% vs. 24.3% on NNRTI+2NRTIs ($p=0.03$). This difference was independent of significant cofounders (CD4 nadir and CPE score vs. 2.0). Relative risk for NNRTI+2NRTIs group was 3.49 (1.02-11.93).

Conclusions: Comparing to HIV-, higher rates of NP decline were only detected in HIV+ AD. Higher rates of NP decline were observed in HIV+ AS on NNRTI+2NRTIs than in HIV+ AS on PI+2NRTIs.

479 CSF Biomarker Profile in HIV Patients With and Without CSF Viral Escape

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[1]Hospital Universitario La Paz, Madrid, Spain, [2]University of California, San Diego, San Diego CA, United States, [3]University of California San Diego, San Diego, CA, United States, [4]Mount Sinai School of Medicine, New York, NY, United States

Background: The association between levels of inflammatory biomarkers and CSF Viral Escape (CVE) is unexplored.

Methodology: Cross-sectional analysis performed to compare levels of inflammatory biomarkers in patients with and without CVE (HIV-RNA >50cop/mL in CSF and <50cop/mL in plasma). Individuals followed in two large HIV Cohorts, tested for CSF and blood biomarkers of immune activation (CXCL10, IL6, TNF-Alpha, MCP-1 and WBC) were included. Blood and CSF biomarkers along with demographics and HIV-related clinical data of patients with and without CVE were compared using multivariable logistic regression.

Results: 296 patients were evaluated: Mean age 46.6 years, 58% Caucasian, 87% male with a mean time of HIV-infection of 12.4 years and median CD4 nadir of 110 cells. CSF Viral Escape was detected in 8 patients (2,7%). Subjects' characteristics were similar, regardless of CVE status, except for a longer HIV-infection (mean time 17.4 vs. 12.3 years; $p=0.049$) and a lower CD4 nadir (median 12 vs. 115 cells; $p=0.038$) associated with CVE. Median CSF CXCL10 levels were higher (6416 vs. 2771; $p=0.011$) while median plasma IL-6 levels were lower (1.56 vs. 2.97; $p=0.049$) in presence of CVE. Proportion of patients presenting CSF WBC pleocytosis was also higher (50% vs. 12.3%; $p=0.002$) in the CVE group. After logistic regression analysis, CXCL10 was the unique factor that remained independently associated with CVE ($p<0.001$).

Conclusions: CSF CXCL10 is elevated in patients with CVE, implying higher immune-activation and inflammation in their CNS, but our cross-sectional study cannot distinguish if these elevated levels are a cause or effect of CVE.

480 Accuracy of NEU Screen for Detecting Cognitive Impairment in Virologically Suppressed HIV Patients

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Background: The NEU Screen is a method recently proposed to help in the diagnosis of HIV-associated neurocognitive disorders (HAND). We tested this tool in a sample of virologically suppressed HIV-infected patients to investigate both sensitivity and specificity in comparison with those found in the original study.

Methodology: In a sample of 156 virologically suppressed HIV-infected outpatients the accuracy of the NEU Screen was analyzed, establishing as a gold standard the existence of neurocognitive impairment (NCI). All subjects had available neurocognitive information through the application of a comprehensive battery of neuropsychological tests, and clinical and demographical information was accessible as well. Sensitivity and specificity tests were applied to study the accuracy of the NEU Screen detecting NCI, and logistic regression was used to analyze clinical and demographic variables linked to the correct classification.

Results: Subjects were mostly men (81%), with a median (IQR) age of 43 (38;50) years, current CD4 cell count of 522 (380;718) cells/µL, nadir CD4 cell count of 188 (80;285) cells/mL, and HCV seronegative (73%). The rate of NCI was 52% and appeared significantly associated with time since HIV diagnosis (p=0.01). A trend towards worse neurocognitive functioning was also observed in relationship with lower nadir cell counts (p=0.17) and existence of potential confounding comorbidities for NCI (p=0.15). When the combination of scores included in the NEU Screen was analyzed for the detection of NCI, the sensitivity (95% CI) observed was 73.1% (62%;82%), specificity 74.3% (62.6%;83.4%), positive predictive value 75.9% (64.7%;84.5%), and negative predictive value 71.4% (59.8%;80.8%). According to logistic regression models, the correct classification of NCI by the NEU Screen was unrelated to any relevant demographic or clinical variable.

Conclusions: The NEU screen confirms in this work fairly high sensitivity and specificity to detect NCI in HIV population. This method includes 3 paper-based neurocognitive tests, has an expected time for administration of ≤10 minutes, and appears to be also useful detecting NCI in virologically suppressed HIV-infected patients.

481 Determinants of Cognitive Impairment in HIV-Positive Men On cART and Uninfected Controls

Judith Schouten[1, 2], Tanja Su[3], Ferdinand W. Wit[2, 4], Neeltje A. Kootstra[5], Matthan W. A. Caan[3], Gert J. Geurtsen[1], Ben A. Schmand[1, 6], Charles B. Majoie[3], Peter Portegies[1, 7], Peter Reiss[2, 4], on behalf of the AGEhIV Cohort Study Group

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Background: HIV-positive individuals may be at increased risk of cognitive impairment (CI). The contribution of HIV-, antiretroviral treatment- and non-HIV-related risk factors towards CI remains to be clarified further.

Methodology: 103 HIV-infected men with suppressed viraemia on cART for ≥12 months and 75 uninfected male controls (comparable regarding age, ethnicity, IQ and education), all aged ≥45 and participating in the AGE_hIV cohort study, underwent neuropsychological assessment (covering fluency, attention, information processing speed, executive function, memory and fine motor function). CI was assessed using Frascati criteria and by multivariate normative comparison (MNC), a novel and more accurate technique for evaluating cognitive impairment (CI). MNC was used to compare all cognitive test scores jointly from each HIV-positive individual with the distribution of scores from the total uninfected control group. The false positive rate (alpha) was set at 5% one-tailed, providing a specificity of at least 95%. Multiple logistic regression was used to identify determinants for CI.

Results: The numbers of participants with CI in each group using either Frascati criteria or MNC are shown in the Table. Adjusting for age, education and native language, depressive symptoms remained borderline significantly associated with CI by both methods, whereas HIV-status did not.

In HIV-positive men after adjusting for the same parameters, depressive symptoms, years spent with CD4 counts <350 cells/mm^3 and higher soluble CD163 levels, were independently associated with CI, both by Frascati criteria and MNC. A lower central nervous system penetration effectiveness (CPE) score was independently associated with CI, but only when applying Frascati criteria.

Risk factors that were not significantly associated with CI are listed in the Table.

Conclusions: The presence of depressive symptoms was associated with cognitive impairment, and in HIV-infected men with suppressed viraemia on cART, together with a longer time spent with reduced CD4 counts and evidence of increased innate immune activation contributed to the risk of CI, regardless of the method by which CI was assessed. The contribution of the CPE score was less consistent.

Cognitive Impairment						
	Frascati			**MNC**		
	HIV+ (no, %)	**HIV- (no, %)**	**p-value**	**HIV+ (no, %)**	**HIV- (no, %)**	**p-value**
HAND ANI MND HAD	49 (48%) 30 (29%) 14 (14%) 5 (5%)	31 (41%) 13 (17%) 17 (23%) 1 (1%)	0.41 - - -	32 (31%) No subclassification	<5%#	
	Outcome: CI using Frascati			**Outcome: CI using MNC ^**		
Multiple logistic regression*	**Odds ratio**	**95% CI**	**p-value**	**Odds ratio**	**95% CI**	**p-value**
HIV-positive status	1.06	0.55-2.03	0.867	-	-	-
Beck Depression Inventory score	1.07	1.00-1.15	0.062	1.08	0.99-1.18	0.070
HIV+ group only	**Odds ratio**	**95% CI**	**p-value**	**Odds ratio**	**95% CI**	**p-value**
Years CD4 <350 cells/mm^3 (per additional year)	1.22	1.03-1.44	0.025	1.17	1.01-1.36	0.032
Soluble CD163 (per 100 ng/mL increase)	1.32	0.99-1.77	0.057	1.32	1.01-1.72	0.045
CNS Penetration Effectiveness score (per point increase)	0.53	0.32-0.88	0.015	0.73	0.47-1.14	0.168
Beck Depression Inventory score (per point increase)	1.10	1.00-1.21	0.050	1.10	1.01-1.21	0.033

ANI=asymptomatic neurocognitive impairment

MND=mild neurocognitive disorder

HAD=HIV-associated dementia

False positive rate (alpha) set at 5% one-tailed, thus specificity was at least 95%.

* Models adjusted for age, education and native language.

^ MNC: logistic regression possible only on the HIV+ group.

The following risk factors were not significantly associated with CI:

Intoxications: Cannabis/cocaine/ecstasy,alcohol,prior IV drug use.

Cardiovascular risk factors: Hypertension, diabetes, smoking,BMI, waist-hip ratio, waist circumference,prior cardiovascular disease (myocardial infarction, angina pectoris, stroke or peripheral arterial insufficiency), dyslipidemia (including total chol, LDL, HDL and triglycerides), lipoprotein(a), lipid lowering medication, positive family history for myocardial infarction.

Inflammatory markers: C-reactive protein, D-dimer, soluble CD14.

HIV-specific factors: Duration of HIV-infection, duration of ART use, mean CD4 count during the year prior to enrolment, years with CD4 <200/100 cells/mm^3, years spent with a(n) (un)detectable plasma viral load, AIDS, current/prior/cumulative duration of efavirenz use.

482 HIV Reactivation by the Histone Deacetylase Inhibitor Panobinostat: Effects On CNS

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Background: Histone deacetylase inhibitors (HDACi) are currently being evaluated in experimental clinical trials for their ability to reactivate HIV-1 expression in latently infected cells with the aim of eradicating the latent HIV-1 reservoir. Panobinostat has previously been shown to reactivate HIV-1 expression in latently infected cells in vitro.

However, caution has been raised that reactivation of latent HIV-1 could potentially have harmful consequences on the brain. The proposed adverse effects on the central nervous system (CNS) include neuronal injury caused by activated T cells or by early viral proteins induced by HDACi, CNS immune reconstitution inflammatory syndrome and, finally, adverse effects on brain function due to elimination of latently infected microglia and/or astrocytes.

Methodology: In a clinical trial among HIV-infected adults on suppressive combination antiretroviral therapy (cART), patients were treated with the potent HDACi panobinostat (20 mg orally 3 times per week every other week over the course of 8 weeks). To address whether viral reactivation induced by panobinostat was associated with adverse effects on CNS, we evaluated biomarkers of neurodegeneration and neuroinflammation in cerebrospinal fluid (CSF) obtained before panobinostat administration and during the final dosing week.

Biomarkers of neurodegeneration and neuroinflammation were determined by enzyme-linked immunosorbent assays. C-reactive protein (CRP) was determined by a particle-enhanced immunoturbidimetric assay. Changes from baseline in biomarker levels were tested using Wilcoxon signed rank test.

Results: Among study subjects who consented to lumbar punctures (11 of 15 participants) we found no significant change from baseline to the final panobinostat treatment week neither in biomarkers of neurodegeneration (total tau, phosphorylated tau, soluble amyloid-β) nor in biomarkers of neuroinflammation (CRP, soluble CD14, soluble CD163, neopterin, monocyte chemotactic protein-1 (MCP-1), interferon-γ induced protein-10 (IP-10), macrophage inflammatory protein-1β (MIP1-β), matrix metallopeptidase-9 (MMP-9)).

Conclusions: Repeated, cyclic treatment with the HDACi panobinostat was not associated with CNS adverse effects as measured by CSF biomarkers of inflammation and neurodegeneration in HIV patients on suppressive cART.

Session P-G8 Poster Session
Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall A**

CNS Inflammation, Immune Activation, and HAND Biomarkers

484 Differences Between Cerebrospinal Fluid and Blood Biomarkers of Inflammation in HIV Infection

Julia Peterson[1], Sheila Keating[2], Dietmar Fuchs[3], Phillip Norris[2], Henrik Zetterberg[4], Barbara Shacklett[5], Serena Spudich[6], Magnus Gisslén[4], Richard W. Price[1]
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Background: HIV central nervous system (CNS) infection is associated with local inflammation that evolves over the course of systemic disease and impacts neurological function. To compare CNS and systemic inflammation, we assessed 10 inflammatory biomarkers in cerebrospinal fluid (CSF) and blood across a spectrum of subject groups.

Methodology: This exploratory cross-sectional study measured 10 inflammatory biomarkers (TNF-α, MMP-9, CXCL10, sCD14, sCD163, sVCAM, CCL2, IL-6, TIMP-1 and neopterin) by EIA in 9 subject groups: HIV uninfected controls (HIV-, N=20); primary HIV infection (PHI, 24); untreated neuroasymptomatic subjects in 4 blood CD4+ cell strata, >350, 200-349, 50-199 and <50 cells/μL (NA, 20 each); untreated HIV-associated dementia (HAD, 12); treated, virally-suppressed (Rx, 19) and elite controllers (EC, 8). Exploratory analysis applied nonparametric methods to *a priori* group comparisons: PHI to HIV-; across the 4 NA groups; HAD to combined subject groups with <200 CD4 cells/μL; and Rx and EC to HIV (significance set at $P<0.05$). Relationships among CSF and blood biomarkers along with background variables including CSF neurofilament light chain protein (NFL) across the entire sample set were explored by Spearman correlation.

Results: CSF and blood showed a broad increase in inflammatory biomarker concentrations in PHI with increases in TNFα, CXCL10, sCD14 and neopterin in both compartments, sVCAM in CSF, and sCD163 in blood. With progression of systemic disease, patterns of biomarker changes in the four NA groups diverged between CSF and blood. Whereas CSF concentrations of TNFα, MMP-9, CXCL10 decreased in the CD4 <50 group compared to one or more groups with higher CD4 counts, blood inflammatory biomarkers either increased with falling CD4 or remained relatively stable across the four groups, with the exception of MMP-9 concentrations which progressively decreased. CSF concentrations of all the inflammatory biomarkers except MMP-9 were higher in the HAD than the combined <200 CD4 groups. By contrast, blood concentrations did not differ between these two groups. CSF blood markers remained above HIV- levels in the Rx and EC groups including: CSF TNFα, CXCL10, sCD14, sCD163 and sVCAM in Rx and all of these except sVCAM in EC; blood sCD14, CCL2 and neopterin in Rx; and blood CXCL10, sCD163 and TIMP-1 in EC. CSF NFL showed highest correlations with CSF sCD14, sCD163, sVCAM, CCL2 and blood sCD14 and neopterin (all $R>0.5$).

Conclusions: Early parallel increases in CSF and blood inflammatory biomarkers diverge with evolving infection and HAD onset, and support the importance of macrophages in neural injury. Persistent CSF and blood inflammation despite viral suppression suggest incomplete - or a required 'cost' for - control of both systemic and CNS infection.

485 Plasma IP-10 and CSF MIP 1beta Contribute To Progressive Brain Injury in Chronic HIV Infection

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Background: We have recently reported that chronically-infected HIV subjects on stable combined antiretroviral therapies showed significant annual decreases in brain metabolite levels as measured by proton magnetic resonance spectroscopy in all regions examined, including NAA (N acetyl aspartate)-2.95% and Cho (Choline) -2.61% in the frontal white matter (FWM); NAA-1.89%, Cho -2.19% and Glx (glutamine/glutamate)-6.05% in the mid frontal cortex (MF); Glx -2.80% in the basal ganglia (BG). These changes correlated modestly with decreases in cognitive function. The mechanisms underlying this form of progressive brain injury remain poorly understood. The current study aimed to identify host and disease related factors including chemokines that contribute to these changes.

Methodology: We first selected the clinical and host predictors (age, ethnicity, current CD4, nadir CD4, HIV RNA concentration, duration of infection, CPE score, Baseline plasma and CSF IP-10, MCP-1, sCD14, fractalkine, and MIP-1b, using linear mixed effect models. The joint effects of these predictors were then assessed using multivariate mixed models, where each longitudinal MRS measure was entered as a response variable and the explanatory variables were those selected in the first step. Associations are reported at $p<0.05$.

Results: Based on the multivariate modeling, the following baseline factors predicted the observed decreases in brain metabolites: elevated plasma IP10 and CSF MIP-1b were associated with decreases in NAA and Cho in the MFC; and Cho in the FWM; increases in plasma IP10 were associated with a decrease in NAA in the FWM and an elevated CSF MCP-1 was associated with a decrease in BG Glx.

Conclusions: Among the host disease and related factors examined, chemokines, in particular plasma IP10 and CSF MIP1b contribute significantly to changes in brain metabolites reflecting neuronal and glial cell dysfunction. Other factors that were assessed may also contribute to regional injury but only to a small degree. This is among the first studies to show that markers of immune activation play a significant role in progressive brain injury in the setting of chronic HIV infection and cART.

486LB Neuroinflammation in Asymptomatic HIV-Infected Subjects On Effective cART

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Background: Neuroinflammation may contribute to the pathogenesis of HIV-associated cognitive impairment. We undertook cerebral PET imaging using the 18kDA translocator protein TSPO radioligand [11C]PBR28 to assess neuroinflammation in treated HIV-infected subjects without neurological symptoms

Methodology: Cognitively healthy, neurologically asymptomatic HIV-infected subjects (cases) on effective combination antiretroviral therapy (viral load <50 copies/mL) and HIV-negative individuals (controls) underwent a cerebral PET scan with [11C]PBR28. Cases had neuropsychological testing and assessment of cerebral metabolites using proton-magnetic resonance spectroscopy ([H1] MRS) in the right basal ganglia (RBG). TSPO binding affinity was assessed with both high affinity (HABs) and mixed affinity (MABs) binders eligible. A two tissue compartmental model was used to estimate the total volume of distribution (VT) and distribution volume ratios (DVR) in regions of interest (ROIs) including brain stem, basal ganglia and cortical regions in each subject. Differences between groups were assessed using ANOVA and relationships between HIV clinical markers and VT were explored by correlation analyses

Results: 8 HABs, and 4 MABs cases (n=12), mean age (SD) 42.7 (6.4) years and 6 HABs and 4 MABs age-matched controls (n=10), mean age 41.6 (8.6) years were enrolled. Cases had a median (range) CD4 count of 645(350-1240) cells/uL and nadir CD4 count of 196(70-350) cells/uL. The median (range) pre-treatment plasma HIV-RNA of 128639 copies/mL(151 to 1624782). There was a global increase in the mean VT in cases compared to controls with significant increase in VT in the basal ganglia based on the parametric analysis after multiple comparisons correction ($p<0.01$). Significant local increases in DVR were found in the parietal cortex ($p<0.01$) and globus pallidus ($p=0.035$) In HIV cases, despite cognitive function being intact, after controlling for age and education, significant negative associations between [11C]PBR28 binding and performance on both visual learning and working memory tasks were observed in the basal ganglia ($p=0.018$) and parietal cortex ($p=0.025$). Greater [11C]PBR28 binding in the basal ganglia also was associated with both a higher RBG brain myo-inositol/creatine ratio (a marker of glial inflammation) as evaluated by MRS ($p=0.011$) and greater pre-treatment plasma viral load ($p=0.029$). Associations between VT in brain regions and other HIV clinical parameters (including nadir CD4 count, $p=>0.1$) were not observed

Conclusions: Evidence of neuroinflammation on cerebral PET is present in neuro-asymptomatic HIV-infected individuals despite effective control of plasma viraemia and is associated with greater pre-treatment viral load but not nadir CD4 count

487 CSF Biomarkers Correlate With Magnetic Resonance Spectroscopy Metabolites During HIV Disease

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Background: HIV-associated neurocognitive disorders (HAND) persist in the cART era. These disorders adversely affect quality of life, work ability, and overall survival. Persistent immune activation appears to contribute to the pathology of HAND and evidence exists that biomarkers of immune activation correlate with cerebral metabolites measured by magnetic resonance spectroscopy (MRS). The purpose of this analysis was to determine associations between cerebrospinal fluid (CSF) biomarkers and regional cerebral metabolites in a multicenter cohort.

Methodology: Data from 91 participants were analyzed from five sites in the US (Galveston, Baltimore, New York, Seattle, and San Diego) as part of the CHARTER study. MRS concentrations of N-acetylaspartate (NAA), choline (Cho), myo-inositol (MI), and creatine (Cr) were quantified using LCModel in frontal white matter (FWM), frontal gray matter (FGM), and basal ganglia (BG). CSF biomarkers were measured by immunoassay. Multivariable mixed effects models accounted for demographic and disease characteristics as well as proportion of relevant tissue volume within each voxel.

Results: Participants were mostly middle-aged (median age 44) men (84%) on ART (76%). 47% were European-American and 43% African-American. Other median values were: current CD4+ count 458/mm^3 (IQR 311-600), nadir CD4+ count 145/mm^3 (IQR 24-238), $\log_{10}$ HIV RNA 1.72 (plasma) and 1.7 (CSF). 26% were hepatitis C seropositive. Higher (↑) levels of MCP-1 and IP-10 were each associated with ↑levels of MI and Cr in FWM (see Table for adjusted R^2 and p value). A particularly strong association was found between ↑MCP-1 and ↑Cho in BG while a weaker association was found between ↑IP-10 and ↑NAA in FWM. No statistically significant associations were present for sCD14 and SDF-1α.

Conclusions: In this cross-sectional analysis of HIV infected individuals from multiple sites, two CSF biomarkers were associated with cerebral metabolites reflecting energy metabolism, membrane remodeling, neuronal integrity, and glial proliferation. The biomarkers are indicators of monocyte chemotaxis (MCP-1) and antiviral immune responses (IP-10). While Cr was not used as a denominator for metabolite-biomarker associations as in previous studies, the unexpected positive association between IP-10 and FWM NAA warrants further investigation. Frontal white matter was the most commonly involved brain region, which may reflect the impact of immune activation on myelin and axonal integrity.

	MRS metabolite				
CSF biomarker	NAA FWM	Cho FWM	Cr FWM	MI FWM	CHO BG
IP-10	4.52 (0.046)	0.98 (0.351)	10.56 (0.003)	4.95 (0.036)	-
MCP-1	-	0.97 (0.353)	7.49 (0.010)	13.7 (0.002)	17.9 (<0.001)

488 Abdominal Obesity, Inflammation, Immune Activation and Neurocognitive Impairment

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Background: Waist circumference (WC) correlates with the severity of HIV-associated neurocognitive disorder (HAND) that still occurs in ~50% of patients. The mechanism for this relationship is unknown. We postulated that patients with abdominal obesity have increased levels of systemic and CNS immuno-inflammatory mediators that cause neurocognitive impairment (NCI).

Methodology: To explore this hypothesis, we tested stored plasma and CSF from 152 HIV+ patients (151 on cART) from CHARTER study visits with: (a) WC measurements, (b) standardized, comprehensive neuromedical and neurocognitive assessment, c) no CNS confounding conditions (e.g. major trauma, stroke), and (d) plasma HIV RNA <1,000c/ml. Levels of biomarkers in plasma (IL-6, sCD163, and sCD14) and CSF (sCD40L, sTNFrII, MCP-1, sICAM, and MMP-9) were measured. NCI was assessed by a standardized battery of 7 test domains of cognition. The global deficit score (GDS) was calculated for each subject after adjustments for their age, race/ethnicity, and education and a value ≥0.5 defined NCI. Correlational and pathway analyses were performed to explore the relationships of WC as the primary predictor and the biomarkers as mediators in models of NCI.

Results: WC and plasma levels of IL-6 correlated with GDS (WC: rho=0.21, p=0.009 and IL-6: rho=0.17, p=0.04). The correlation of WC with GDS was strongest in participants with the highest tertile of IL-6 levels (rho=0.39, p=0.005) compared to those with the lowest tertile (rho=-0.07, p=0.65). IL-6 only correlated with GDS if WC ≥99cm. For subjects with the highest tertile of CSF sCD40L, a marker of CNS macrophage and microglial activation, the relationship of IL-6 to GDS was greater (rho=0.60, p<0.0001). In subjects with GDS measures at ≥3 visits (6 month intervals) within ±1 year of the index visit, higher IL-6 levels predicted a positive slope of GDS (rho=0.28, p=0.06), implying worsening NCI.

A separate Pathway analysis based on β-regression coefficients produced a strong, integrated model (highly consistent with the data) for subjects in the highest tertile of CSF sCD40L, which showed that a) WC directly affected GDS, b) the effects of WC on GDS were also mediated by IL-6 and c) plasma sCD14, a microbial translocation and monocyte activation marker, positively affected the relationship of WC and IL-6 to GDS.

Conclusions: Abdominal obesity was related to cognitive impairment in well-controlled HIV+ patients with high levels of systemic inflammation (IL-6) and CNS immune activation (sCD40L). These data are consistent with our postulate that abdominal fat releases mediators that drive systemic inflammation and CNS immune activation thereby worsening NCI. These effects may be amplified by monocyte activation (sCD14) due to intestinal translocation of bacterial products.

489 Blood Cell Indices and Neurocognitive Impairment in the HAART Era: A CHARTER Study

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Background: Red blood count (RBC), mean cell volume (MCV), mean cell hemoglobin (MCH), and hemoglobin (Hgb) levels reflect both iron status and changes due to inflammation. Since iron is critical for maintenance of mitochondrial energetics and brain function, and anemia was a risk factor for HIV-associated dementia in the pre-HAART era, we examined the relationship of these indices to risk of neurocognitive disorders (HAND) in the HAART era.

Methodology: We evaluated cross-sectional associations of red cell indices, and time-dependent associations of Hgb, with HAND in the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study, a U.S.-based cohort study of neurological complications in the HAART era. CHARTER study subjects underwent standardized neurocognitive and neuromedical assessments, including RBC, MCV, MCH, and Hgb. HAND was defined by Frascati criteria (absence of neuromedical confounds, at least two impaired cognitive domains, and combined self-report and performance-based assessment of functional impairment). Adjusted β-coefficients (β), odds ratios (OR), or hazard ratios (HR) and their 95% confidence intervals (CIs) were estimated for RBC, MCV and MCH associations with HAND using multivariable (and for Hgb, also time-dependent) regression to adjust for age, sex, ethnicity, HAART, zidovudine (ZDV) use, CD4 nadir, plasma viral load, and wide-range achievement test score at entry.

Results: Neurocognitive performance data, red cell indices, and Hgb were available in 1235 CHARTER enrollees [median age 43 years, 23% women, med. CD4 nadir 181 cells/mm3, 864 (70%) on HAART, 17% ZDV use]. HAND was present in 584 subjects (43%) at entry. MCV and MCH were associated with HAND in unadjusted analyses [OR 1.02 (p=0.003) and OR 1.05 (p=0.005), respectively] and adjusted analyses [OR 1.02 for MCV (2% increase in risk per femtoliter rise in MCV, p=0.02 and OR 1.04 for MCH (4% increase in risk per picogram/cell rise in MCH, p=0.02, respectively]. MCV and MCH were also associated with cognitive impairment [Global Deficit Score (GDS)] as a continuous measure [β for MCV and MCH were 0.006 (p<0.001) and 0.015 (p<0.01), respectively]. RBC was inversely associated with continuous GDS (β= -0.054 (p=0.06), and anemia was associated with cognitive impairment (GDS≥0.5) over 18 to 36 months of follow-up (adjusted HR 1.21, p<0.01). Mild neurocognitive disorder was associated with RBC, MCV, and MCH [OR 0.57 (p=0.01), OR 1.03 (p=0.04), and OR 1.10 (p<0.01), respectively], and dementia was associated with MCV [OR 1.10 (p<0.05)].

Conclusions: Red cell indices and anemia, which as markers of iron metabolism are intimately linked to inflammation, oxygen delivery, and mitochondrial function, remain associated with HAND susceptibility in the HAART era.

490 CNS Immunoactivation in HIV Patients On ART With HIV-Associated Mild Neurocognitive Impairment

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Background: Even in patients responding well to current antiretroviral therapy (ART), HIV-associated neurocognitive disorders (HAND) remain prevalent. However, it is unclear if neuronal damage continues despite effective suppression of HIV-1. The light subunit of the neurofilament protein (NFL) is a component of myelinated axons, and elevated concentrations in cerebrospinal fluid (CSF) are a sensitive marker of ongoing axonal injury in HIV-associated dementia (HAD). To investigate if milder forms of neurocognitive impairment - asymptomatic neurocognitive impairment (ANI) and minor neurocognitive disorder (MND) - are associated with ongoing neuronal damage, we analyzed CSF NFL in a well characterized cohort of virally suppressed subjects on ART with or without ANI/MND.

Methodology: In a cross-sectional analysis, subjects on ART with plasma HIV-1 RNA <50 c/ml without significant confounding conditions (e.g., current substance dependence) were identified from longitudinal studies (CHARTER and HNRC). Standardized neurocognitive performance (NP) testing was performed. Subjects were classified as NP-normal (NPN) or NP-impaired (ANI/MND) based upon demographically-adjusted norms. Subjects were selected to yield approximately equal samples of NPN, ANI, and MND. CSF concentrations of NFL were measured by an enzymatic 2-site quantitative immunoassay (UmanDiagnostics, Umea, Sweden). CSF neopterin was measured by ELISA. Continuous variables were log10 transformed where appropriate. For two group comparisons, Mann- Whitney-U-test was used. The relationship between CSF NFL levels and age in the two groups were analyzed with a linear mixed effects model. Correlations were calculated using Pearson correlation coefficients test.

Results: 100 (91% male) subjects were included in the analysis, 29 NPN and 71 with ANI/MND (ANI=38; MND=33). Median (IQR) age was 47 (41-54) years, with current CD4+ 524 (359-771) and nadir 72 (10-224) x106 cells/l. No statistically significant difference was found in NFL between the NPN and ANI/MND groups. We found no correlation between CD4 cell count or CD4 nadir and NFL, however CSF neopterin was significantly correlated to NFL in the whole study population (r=0.21; p=0.035) and CSF neopterin was higher in the ANI/MND group (median 7.3, IQR 4.9-12 nmol/l) than in the NPN group (median 4.8, IQR 4.7-7-4 nmol/l) (p<0,01).

Conclusions: In this cross sectional analysis we found no difference in NFL in subjects with ANI/MND compared to subjects without neurocognitive impairment. Interestingly, CSF neopterin was higher in the ANI/MND group indicating an association between increased intrathecal immunoactivation and neurocognitive impairment in patients on ART.

491 CNS Inflammation During Treatment-Induced Viral Suppression

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Background: Several studies have shown that antiretroviral therapy (ART) reduces the intrathecal inflammation characteristic of HIV infection, but the extent and character of any residual central nervous system (CNS) inflammation that may persist despite clinical viral suppression or in the presence of very low-level viral detection is not well characterized. This study measured a panel of inflammatory biomarkers in cerebrospinal fluid (CSF) in a group of treatment-suppressed subjects in which low-level virus was also measured by single copy assay (SCA) in both CSF and paired plasma samples.

Methodology: Archived samples of CSF and plasma from 45 HIV-positive subjects with >2 years of treatment and viral suppression (<40 HIV RNA cpm) were included, with repeated sampling of 18 of the subjects so that a total of 76 sample pairs were included. Both CSF and blood viral load was further evaluated using the sensitive SCA method to measure virus levels down to <0.3 cpm. Using multiplex bead array or ELISA, we measured CSF IL-6, TNF-α, IP-10, MCP-1, MMP-9, sVCAM, sCD14, TIMP-1, sCD163, and neopterin in CSF in this sample set along with neurofilament light chain protein (NFL) to assess neural injury. Biomarker results in these samples were compared to CSF in 21 age-matched HIV-uninfected controls. Additionally, the CSF samples with <0.3 RNA cpm (SCA-) were compared to those with >0.3 cpm (SCA+) to see if detection of low level CSF virus associated with enhanced intrathecal inflammation. All comparisons used unpaired Mann-Whitney's test.

Results: The treated-suppressed subjects had: documented infection for a median of 8.1 years; plasma viral suppression by clinical assay for 2.8 years; median age 48 years; median CD4+ T cell count at sampling of 613 cells/μL with nadir of 193 cells/μL. HIV-1 RNA was detected by SCA in 6% of the subject's CSF and in 20% of the subject's plasma at baseline. Of the CSF biomarkers assessed, significant elevations in the treated-suppressed group compared to HIV- controls were detected in CSF TNF-α (p<0.0001) and CSF sCD163 (p<0.0001). There were no significant differences between treated-suppressed and HIV- subjects in other inflammatory biomarkers or NFL. When SCA- and SCA+ specimens were directly compared, significant elevations in the SCA+ group were detected only in neopterin (p=0.0085). Other inflammatory markers and NFL did not significantly differ between subjects with or without low level CSF virus detected by SCA.

Conclusions: While ART that suppresses CSF HIV RNA below clinical detection levels also reduces local immune activation, some subjects exhibit persistent, though restricted low-level, inflammation that associates with virus detected by SCA. The pathobiology and clinical consequences of these findings merit further study.

492 CSF Viremia and Inflammatory Markers in Pts With NCI On TDF/FTC/EFV and After Switch To ABC/3TC/MVC

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Background: A low-level viremia in cerebrospinal fluid (CSF) while on cART may promote local immune activation, and inflammatory responses. The aim of this study was to evaluate HIV-1 viral load (VL) and inflammatory markers in CSF, as well as the impact on neurocognitive performance in patients with neurocognitive impairment (NCI) while receiving TDF/FTC/EFV and after switching to a regimen with enhanced CNS penetrability.

Methodology: Cross sectional and longitudinal study. HIV+ virologically suppressed pts on TDF/FTC/EFV with documented NCI were included and switched to ABC/3TC/MVC. Pts with NCI due to a cause other than HIV were excluded. A trained neuropsychologist performed a 7-domain neurocognitive assessment at baseline and week 48. CSF and blood samples were taken at BL and week 24-36. HIV-1 RNA in plasma (LOD 40 c/ml) and CSF (LOD 2.5

c/ml) were determined by real-time PCR. Inflammatory markers in CSF were measured by ELISA. Baseline inflammatory markers were compared with already published data of healthy subjects.

Results: 70 pts receiving TDF/FTC/EFV were tested, 12 of them had documented NCI, CCR5 tropic virus determined from proviral HIV-1 DNA, and lacked the HLA-B*57:01 haplotype. Median (IQR) age was 54 (33-65) years, CD4 T count 529 (483-576) cells/µl, and nadir CD4 T cells 178 (15-482) cells/µl. Median time on TDF/FTC/EFV was 42.5 (15-86) months and time with undetectable VL 78 (24-144) months. At BL, 8 pts had CSF VL between 2 and 40 c/ml while suppressed in blood plasma and all of them had increased neopterin and MCP-1 levels.

Eight patients had a complete assessment at follow-up, a second lumbar puncture (LP) was performed in 9 pts a median of 36 (24-36) weeks after baseline, and 9 had a neurocognitive assessment at week 48. One pt was lost, a non-compliant pt presented viral failure at week 36, one did not accept a second LP, and another one a second NC test.

Conclusions: Most pts with NCI while receiving TDF/FTC/EFV had low-level viremia in CSF and/or increased inflammatory markers. After switching to a regimen with better CNS penetration, an improvement in neuropsychological tests was observed, as well as a significant reduction in TNFa concentration in CSF, but with viral suppression in only 2 pts. Larger studies are needed to confirm if there may be a benefit from switching from TDF/FTC/EFV to ABC/3TC/MVC and to elucidate if this improvement is related to either a reduction in toxicity or to a better antiviral activity in CNS, or both.

Table1. Cerebrospinal Fluid and Neurocognitive Results

	Baseline visit		Follow-up visit		
CSF Determinations	n	Mean SD	n	Mean SD	p-value
Neopterin (nM)	12	93.6 (38.9)	9	83.2 (38.7)	0.91
Tau (pg/mL)	12	264.9 (83.2)	9	289.6 (114.4)	0.12
MCP-1 (ng/mL)	12	1.0 (0.3)	9	1.1 (0.3)	0.47
TNFa (pg/mL)	12	0.5 (0.2)	9	0.3 (0.2)	0.02
Fractalkine (pg/mL)	12	101.4 (32.8)	9	94.0 (20.4)	1.00
IL-6 (pg/mL)	12	1.2 (0.9)	9	1.6 (1.4)	0.82
CSF HIV-1 RNA (c/mL)	12	7.5 (11.7)	9	3.4 (4.5)	0.21
Neurocognitive Tests					
Global Deficit Score (GDS)	12	0.6 (0.4)	9	0.4 (0.2)	0.08

Session P-H1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Clinical Pharmacology of TB and HCV Coinfection

493 Rifapentine Once-Weekly Dosing Effect On Efavirenz, Emtricitabine and Tenofovir PKs

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Background: A large Phase 3 trial (Prevent TB TBTC Study 26) indicated that rifapentine (RPT) plus isoniazid (900 mg each once a week) for 3 months was effective and well tolerated for the treatment of latent tuberculosis infection (TB). RPT, an inducer of both CYP3A4 and CYP2B6, is expected to affect the efavirenz (EFV) PK which is a potential concern for Drug-Drug Interaction if RPT is administered in HIV infected subjects under treatment with EFV-based antiretroviral therapy (ART). Interaction towards emtricitabine (FTC) and tenofovir cannot not be ruled out, since these compounds are substrates of transporters and rifamycins, such as RPT may lead to up-regulation of transporters via PXR activation. In this context, a clinical interaction study between RPT and ATRIPLA™ fixed-dose combination of EFV 600 mg, FTC 200 mg, and tenofovir disoproxil fumarate (TDF) 300 mg, was conducted.

Methodology: 12 HIV+ TB free subjects with a CD4 > 350 cells/mm^3 and viral load<LOQ, receiving ATRIPLA™ as background therapy, were enrolled in an open-label, single sequence, two periods, non-randomized study. PK interactions were evaluated after single and repeated administration of RPT 900 mg once weekly. In order to evaluate the maximal effect of induction, study design was optimized using a Physiological Based PK model. Blood samples were collected over 24-h post-dose of ATRIPLA™, before RPT administration, following the first RPT dosing and 38 h after the 3rd RPT dosing. Plasma concentrations were quantified by LC/MS. PK parameters were calculated by a non-compartmental analysis. Estimates of C_{min} ,C_{max} and AUC_{0-24}, geometric mean ratios (GMR) (with versus without RPT) with 90% CIs for EFV, FTC and tenofovir were obtained using linear mixed effects model for single and repeated administration of RPT.

Results: GMR and 90%CIs are presented in table 1

Conclusions: Steady state exposures of EFV, FTC and tenofovir in HIV infected subjects, with and without RPT co-administration were generally comparable. However, a single administration of RPT, increased Cmax of tenofovir by 23% while repeated weekly RPT administration resulted in a modest reduction (15%) in tenofovir C_{min} and both EFV C_{min} and AUC_{0-24}. Overall, the co-administration of ATRIPLA™ with RPT was well tolerated and, no clinically significant modifications of CD4 cell counts or viral loads were observed.

GMR 90%CI (with/without single or repeated dose of RPT)			
	EFV	FTC	tenofovir
GMR 90%CI (with/without single dose of RPT)			
Cmax	1.01 (0.94-1.08)	1.03 (0.93-1.14)	1.23 (1.00-1.51)
Cmin	1.00 (0.95-1.05)	1.07 (0.99-1.15)	0.93 (0.84-1.03)
AUC0-24	0.97 (0.93-1.01)	0.96 (0.92-1.01)	1.02 (0.91-1.15)
GMR 90%CI (with/without repeated doses of RPT)			
Cmax	0.92 (0.82-1.03)	0.95 (0.81-1.10)	1 (0.82-1.22)
Cmin	0.85 (0.79-0.93)	0.97 (0.90-1.05)	0.87 (0.73-1.05)
AUC0-24	0.86 (0.79-0.93)	0.93 (0.89-0.98)	0.91 (0.85-0.98)

494 Relationship Between Efavirenz Trough & CYP2B6 Genotypes With Rifampin-Based TB Therapy in STRIDE

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Background: Rifampin(RIF) induces cytochrome P450 (CYP) isoforms, which can lower plasma EFV exposure. However, in STRIDE, RIF-containing tuberculosis therapy was associated with increased EFV C_{min}. As *CYP2B6* polymorphisms predict EFV exposure, we conducted a nested pharmacogenomics study to evaluate EFV C_{min} by *CYP2B* metabolizer status in STRIDE participants.

Methodology: EFV C_{min} was measured by HPLC(LLQ = 0.1 µg/mL) in samples obtained 20-28 hours post-dose following no missed doses in prior 3 days(self report). *CYP2B6* genotyping was by MassARRAY iPLEX Gold (Sequenom, Inc). Metabolizer status was defined by three *CYP2B6* polymorphisms; 15582C→T, 516G→T, and 983T→C as follows: extensive =CC-GG-TT or CT-GG-TT; intermediate = TT-GG-TT, CC-GT-TT, CC-GG-TC, CT-GG-TC,or CT-GT-TT; slow = CC-TT-TT, CC-GT-TC, or CC-GG-CC. Only subjects who consented for genetic testing under protocol A5243 were included.

Results: 32 subjects with both on-RIF and off-RIF EFV C_{min} values and *CYP2B6* genotype were included from South Africa (12), Peru (12) and Uganda (8). Median age 31(IQR 22, 56), 15 male, race: 20 Black, 12 Hispanic. On-RIF C_{min} was >1.0 µg/mL in 31; 1 was 0 µg/mL, likely spurious. Metabolizer status was slow (10), intermediate (13) and extensive (9). Of slow metabolizers, 5 had higher EFV C_{min} on- vs. off-RIF; 2 had marked increases on- vs. off-RIF (11.3 and 9.7 µg/mL). On- and off-RIF medians (min, max) were 6.80 µg/mL(2.73, 21.34) vs. 5.43(3.20, 11.69). Of intermediate metabolizers, on- and off-RIF medians were 1.46 (0.05, 3.67) vs. 1.84 (1.00, 2.42). Of extensive metabolizers, on- and off-RIF medians were 1.40 (1.29, 2.65) vs. 1.65 (0.96, 2.94). Slow metabolizer C_{min} were consistently elevated vs. intermediate and extensive metabolizers, both on- and off-RIF (Figure 1). Median within-subject differences in EFV C_{min} (on- minus off- RIF) by haplotype were: slow 0.07 (range -1.93, 11.42),

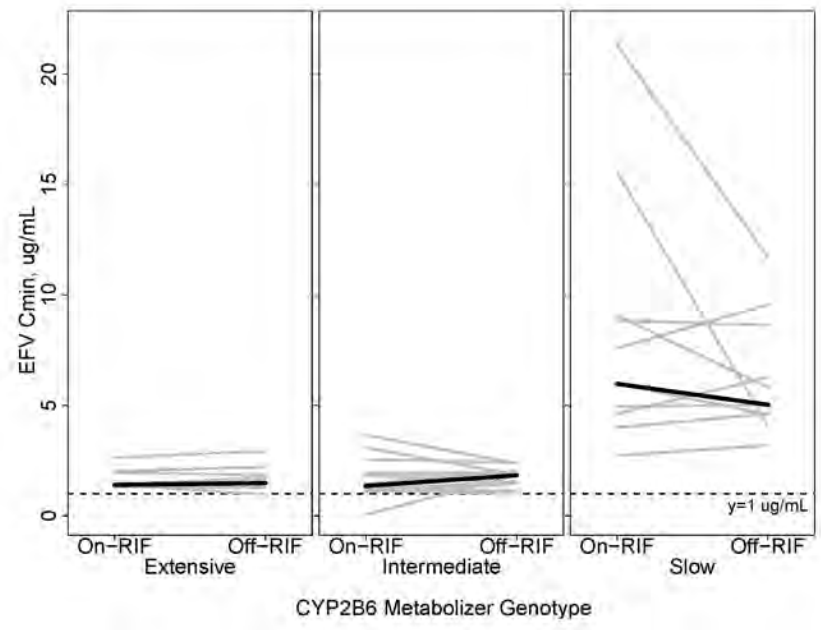

Figure: Each line represents on- & off-RIF EFV C_{min} for each subject. Bolded black lines = group medians

intermediate -0.01 (-1.78, 1.29) and extensive 0.01 (-0.33, 0.44). By metabolizer status, within-subject differences did not differ from zero by Wilcoxon signed rank nor between groups by rank-sum test.

Conclusions: In a subset of STRIDE subjects genotyped for *CYP2B6*, slow metabolizer status was associated with high EFV concentrations off-RIF; 50% had even higher EFV C_{min} on-RIF. This suggests that increased EFV C_{min} with rifampin is driven in part by slow metabolism genotypes.

495 Concentrations of Nevirapine or Efavirenz On and Off Anti-Tuberculosis Therapy (ANRS12214)

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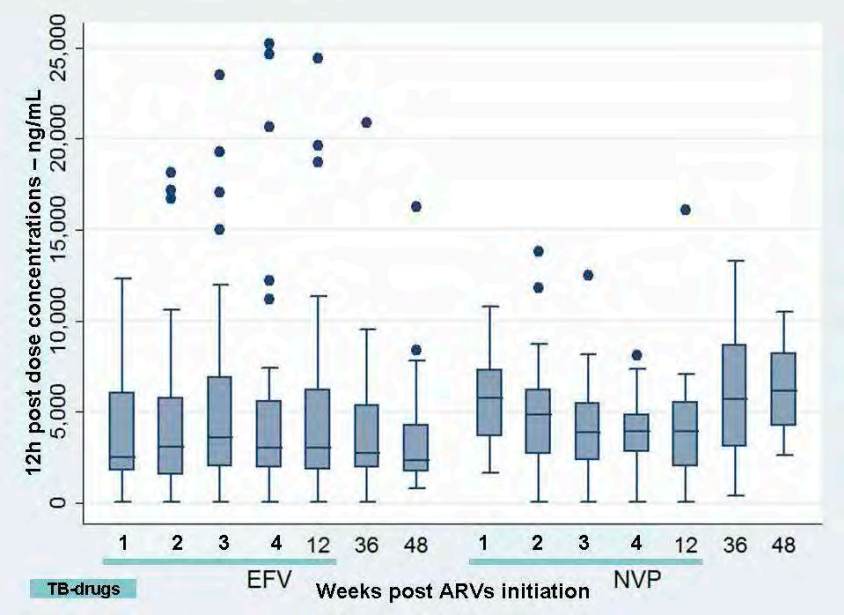
Background: The randomized ANRS12146-CARINEMO clinical trial enrolled Mozambican HIV-tuberculosis (TB) coinfected patients with the objective to compare efficacy and tolerance of nevirapine (NVP) or efavirenz (EFV)-based antiretroviral (ARV) therapy. Non inferiority of NVP could not be demonstrated. A substudy was designed to compare concentrations (conc.) of NVP or EFV during coadministration with TB treatment and after discontinuation.

Methodology: Sixty-two patients agreed to participate to the ANRS12214 substudy. They received rifampicin and isoniazid for six months combined to ethambutol and pyrazinamide during the first two months. ARVs were initiated between 4 and 6 weeks of antiTB treatment and patients were randomized to receive either NVP200mg bid or EFV600 mg qd both combined with lamivudine and stavudine. Blood samples for pre-dose conc. of NVP and mid-dose conc. of EFV were collected at weeks (wk) 1, 2, 3, 4 and 12 after ARVs initiation when patients were on TB treatment and at wks 36 and 48 after cessation of TB treatment. NVP and EFV were assayed by HPLC (limit of quantification 50ng/mL for EFV and 25 ng/mL for NVP, between run variability <12%). Mixed models were used to analyse the change in log-transformed conc. with time, time being a fixed effect in the model.

Results: Median age and weight of patients (60% male) at inclusion were 34 years and 52 kg, respectively. They had a median CD4 of 100 cells/µL and median HIV-RNA of 5.6 log_{10} copies/mL. Twelve hour-post dose conc. of NVP and EFV as a function of time were available for 32 patients on NVP and 30 patients on EFV (figure below showing medians as bold line, interquartile ranges as boxes and adjacent lines as minimum and maximum without outliers; dots are outliers). During co-administration, NVP conc. decreased over time (p=0.002), then increased when off TB drugs (p<0.001). EFV conc. decreased significantly after TB drugs discontinuation (p<0.001). Median conc. of EFV at wks 4 and 48 were 3555 ng/mL and 2329 ng/mL and conc. of NVP were 3844 ng/mL and 6123 ng/mL. At wk 4, 43.3% of patients had NVP conc. <3000 ng/mL vs 7.1% at wk48, and 7.7% of patients had EFV conc. <1000 ng/mL at both time periods.



Conclusions: Omitting the leading dose allowed high NVP conc. at initiation of treatment; however the decrease in conc. thereafter is of concern. Conversely, EFV conc. was lower after discontinuation of TB treatment. Different pharmacokinetic behaviour of NVP and EFV warrants further investigation in relationship with virological outcome.

496 Pharmacokinetics of Raltegravir 400 vs 800 mg BID With Intermittent Rifampicin Dosed Thrice Weekly

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Background: 'DOTS' strategies involve directly observed medication intake to maximise adherence to antituberculous therapy (ATT), utilising either daily, or thrice-weekly rifampicin (RIF)-based regimens. In HIV-TB coinfection, raltegravir (RAL) represents an alternative antiretroviral for patients with efavirenz resistance or intolerance. As drug interactions with intermittent RIF regimens have not been studied we evaluated the effect of thrice-weekly RIF on pharmacokinetics (PK) of RAL dosed at 400mg and 800mg bid

Methodology: Open-label, 3 phase healthy volunteer study. Subjects received RAL 400 bid for 5 days, then 33 days of RAL (400mg bid) + RIF(900mg thrice weekly; all subjects >50kg), then 5 days of RAL (800mg bid) + RIF as above. Blood samples were collected at 0,1,2,4,6,8,12h post-dose and RAL determined by validated LC-MS/MS. PK parameters were estimated (nonparametric; WinNonLin). The primary endpoint was change in RAL AUC(0-12h), secondary endpoints were change in Cmin, Cmax and tolerability of the combination. Putative efficacy targets for RAL have been proposed as 15ng/

mL (MEC1- in vitro IC95 in presence of 50% HSA) and 21ng/mL (MEC2- the upper bound of the lowest quartile from QDMRK, associated with blunted therapeutic response).

Results: Of 18 healthy volunteers recruited, PK data were available for 16 (1 subject was excluded for asymptomatic rise in creatinine kinase which resolved 17d after stopping RAL, another for taking the wrong dose of RIF). PK data are shown below:

Conclusions: Following co-administration of thrice weekly RIF, the AUC and Cmax of RAL were not significantly lowered with 400mg bid dosing, but were significantly greater with 800bid dosing; the combination was well-tolerated. In contrast, when coadministered with RIF, C12h of RAL was reduced by 40% with 400mg bid dosing, although this impact was not seen with 800mg RAL. Importantly, a significant proportion of subjects taking RAL 400mg bid (4/16) had C12h at/below MEC2. Similar findings were observed with RAL + daily RIF in patients (the REFLATE study) suggesting RIF induction of RAL is comparable between daily and intermittent RIF. In the absence of definitive clinical efficacy data to suggest otherwise, doses of RAL800mg bid with thrice-weekly RIF are well tolerated and yield higher AUCs and comparable C12 compared to RAL alone.

PK of RAL with and without RIF					
PK Parameter	Raltegravir 400 mg bd	Raltegravir 400 mg bd plus rifampicin	GMR* (90% CI)	Raltegravir 800 mg bd plus rifampicin	GMR** (90% CI)
AUC0-12h Geometric mean (range) ng.h/mL	7141 (1970-17080)	7727 (2842-24610)	1.08 (0.71-1.66)	13111 (3514-31805)	1.84 (1.29-2.61)
CMAX Geometric mean (range) ng/mL	2095 (378-6738)	2420 (576-9422)	1.16 (0.69-1.93)	3689 (749-9506)	1.76 (1.18-2.63)
C12h Geometric mean (range) ng/mL	60 (20-193)	36 (15-242)	0.60 (0.44-0.82)	53 (16-86)	0.89 (0.66-1.19)
T1/2 Geometric mean (h)	3.56	2.16	0.99 (0.70-1.20)	2.22	0.84 (0.66-1.06)
N (%) with C12h ≤ 15ng/mL MEC1	0	1 (6)	ND	0	ND
N (%) with C12h ≤ 21ng/mL MEC2	1 (6)	4 (25)	ND	1 (6)	ND
* RAL (400mgbid)+RIF versus RAL 400mg bid without RIF ** RAL (800mg bid)+RIF versus RAL 400mg bid without RIF					

497 Pharmacokinetics of Faldaprevir and Antiretrovirals in Patients With HIV/HCV Coinfection

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Background: Faldaprevir (FDV) is a potent, once-daily HCV NS3/4A protease inhibitor being developed for the treatment of HCV genotype 1 infection in mono-infected patients and HIV co-infected patients. In studies in healthy volunteers, FDV increased raltegravir (RAL) exposure by about 2.5-fold and had no substantial effect on the pharmacokinetics (PK) of darunavir/ritonavir (DRV/r), efavirenz (EFV), or tenofovir (TDF). We present here an interim analysis of PK interactions between FDV and antiretrovirals (ARV) in STARTVerso4, an ongoing Phase 3 study assessing the efficacy and safety of FDV + pegylated interferon alfa-2a/ribavirin (PR) in HIV patients co-infected with HCV genotype 1.

Methodology: HCV/HIV co-infected patients on a DRV/r- or atazanavir/r (ATV/r)-based ARV regimen were assigned to FDV 120 mg QD; those on EFV were assigned to FDV 240 mg QD. The FDV dose for patients on other ARV regimens was randomly assigned. Pre-dose blood samples were collected in the morning on Day 1 (baseline) and Weeks 2, 4, 8, 24, and 36 for ARVs and on Day 1 and Weeks 1, 2, 4, 8, and 12 for FDV. Plasma drug concentrations were determined by validated HPLC-MS/MS.

Results: Of 308 treated patients, 297 were receiving ARV therapy (ATV/r [n=12], DRV/r [n=55], EFV [n=84], RAL [n=143], or other ARV [n=3]). In the FDV 120 mg group, pooled FDV trough concentrations were higher with DRV/r than RAL (gMean $C_{pre.ss}$ 2010 ng/ml vs. 1390 ng/ml, respectively). In the FDV 240 mg group, pooled FDV trough concentrations were lower with EFV than with RAL (gMean $C_{pre.ss}$ 1250 ng/ml vs. 4840 ng/ml, respectively). FDV had no effect on EFV C_{12} levels and reduced DRV C_{pre} levels by about 50% (Table). RAL C_{pre} was similar with or without FDV treatment. A substudy with intensive PK sampling showed no effect of FDV on ATV PK parameters. The adverse event profile was consistent with historical data on PR treatment and HAART in HIV/HCV co-infected patients.

Conclusions: In this interim analysis of data from STARTVerso4, consistent with observations from studies in healthy volunteers, there were no clinically relevant drug interactions with FDV on studied ARVs in patients co-infected with HIV and HCV.

Summary of effect of FDV on ARV trough concentrations, Cpre,ss, ng/mL			
ARV FDV dose	**gMean with FDV[b]**	**gMean without FDV[c]**	**Adjusted gMean ratio, % (90% CI)**
EFV[a] FDV 240 mg	2785.77 (n=43)	3005.60 (n=42)	92.69 (84.19, 102.04)
DRV FDV 120 mg	2221.91 (n=15)	4258.41 (n=10)	52.18 (32.16, 84.65)
RAL			
FDV 120 mg	242.22 (n=24)	255.07 (n=21)	94.96 (52.90, 170.48)
FDV 240 mg	305.82 (n=34)	429.90 (n=21)	71.14 (41.54, 121.83)
TDF			
FDV 120 mg	71.14 (n=21)	88.87 (n=25)	80.06 (70.92, 90.37)
FDV 240 mg - EFV	73.89 (n=25)	83.66 (n=13)	88.31 (63.32, 123.17)
FDV 240 mg + EFV	79.51 (n=38)	83.03 (n=39)	95.76 (84.56, 108.45)

[a]EFV is taken in the evening, so C_{12} concentrations are presented instead of C_{pre} concentrations. [b]At week 2. [c]At week 0.
ARV, antiretrovirals; $C_{12,ss}$ = steady-state concentration 12 hours post last dose; $C_{pre,ss}$ = steady-state pre-dose concentration; CI, confidence interval; DRV, darunavir; EFV, efavirenz; FDV, faldaprevir; gMean = geometric mean; RAL, raltegravir; TDF, tenofovir.

498 Pharmacokinetic Interactions Between the HCV NS5A Inhibitor MK-8742 and Efavirenz

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Background: MK-8742, an inhibitor of the hepatitis C virus (HCV) NS5A protein, is being developed for the treatment of HCV infection. HCV infection is a major cause of morbidity and mortality in patients coinfected with human immunodeficiency virus-1 (HIV) and HCV. This study evaluated the pharmacokinetic interactions and safety of MK-8742 coadministered with either TDF, RAL, or EFV in healthy subjects.

Methodology: This was a 3-part, open-label, fixed-sequence study in 30 healthy adult male and female volunteers, ages 19-55 years. In Part 1, 10 subjects received oral doses of 300 mg TDF once daily for 7 days followed by a 7-day washout, 50 mg MK-8742 once daily for 8 days, and then 50 mg MK-8742 and 300 mg TDF coadministered once daily for 7 days. In Part 2, 10 subjects received a single oral dose of 400 mg RAL followed by a 4-day washout, a single oral dose of 50 mg MK-8742 followed by a 7-day washout, and then a single oral dose of 400 mg raltegravir coadministered with a single oral dose of 50 mg MK-8742. In Part 3, 10 subjects received oral doses of 50 mg MK-8742 once daily for 7 days followed by a 7-day washout, oral doses of 600 mg EFV once daily for 14 days, and then oral doses of 50 mg MK-8742 and 600 mg EFV coadministered once daily for 7 days. Safety assessments included electrocardiograms, vital signs, clinical laboratory tests, physical examination, and adverse event monitoring.

Results: Coadministration of MK-8742 with either TDF, RAL or EFV was safe and generally well-tolerated. In Part 1, multiple oral doses of MK-8742 increased the steady-state AUC_{0-24h} of TDF with (TDF+MK-8742/TDF) geometric mean ratio (GMR) [90% confidence intervals (CIs)] of 1.34 [1.23, 1.47]. Multiple oral doses of TDF did not meaningfully alter the steady-state AUC_{0-24h} of MK-8742 with (MK-8742+TDF/MK-8742) GMR of 0.93 [0.82, 1.05]. In Part 2, coadministration of MK-8742 did not alter the steady-state $AUC_{0-\infty}$ of RAL with (RAL+MK-8742/RAL) GMR of 1.02 [0.81, 1.27]. Coadministration of RAL did not alter the steady-state $AUC_{0-\infty}$ MK-8742 with (MK-8742+RAL/MK-8742) GMR of 0.81 [0.57, 1.17]. In Part 3, multiple oral doses of EFV decreased the AUC_{0-24} of MK-8742 with (MK-8742+EFV/MK-8742) GMR of 0.46 [0.36, 0.59]. Multiple oral doses of MK-8742 did not meaningfully change the steady-state AUC_{0-24} of EFV with (EFV+MK-8742/EFV) GMR of 0.82 [0.78, 0.86].

Conclusions: MK-8742 concentrations decreased following coadministration with EFV, likely as a result of CYP3A4 induction by EFV. Co-administration of MK-8742 and either RAL or TDF in healthy volunteers did not result in clinically meaningful drug-drug interactions.

499 Effect of Faldaprevir On Atazanavir Pharmacokinetics in Patients With HIV/HCV Coinfection

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Background: Faldaprevir (FDV) is a potent, once-daily HCV NS3/4A protease inhibitor being developed for the treatment of chronic HCV infection in mono-infected patients and those co-infected with HIV. In healthy subjects, FDV had no clinically relevant effect on the exposure of tenofovir, darunavir, raltegravir,

and efavirenz. The objective of this substudy of STARTVerso4 was to assess the effect of FDV on the pharmacokinetics (PK) of atazanavir/ritonavir (ATV/r) in patients co-infected with HIV and chronic HCV genotype (GT) 1.

Methodology: In STARTVerso4, HCV/HIV co-infected patients receiving ATV/r-based highly active antiretroviral therapy (HAART) were assigned to receive FDV 120 mg QD + pegylated interferon alfa-2a/ribavirin (PR) for 24 weeks. Since both ATV and FDV are inhibitors of UGT1A1, patients on an ATV/r regimen with baseline bilirubin levels >2.5 x ULN were excluded. PK sampling was performed at baseline (Day -1) before HCV treatments and after 2 weeks of combined treatment. Concentrations of ATV were determined by a validated HPLC-MS/MS assay. Safety was assessed throughout the study.

Results: Among 308 patients treated in STARTVerso4, 12 were on ATV/r-based HAART. ATV steady-state PK was comparable with FDV vs. without FDV: geometric mean ratios of 1.00, 1.02, and 1.09, for $AUC_{0\text{-}24h}$, C_{max}, and C_{24h}, respectively (Table). In all 12 patients, the C_{24h} was at least 4x higher than the ATV EC_{90} for wild-type HIV (14 ng/mL). PK parameters for ritonavir were also similar with and without co-administration of FDV (Table).

Compared with the overall FDV 120 mg study arm, patients on an ATV/r regimen showed a comparable AE profile and a similar incidence of bilirubin-associated AEs (8.9% overall; 16.7% with ATV/r [jaundice in 2 patients]). Mean increases in total bilirubin from baseline to week 4 were 0.9 mg/dL for FDV 120 mg overall and 1.1 mg/dL for patients on ATV/r; increases were mainly unconjugated bilirubin (0.7 mg/dL and 1.0 mg/dL, respectively).

Conclusions: In patients co-infected with HIV and HCV, the PK parameters of ATV/r in the presence of FDV were similar to ATV/r alone. These results indicate that FDV 120 mg QD and ATV/r can be safely co-administered without dose modification in HIV/HCV co-infected patients.

Summary of PK results				
	Without FDV gMean (% CV)	With FDV gMean (% CV)	Adjusted GMR (%)	90% CI (%)
ATV (n=12)				
$AUC_{0\text{-}24h,ss}$ [ng*h/mL]	38100 (34.5)	38200 (75.1)	100.11	69.09, 145.07
$C_{max,ss}$ [ng/mL]	3190 (50.7)	3260 (78.3)	102.01	67.25, 154.75
$C_{24h,ss}$ [ng/mL]	789 (94.3)	863 (132)	109.33	65.64, 182.08
$T_{max,ss}$ [hrs]	2.6 (76.7)	3.3 (80.2)	Not determined	
Ritonavir (n=12)				
$AUC_{0\text{-}24h,ss}$ [ng*h/mL]	11500 (58.9)	10300 (61.3)	89.80	64.54,124.95
$C_{max,ss}$ [ng/mL]	1330 (59.3)	1270 (40.2)	95.30	68.32, 132.94
$C_{24h,ss}$ [ng/mL]	86.8 (223)	95.1 (186)	109.58	72.86, 164.80
$T_{max,ss}$ [hrs]	2.7 (81.5)	3.0 (117)	Not determined	
ATV, atazanavir; CI, confidence interval; CV, coefficient of variation; FDV, faldaprevir; gMean, geometric mean; GMR, geometric mean ratio.				

500 No Meaningful PK Interaction Between HCV Protease Inhibitor MK-5172 and Tenofovir or Raltegravir

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Background: MK-5172 is a potent, once-daily inhibitor of the hepatitis C virus (HCV) NS3/4A protease that is being developed for the treatment of chronic HCV infection in mono- and HCV/human immunodeficiency virus (HIV)-coinfected patients. The present study evaluated the pharmacokinetic interactions and tolerability of MK-5172 coadministered either with tenofovir (TDF, HIV NRTI) or raltegravir (RAL, HIV integrase inhibitor) in healthy subjects.

Methodology: This was a 2-part, open-label, multiple-dose study in 24 healthy adult male and female volunteers, ages 19-55 years. Part 1: 12 subjects received oral doses of 300 mg TDF once daily on Days 1 to 7 in Period 1. After an 8 day washout, subjects received oral doses of 200 mg MK-5172 once daily on Days 1 to 7 in Period 2. In **Period 3,** subjects were coadministered 200 mg MK-5172 and 300 mg TDF once daily on Days 1 to 10. Part 2: 12 subjects received oral doses of 400 mg RAL twice daily on Days 1 to 4 in Period 1. After an 8 day washout, subjects received oral doses of 200 mg MK-5172 once daily on Days 1 to 7 in Period 2. In **Period 3,** subjects were coadministered 200 mg MK-5172 once daily and 400 mg RAL twice daily on Days 1 to 7. Plasma samples were collected for the PK assessment of MK-5172, TDF, and RAL.

Results: Co-administration of MK-5172 with either TDF or RAL was generally well-tolerated. In Part 1, multiple oral doses of MK-5172 slightly increased the steady-state $AUC_{0\text{-}24h,}$ $C_{max,}$ and C_{24h} of TDF with (TDF+MK-5172/TDF) geometric mean ratios (GMRs) [90% confidence intervals (CIs)] of 1.18 [1.09, 1.28], 1.14 [1.04, 1.25], and 1.24 [1.10, 1.39], respectively. Multiple oral doses of tenofovir did not meaningfully alter the steady-state $AUC_{0\text{-}24h,}$ $C_{max,}$ or C_{24h} of MK-5172 with (MK-5172+TDF/MK-5172) GMRs [90% CIs] of 0.86 [0.65, 1.12], 0.78 [0.51, 1.18], and 0.89 [0.78, 1.01], respectively. In Part 2, multiple oral doses of MK-5172 did not meaningfully alter the steady-state $AUC_{0\text{-}24h,}$ $C_{max,}$ or C_{24h} of RAL with (RAL+MK-5172/RAL) GMRs [90% CIs] of 1.43 [0.89, 2.3], 1.46 [0.78, 2.73], and 1.47 [1.08, 2.00], respectively. Multiple oral doses of RAL did not meaningfully alter the steady-state $AUC_{0\text{-}24h,}$ $C_{max,}$ or C_{24h} of MK-5172 with (MK-5172+RAL/MK-5172) GMRs [90% CIs] of 0.91 [0.72, 1.15], 0.85 [0.62, 1.16], and 0.90 [0.82, 0.99], respectively.

Conclusions: The coadministration of MK-5172 and TDF, or MK-5172 and RAL in healthy volunteers did not result in clinically significant drug-drug interactions. These results suggest that no dose adjustments of MK-5172, TDF, or RAL are needed for coadministration in HCV/HIV coinfected patients and support further studies of MK-5172 with ARV regimens based on TDF and RAL in the co-infected population.

501 Effect of Faldaprevir On Raltegravir Pharmacokinetics in Healthy Volunteers

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Background: Faldaprevir (FDV) is a potent, once-daily HCV NS3/4A protease inhibitor being developed for the treatment of chronic HCV infection in mono-infected patients and patients co-infected with HIV. Raltegravir (RAL), an HIV integrase inhibitor, might be used in combination with FDV to treat HIV patients co-infected with chronic HCV. The objective of this study was to assess the effect of FDV on the steady state pharmacokinetics of RAL.

Methodology: This was an open-label, 2-period, fixed-sequence study in healthy subjects (N=24; 12 males and 12 females). FDV and RAL were administered as 240 mg and 400 mg doses, respectively. Treatment A: RAL BID on Days 1-3, RAL QD on Day 4; Treatment B: RAL BID and FDV BID (loading dose) on Day 1, RAL BID and FDV QD on Days 2-5, RAL QD and FDV QD on Day 6. All subjects received both treatments separated by a washout phase of at least 7 days. Pharmacokinetic and safety assessments were performed over a 132-hour period following dosing.

Results: Compared with RAL alone, co-administration with FDV led to an approximately 2.7-fold increase in geometric mean (gMean) $AUC_{\tau,ss}$ and an approximately 2.5-fold increase in gMean $C_{max,ss}$ of RAL (Table). Similar increases were observed for the RAL-glucuronide metabolite (2.5-fold increase in gMean $AUC_{\tau,ss}$ and 2-fold increase in gMean $C_{max,ss}$). No serious adverse events (AEs) were reported and no subject discontinued the trial due to an AE. The incidence of AEs was higher with combined treatment of RAL plus FDV compared with RAL alone (17 vs. 7 subjects). All AEs were consistent with the known safety profiles of both drugs and reported as mild in severity apart from one AE (flatulence) which was reported as moderate. A reversible increase in bilirubin (predominantly indirect) was observed, which was not accompanied by changes in levels of markers of liver toxicity and not considered clinically relevant.

Conclusions: Overall, both treatments administered in the trial were well tolerated by healthy subjects. RAL plus FDV co-administration resulted in an approximately 2.7-fold increase in RAL overall exposure in healthy volunteers. Data from the STARTVerso4 study in HCV/HIV co-infected patients taking concomitant RAL and FDV showed that RAL trough exposure was similar with or without concomitant FDV administration. These data suggest that no dose adjustment is required with concomitant administration of FDV and RAL.

RAL parameter	RAL alone (Ref, N=24), gMean	RAL + FDV (Test, N=23)[a], gMean	Adjusted gMean ratio [%] (Test/Ref)	Two-sided 90% confidence interval		Intra-individual gCV[%]
				Lower limit [%]	Upper limit [%]	
AUC [ng·h/mL]	4072	11079	272.1	199.7	370.7	67.9
C_{max} [ng/mL]	1300	3194	245.7	168.5	358.4	87.1

[a]One subject discontinued FDV treatment on Day 4.
AUC, area under the curve; C_{max}, maximum concentration; FDV, faldaprevir; gCV, geometric coefficient of variation; gMean, geometric mean; RAL, raltegravir.

502 No Clinically Relevant Interactions Between Daclatasvir and Cyclosporine or Tacrolimus

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Background: Chronic HCV infection is the main cause of liver transplantation (LT). HCV recurrence, seen in ≈50% of HCV-infected LT patients during the first postoperative year, is the main cause of graft failure (despite long-term treatment with immunosuppressants eg cyclosporine [CSP] or tacrolimus [TAC]) and death in HCV-infected LT patients. Drug-drug interactions (DDIs) with CSP and TAC hinder the use of boceprevir and telaprevir in LT patients. Daclatasvir (DCV), a first-in-class HCV NS5A inhibitor with pan-genotypic activity *in vitro* and demonstrated clinical efficacy as part of multiple (including

all-oral) regimens, has a pharmacokinetic (PK) profile supportive of QD dosing and a low probability of DDIs as a perpetrator and manageable DDIs as a victim. It is anticipated that DCV will be co-administered with CSP and TAC in the clinical setting.

Methodology: Healthy fasted subjects (age 18-49 years; BMI 18-32 kg/m^2) received a single oral dose of CSP 400 mg on Days 1 and 9 and DCV 60 mg QD on Days 4-11 (Group 1), or received a single oral dose of TAC 5 mg on Days 1 and 13 and DCV 60 mg QD on Days 8-19 (Group 2). Blood samples for PK analysis were collected on Days 1 and 9 for CSP (72h), 1 and 13 for TAC (168h), and 8 and 9 (Group 1) or 12 and 13 (Group 2) for DCV (24h). Statistical analyses (geometric mean ratios [GMR] and 90% confidence intervals [CI]) on the PK parameters of CSP, TAC and DCV (max. plasma conc. [C_{max}], AUC from time zero until the time of last quantifiable concentration [$AUC_{0-\tau}$],end of the dosing interval [AUC_{0-TAU}] or extrapolated to infinity [$AUC_{0-\infty}$] and plasma conc. 24h post-dose [C_{24}]) were performed.

Results: Evaluable data from 14 subjects in each group were collected. DCV did not affect the PK parameters of either CSP or TAC, and TAC did not affect the PK parameters of DCV; all GMRs were close to 1 and the 90% CIs were contained within the accepted no-effect boundary (0.80-1.25). Co-administration of CSP resulted in modest increases in DCV AUC_{0-TAU} (40%) and C_{24} (56%); C_{max} was unaffected.

Conclusions: No clinically-relevant DDIs were observed when DCV was co-administered with CSP or TAC; CSP caused a modest increase in DCV exposure. Dose adjustments for DCV, TAC, or CSP during co-administration of DCV with CSP or TAC are unlikely to be required.

	GMR (90% CI)				
Treatment comparison	**C_{max}**	**$AUC_{0-\tau}$**	**AUC_{0-TAU}**	**$AUC_{0-\infty}$**	**C_{24}**
CSP + DCV vs CSP alone	0.96 (0.91, 1.02)	1.02 (0.96, 1.08)	NA	1.03 (0.97, 1.09)	NA
CSP + DCV vs DCV alone	1.04 (0.94, 1.15)	NA	1.40 (1.29, 1.53)	NA	1.56 (1.41, 1.71)
TAC + DCV vs TAC alone	1.05 (0.90, 1.23)	1.00 (0.87, 1.15)	NA	1.00 (0.88, 1.13)	NA
TAC + DCV vs DCV alone	1.07 (1.02, 1.12)	NA	1.05 (1.03, 1.07)	NA	1.10 (1.03, 1.19)

Session P-H2 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Pharmacogenetics: Drug Disposition To Therapeutics

503 ABCC4 3348 T>C SNP Affects Tenofovir Urinary Output in HIV-Positive Patients

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Background: Several proteins have been involved in tenofovir transport both in the intestinal lumen and at the proximal tubular renal cells; single nucleotide polymorphisms (SNPs) in *ABCC2* and *ABCC10* have been associated with kidney tubular dysfunction along with tenofovir exposure. No study has so far assessed the influence of genetic profile on urinary and plasmatic tenofovir pharmacokinetic parameters.

Methodology: Adult HIV-positive patients on tenofovir-containing HAARTs since at least six months, presenting estimated creatinine clearance (eCRCL) above 60 ml/min and signing an informed consent were included. Twelve hours tenofovir plasma (pC_{12}) and urinary concentration (uC_{12}) were measured through HPLC/MS-MS methods. SNPs in the following genes were obtained through real-time PCR: *ABCB1, ABCC2, ABCC4, ABCC10, AK1, SLC22A6, hENT1, CNT2*. Results are expressed as median (IQR); non-parametric tests were used for all analysis.

Results: 194 patients (70.1% male) were enrolled. Age, BMI and eCRCL were 45.2 years (39-51), 23.7 kg/m^2 (21.8-26.0) and 91.7 ml/min (80-109) respectively. Tenofovir pC_{12} and uC_{12} were respectively 68 ng/mL (50-97) and 25722 ng/mL (14437-38598) with a U/P ratio of 398 (230-610). Tenofovir pC_{12} correlated with age (rho=0.21, p=0.03) and eCRCL (rho=-0.22, p=0.002) while uC_{12} with BMI (rho=-0.15, p=0.04); U/P ratio correlated with age (rho=-0.17, p=0.02) and borderline with eCRCL (rho=0.13, p0.07). Urine-to-plasma tenofovir ratio was lower in *ABCC4 3348* (rs1751034) CC carriers [87.5 (58-347) vs. 396 (235-558), p=0.008], in *ABCC10 2759* (rs2125739) TT carriers [386 (214-38) vs. 451 (314-743), p=0.028], in *ABCB1 3435* (rs1045642) TT carriers [311 (150-444) vs. 406 (238-671), p=0.024], in *CNT2 124* (rs11854484) CT/TT carriers [386 (214-505) vs. 438 (247-683), p=0.042]. At multivariate linear regression analysis (including BMI, ethnicity, gender, tenofovir duration, PI use, ABCB1 3435 SNPs, ABCC10 2759 SNPs) age (p=0.001, 95CI 3.2-16.4) and *ABCC4 3348* CC genotype (p=0.041, 95CI 14.5-679) were independent predictors of tenofovir urinary output.

Conclusions: Age and single nucleotide polymorphisms in the *ABCC4* gene are independent predictors of tenofovir urinary output: this finding confirms the relationship between genetic factors and tenofovir exposure in the suggested mechanism underlying proximal tubular dysfunction. Given the interplay between genetic and pharmacokinetic factors in determining renal tubular damage, treatment tailoring in tenofovir-treated patients deserves further clinical evaluation.

504 Relative Genetic Contribution To the Pharmacokinetics of Commonly Prescribed Antiretrovirals

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Background: Variability in antiretroviral pharmacokinetics is influenced by numerous factors affecting absorption, distribution, metabolism and elimination. Recently, a relative genetic contribution (rGC) of 0.904 (0.64 - 0.97) was reported for nevirapine (NVP) AUC0-6h (Micheli et al, Pharmacogenet Genomics, 2013). The aim of this study was to assess the rGC of a panel of antiretroviral drugs to assess the degree by which heritability influences their pharmacokinetics.

Methodology: Patients from the Therapeutic Drug Monitoring Registries of the University of Turin and the University of Liverpool were included in the study. Inclusion criteria were as follows: receiving boosted lopinavir (LPV/r, 300/100 mg b.i.d.), boosted atazanavir (ATV/r 300/100 q.d.), unboosted ATV (ATV, 400mg q.d.), efavirenz (EFV, 600 mg q.d.), NVP (400 mg q.d.) or raltegravir (RAL, 400 mg b.i.d), age>18 years, not receiving drugs known to contribute to drug-drug interactions. Plasma drug concentrations were determined using HPLC or LC-MS/MS methods. Intrapatient (SDw) and interpatient (SDb) variability were measured in patients with Cmin or C12h available from more than one visit. The rGC was calculated using the following equation: 1-(1/F) where F= SDb2/SDw2. Statistical significance for genetic contribution was calculated using F-test, $\alpha = 0.05$.

Results: A total of 211 patients were included in the study. SDw and SDb were 38% and 43% for LPV/r (n = 37), 49% and 50% for ATV/r (n = 24), 54% and 104% for ATV (n = 24), 33% and 60% for EFV (n = 82), 19% and 44% for NVP (n = 20), and 81% and 95% for RAL (n = 24), respectively. Mean with 95% CI rGC was calculated to be 0.35 (0.06 - 0.55) for LPV/r, 0.15 (0 - 0.6) for ATV/r, 0.55 (0.35 - 0.7) for ATV, 0.78 (0.68 - 0.85) for EFV, 0.82 (0.62 - 0.91) for NVP and 0.08 (0 - 0.56) for RAL (Figure). Genetic contribution was statistically significant ($p < 0.05$) for ATV, EFV and NVP. All patients were of Caucasian ancestry and neither age nor gender was significantly associated with plasma concetrations for any drug.

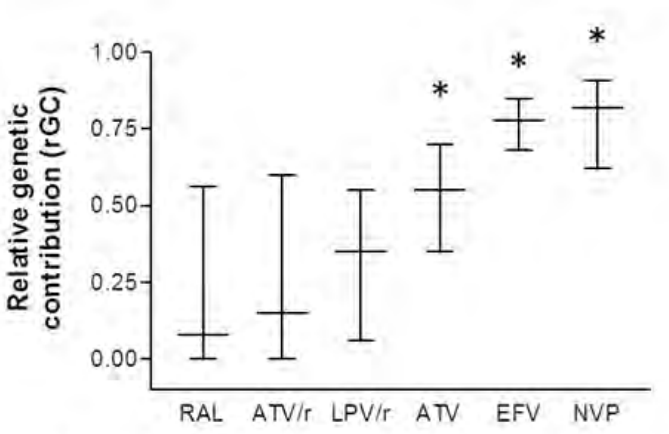

Figure: Relative genetic contribution for each study drug with 95% confidence intervals. *P < 0.05.

Conclusions: The rank order for genetic contribution to variability in PK for the study drugs was NVP > EFV > ATV > LPV/r > ATV/r > RAL indicating class-specific differences exist. Interestingly, these data indicate that ritonavir reduces the genetic contribution to variability in ATV concentrations presumably through inhibition of gene products such as CYP3A4 and ABCB1. Drugs with higher rGC scores may represent better candidates for pharmacogenetic studies.

505 Leveraging Genomics in HIV Treatment Decisions

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Background: Patient genotype influences outcome of HIV infection and treatment. In a pilot project, we test implementation (operational, semantic, procedures for delivery), doctor's perception and predictive power of a custom genotyping array that synthesizes current knowledge on genetic variants that contribute to clinical phenotypes in HIV.

Methodology: The array includes 4,146 SNPs that capture known functional variants and tags common variation (>5% frequency) in relevant genes and also allows prediction of class I HLA types. Of these, 81 SNPs are reported markers associated with HIV/HCV disease progression, adverse drug events, pharmacokinetics or metabolic traits.

Results: In this first interim analysis, 89 HIV infected patients were enrolled prior to the initiation of cART. Genotyping was performed and reports of genetic predisposition were returned to clinicians after initiation of treatment. Of these, 84 (94%) carried genetic risk factors for at least one trait. To assess predictive power, we explored metabolic parameters and drug levels in detail. A total of 203 metabolite measurements were available for bilirubin, HDL cholesterol, non-HDL cholesterol, triglycerides and glucose and 28 measurements of drug levels for which genetic predictions exist (EFV, ETV and LPV/r).

We observed 39 metabolite measurements that exceeded the threshold for reporting. In 5 individuals (13%), relevant genotypes were observed and correct predictions made. Conversely, 13 of 164 individuals (8%) carried relevant genetic markers without the associated trait. We observed 6 drug levels that were at or above the 75th percentile. In 3 individuals (50%), relevant genotypes were observed and correct predictions made. Conversely, 1 of 22 individuals carried relevant genetic markers without the associated trait. In a survey aimed at gauging the utility of this information as seen by the physician, 57% said they found the information useful or potentially useful. In 7 of 57 (12%) instances, the treating physician would have been inclined to prescribe a different treatment, 9 of 58 (16%) would consider additional laboratory tests and 20 of 58 (34%) would discuss cardiovascular risk factors.

Conclusions: The interim analysis demonstrates the feasibility and general acceptance of returning genetic data to clinicians and the modest predictive power of the genetic testing. Based on physician responses, these tests could have lead to a change in clinical decisions.

506 Contribution of CYP2A6, UGT2B7, and Other Non-CYP2B6 Polymorphisms To Plasma Efavirenz Exposure

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Background: Two CYP2B6 variants, 516G→T and 983C→T, define high efavirenz (EFV) concentration strata (slow metabolizers). Contributions by CYP2A6, UGT2B7, CYP3A4 and CYP3A5 variants have been reported, but have been inconsistent. We characterized associations between EFV concentrations and genetic variants in 84 AIDS Clinical Trials Group (ACTG) study participants, all with CYP2B6 516/983 slow metabolizer genotypes.

Methodology: Several randomized ACTG treatment trials (esp. A5202, A5095/A5097s, and ACTG 384) included EFV-containing arms, and plasma sampling for EFV at multiple study weeks. We included subjects with minimal intraindividual variability between ≥2 EFV determinations at 8-19 hours post-dose. Slow metabolizer CYP2B6 genotypes (CYP2B6 516TT, 516T/983C, and 983CC) were available from previous analyses. Genotyping of UGT2B7 was by sequencing, and 198 additional loci (107 polymorphic) in 40 drug metabolism/transport genes by iPLEX ADME PGx platform. Race/ethnicity was by self-report. Associations with the mean of log10-transformed EFV concentrations were assessed by linear regression.

Results: Analyses included Black (56%), White (29%), and Hispanic (15%) subjects. CYP2B6 genotypes were 516TT in 71 subjects, 516T/983C in 12, and 983CC in 1. EFV concentrations were somewhat higher with 983C alleles (P=0.12). In univariate analyses (additive models), CYP2A6 -48T→G (rs28399433) was significantly associated with increased EFV concentrations in all subjects (P=3.8x10E-4, Figure, top); this was consistent in Black and White groups analyzed separately. UGT2B7 735A→G (rs28365062, *1c) and 801T→A (rs7438284, *2) were not associated with EFV concentrations by univariate analysis (p=0.34 and P=0.63), and after controlling for CYP2A6 -48T→G (p=0.42 and P=0.67, respectively). Homozygosity for UGT2B7 735GG (n=3), but not heterozygosity, was associated with higher EFV concentrations (P=0.006, Figure, bottom). With correction for multiple comparisons, no iPLEX ADME PGx variant other than CYP2A6 -48T→G was associated with EFV concentrations, including 22 in CYP2A6 and 3A4/5.

Conclusions: In CYP2B6 slow metabolizers, CYP2A6 -48T→G is associated with higher EFV concentrations. An effect of UGT2B7 735A→G on EFV concentrations, if true, is much less. No other significant associations in these or other genes were found. These findings support a contribution of CYP2A6, and possibly UGT2B7 variants to even higher EFV concentrations in CYP2B6 slow metabolizers.

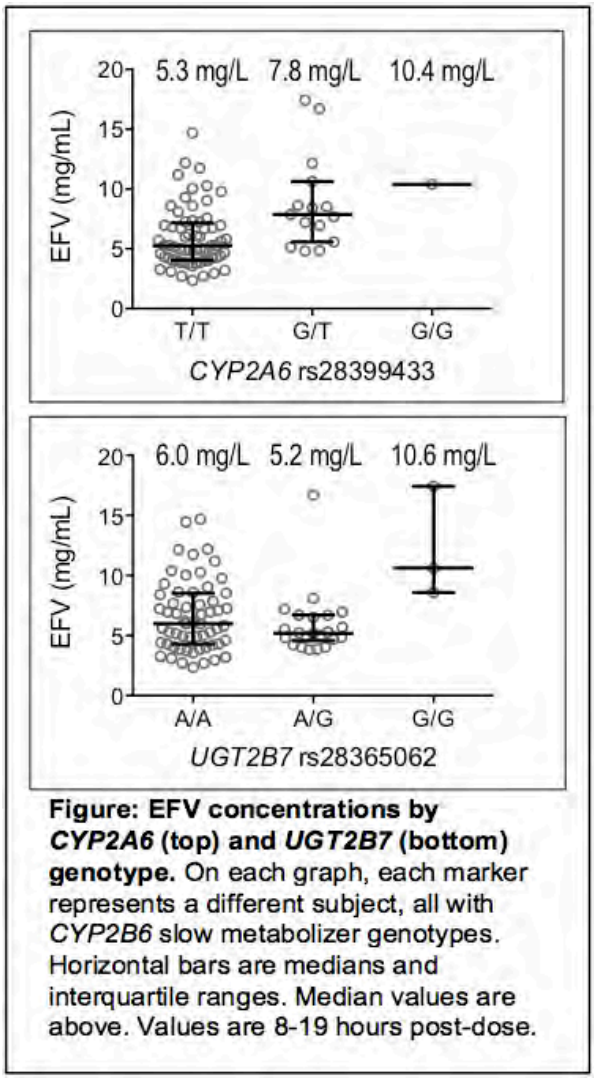

Figure: EFV concentrations by *CYP2A6* (top) and *UGT2B7* (bottom) genotype. On each graph, each marker represents a different subject, all with *CYP2B6* slow metabolizer genotypes. Horizontal bars are medians and interquartile ranges. Median values are above. Values are 8-19 hours post-dose.

Session P-H3 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

ARV Pharmacokinetics, Drug Interactions, and Pharmacodynamics

507 Rilpivirine With Darunavir/Ritonavir: Pharmacokinetics & Safety in HIV Therapy-Naïve Patients

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Background: A combination of ritonavir-boosted darunavir (DRV/*rtv*) and rilpivirine (RPV) could potentially form a once-daily nucleoside-sparing regime for therapy-naïve treatment. RPV is subject to the boosting effect of hepatic cytochrome inhibition, and in an interaction study in healthy volunteers DRV/*rtv* increased RPV pharmacokinetic (PK) exposures, of a RPV 150mg daily dose, by 80 to 180%without altering DRV or *rtv*. This study investigates the safety, steady state PK and antiviral activity of this combination in therapy-naïve HIV-infected adults.

Methodology: HIV-1 infected adults, after giving informed consent, were screened by medical history, examination, laboratory bloods and ECG. Important exclusion criteria were: significantly abnormal ECG (particularly QT prolongation), hepatitis B or C co-infection, screening viral genotype showing reduced susceptibility to planned therapy, and use of any drug with PK interaction with study medications. All received treatment with DRV/*rtv* 800/100mg and RPV 25mg once daily, administered with a meal of > 533kcal, and weekly viral load (VL) monitoring was performed prior to a formal 24hr PK profile at day

28. Ongoing monitoring of clinical response continued to 48 weeks. RPV, DRV and *rtv* plasma concentrations were determined by validated HPLC-MS/MS method; PK parameters (C_{max}, C_{trough} and AUC_{0-24h}) were determined using non-compartmental analyses (WinNonLin).

Results: Twenty-five eligible patients were enrolled (majority white males with 1 white female and 4 Hispanic). In ten, viral load at baseline was above 5.0 log_{10} copies/mL (median 4.7, range 3.0 - 7.7). There was no significant change from baseline in corrected QT interval (Fridericia method), and no clinical or laboratory adverse events of greater than grade2 intensity or of a serious nature were observed. At day 28, geometric mean (90% confidence intervals) of RPV C_{max}, C_{trough} and AUC_{0-24h} were 183 (171 - 233) ng/mL, 114 (108 - 146) ng/mL and 2966 (2793 - 3731) ng.h/mL; higher on average than RPV PK parameters with NRTI, but within the range observed in phase III patient studies. DRV and *rtv* exposures were consistent with historical controls. Median VL reduction from baseline, comparing pre-treatment VL below to above 5.0 (log_{10} copies/mL) respectively, was 2.0 *versus* 2.1 at day 28 and 2.3 *versus* 2.5 at day 56.

Conclusions: The combination of DRV/*rtv* and RPV in this study was well tolerated, giving PK exposures of RPV within the range of those in the ECHO and THRIVE studies. Good initial virologic responses, independent of baseline viral load, and good safety data supports further exploration of this regime for first-line, nucleoside-sparing therapy.

508 Rilpivirine Pharmacokinetics With/Without Darunavir/r in Adolescents and Young Adults

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Background: Rilpivirine (RPV), a second generation non-nucleoside reverse transcriptase inhibitor (NNRTI), is not recommended for patients <18 years of age. Once daily dosing of RPV makes it an attractive option for HIV-infected adolescents. We report the pharmacokinetic (PK) data of RPV once daily either alone or in combination with DRV/r as part of antiretroviral therapy in HIV-infected adolescents and young adults.

Methodology: IMPAACT P1058A is an ongoing observational study designed to evaluate the PK of antiretroviral drug combinations commonly used by HIV-infected children and adolescents. Patients <24 years old receiving RPV 25 mg once daily (with background NRTIs) either alone or combined with DRV/r 800/100 mg once daily were enrolled. Plasma samples were collected at pre-dose and 1, 2, 4, 6, 8, 12 and 24 hours after an observed dose. RPV and DRV plasma concentrations were determined using validated HPLC-UV and LC-MS/MS assays, respectively. The 90% confidence intervals (90% CI) for the geometric mean (GM) of the AUC and Cmin were compared with target ranges reported in adults.

Results: Data from 26 subjects were analyzed; 15 receiving RPV alone (8 male), and 11 receiving RPV in combination with DRV/r (7 males). The median (range) age and weight were 20 (13-23) years and 75 (40-117) kg, in the RPV alone group, and 20 (17-23) years and 68 (49-97) kg in the combination group. RPV and DRV PK parameters and adult target ranges are presented below:

The mean RPV AUC and Cmin for RPV alone were within the adult target ranges and the 90% CI had substantial overlap. In contrast, the mean and entire 90% CI for AUC and Cmin for RPV substantially exceeded the corresponding adult target when co-administered with DRV/r.

Conclusions: RPV alone in this age group provides similar exposure to adults. However, RPV exposure in patients receiving concomitant DRV/r was elevated two to three fold. It remains to be determined if this increased exposure leads to increased toxicity or side effect profiles, but currently, RPV dose reduction is not recommended. Further studies of this interaction are warranted.

PK Parameters GM (90% CI)	Rilpivirine 25 mg QD (n=15)	Rilpivirine 25 mg QD + DRV/r 800/100 mg QD (n=11)		Ratio of GM RPV With/Without DRV/r
	RPV	RPV	DRV	
AUC (µg.hr/mL)	2.38 (1.92,2.94)	6.93 (4.57,10.51)	76.6 (57.3,102.4)	2.91
Cmax (µg/mL)	0.14 (0.11,0.17)	0.42 (0.26,0.67)	6.06 (4.97,7.39)	2.98
Clast (µg/mL)	0.08 (0.06,0.10)	0.23 (0.15,0.35)	2.30 (1.43,3.69)	3.08
Cmin (µg/mL)	0.07 (0.05,0.09)	0.16 (0.10,0.27)	0.77 (0.40,1.50)	2.31
AUC Target range	1.4 to 2.2	1.4 to 2.2	48.8 to 76.3	
Cmin Target range	0.05 to 0.07	0.05 to 0.07	0.9 to 1.4	

509 The Cerebrospinal Fluid HIV Risk Score for Assessing Central Nervous System HIV Activity

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Background: Detectable cerebrospinal (CSF) HIV ribonucleic acid (RNA) is associated with central nervous system (CNS) complications, including neurocognitive impairment and depression. Routine monitoring of CSF HIV RNA presents a valuable key to reducing HIV CNS complications. However lumbar puncture procedures pose resource utilization challenges. We developed a prediction model to estimate the risk of detectable CSF HIV RNA (threshold >50copies/ml) that will help identify patients who might benefit most from CSF monitoring.

Methodology: The CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) prospective cohort is an ongoing 6-Center, US-based study. We evaluated 811 participants on combination antiretroviral therapy (cART) who underwent CSF evaluation at study entry (2004-2007). We applied points to the final multivariable logistic regression prediction model to develop a detectable CSF HIV Risk Score.

Results: Plasma HIV RNA, CNS Penetration Effectiveness (CPE 2.0), duration of cART, adherence, race and depression were retained predictors of CSF HIV RNA (Table 1). The CSF HIV Risk Score ranges from 0 to 42 points and displays good calibration, Hosmer-Lemeshow P-value=0•85, and discrimination, c-statistic=0•90. The distribution of risk scores in our sample ranged from 0 to 39 points, with mean [standard deviation (SD)] of 15.4 (7.3). Predicted probabilities [95% Confidence Interval (CI)] for detectable CSF HIV RNA at various CSF HIV Risk Scores include; 10 =2.3% (95% CI: 1.5-3.7); 15 =7.0% (95% CI: 5.1-9.5); 20 =19.2% (95% CI: 15.7-23.2); 25 =42.9% (95% CI: 34.6-49.6); and 30 =70.3% (95% CI: 61.5-77.9). For example, a Black patient (3 points), with plasma HIV RNA of 300 copies/mL (10 points), who is presently depressed (4 points), and is fully adherent to cART regimen (0 points), with total CPE score of 9 (6 points), for a duration of 10 months (4 points; total CSF HIV Risk Score =27 points), has a 54.3% (95% CI: 46.5-62.0) probability of detecting CSF HIV RNA. For each point increase, the odds of detecting CSF HIV RNA increase by 26% (Odds Ratio =1.26, 95%CI 1.21-1.31; P<0.01).

Conclusions: The CSF HIV Risk Score predicts detection of HIV RNA in the CSF. An elevated risk score suggests which patients will benefit from CSF monitoring. It presents an advance in HIV management and monitoring of CNS effects of HIV, and provides a potentially useful tool for clinicians.

Adjusted Odds Ratios and Points for Retained Predictors of Detectable CSF HIV RNA			
Predictor variable	Odds Ratio (95% CI)	P-value	Points
Race; White	1.00 (ref.)		0
Black	1.81(1.06-3.09)	0.02	3
Hispanic & Other	2.39 (1.16-4.95)	0.02	4
Depression	2.25 (1.18-4.28)	0.01	4
cART Adherence; >95%	1.00 (ref.)		0
85-95%	1.79 (0.67-4.79)	0.23	3
<85%	1.82 (0.90-3.68)	0.10	3
Plasma RNA, copies/ml	4.88 (3.91-6.09)	<0.001	0 to 18
CPE 2.0	0.77 (0.67-0.88)	<0.001	0 to 9
Current cART duration, months	0.99 (0.98-1.00)	0.07	0 to 4

510 Efavirenz (EFV) 400 Versus 600 mg Daily: Results of the ENCORE1 Intensive PK Substudy

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Background: ENCORE1 is an ongoing study in treatment-naïve, HIV-1 infected adults randomized to TDF/FTC with either reduced (400 mg, EFV400) or standard dose EFV (600 mg, EFV600). EFV400 was virologically non-inferior to EFV600 with greater than 80% suppression to <50 HIV-RNA copies/mL in both groups at 48 weeks. This intensive pharmacokinetic (PK) study compared EFV plasma exposures between doses in a subset of subjects.

Methodology: Serial 24 hour plasma samples were collected between weeks 4 and 8 from subjects consenting prior to randomization in the parent trial. EFV concentrations were determined by validated LC-MS/MS and steady-state PK parameters calculated using WinNonlin™. To assess between-dose differences in parameters, geometric mean ratios (GMR) and 90% CI were calculated using log transformed data, then

expressed as linear values (primary analysis). Given that log transformation did not correct for non-normality of data, post-hoc non-parametric analysis was performed (Mann-Whitney U test).

Results: Forty six (15 female) subjects were enrolled at four study sites; Argentina, South Africa, Thailand and United Kingdom. Despite disparate numbers in treatment groups (EFV400=28, EFV600=18), substudy arms were matched for age (mean 36 yrs), BMI (mean 25 kg/m^2) and ethnicity [17 (37%) African, 10 (22%) Asian and 19 (41%) Caucasian]. PK parameters are summarised (Table 1). EFV $AUC_{0\text{-}24}$, C_{max} and C_{12} (representing mid-dose interval concentration) were significantly lower for EFV400. C_{12} was <1.0 mg/L (suggested MEC) in 7 (25%) EFV400 and 1 (6%) EFV600 participants and the C_{24}

<1.0 mg/L in 13 (46%) EFV400 and 5 (28%) EFV600 subjects, respectively. Three subjects did not complete week 48 (EFV400=2, EFV600=1). At week 48 for EFV400, 3 (11%) had HIV-RNA >50 copies/mL, 2 of which had C_{12} and C_{24} <MEC at the time of sampling. For EFV600, 4 (22%) patients had >50 copies/mL, 1 of which had C_{24} below 1.0 mg/L.

Conclusions: Dose-proportional plasma exposure to EFV was observed. Subjects receiving EFV400 had comparable virological suppression consistent with the main ENCORE1 study) at week 48 despite lower AUC_{0-24} and C_{12} and a higher proportion of subjects below the recommended MEC at PK sampling (week 4-8). This suggests that C_{12} or C_{24} lower than 1.0 mg/L was not associated with virus suppression at 48 weeks in this population. Taken together with the ENCORE1 results, these results challenge the conventional PK targets for therapeutic success.

Table 1. PK parameter summary

		EFV400	EFV600	GMR (90%CI)	p
CL (L/h)	GM (90%CI)	10.5 (10.2-13.2)	11.1 (9.96-15.0)	0.95 (0.73-1.23)	0.747
	Median (IQR)	11.5 (8.27-15.4)	11.2 (9.75-13.8)	-	0.857
AUC0-24 (mg.h/L)	GM (90%CI)	38.0 (34.4-54.0)	54.2 (47.8-75.8)	0.70 (0.54-0.91)	0.026
	Median (IQR)	34.8 (26.0-48.4)	53.6 (43.5-61.6)	-	0.007
Cmax (mg/L)	GM (90%CI)	2.65 (2.46-3.36)	4.09 (3.72-5.23)	0.65 (0.52-0.81)	0.002
	Median (IQR)	2.43 (2.21-3.30)	4.18 (2.77-5.60)	-	0.002
C12 (mg/L)	GM (90%CI)	1.50 (1.36-2.25)	2.05 (1.81-2.92)	0.73 (0.55-0.97)	0.067
	Median (IQR)	1.54 (0.98-1.95)	1.95 (1.61-2.39)	-	0.029
C24 (mg/L)	GM (90%CI)	1.12 (1.01-1.72)	1.52 (1.33-2.47)	0.73 (0.54-1.01)	0.107
	Median (IQR)	1.08 (0.78-1.39)	1.54 (0.91-2.07)	-	0.065

511 Correlation Between Atazanavir Concentrations, Clinical Covariates and Side Effects

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Background: Although significant relationships have been reported between atazanavir (ATV) trough concentrations and clinical outcome, therapeutic drug monitoring (TDM) of ATV is not routinely adopted in clinical practice. ATV plasma concentrations >150 ng/mL are currently considered the minimum level needed to achieve viral undetectability, while concentrations >800 ng/mL are associated with increased risk of hyperbilirubinemia. No specific associations have been reported between ATV levels and other drug related complications. Similarly, no clinical covariates affecting ATV concentrations have been conclusively identified.

Methodology: ATV trough concentrations were determined in a consecutive series of HIV patients receiving ATV for at least 3 months. The presence of hyperbilirubinemia (total bilirubin >1.8 mg/dL excluding UGT1A1*28 homozygous genotype), dyslipidemia (total cholesterol >200 mg/dL, triglycerides >180 mg/dL or statin therapy) and nephrolitiasis (renal colics without urinary oxalate or urate crystals) were assessed. Multivariate regression analyses were performed using ATV-related complications as the dependent variable and demographic, clinical and laboratory data as independent covariates.

Results: Nearly 45% of 273 enrolled patients (68% on ATV/r 300/100) had ATV concentrations out of the therapeutic drug window (set at 150-800 ng/mL). Patients with hyperbilirubinemia (n=125), hypercholesterolemia (n=116), hypertriglyceridemia (n=92) or nephrolitiasis (n=13) had ATV concentrations significantly higher (1025±920, 770±858, 838±791 or 1121±886 ng/mL, respectively) compared with those measured in patients without ATV-related complications (n=71; 461±678 ng/mL, p<0.001). The independent significant association between ATV plasma concentrations and drug-related toxicity was confirmed also by multivariate logistic regression analysis (p<0.05). The only factors independently associated with ATV levels were ritonavir use (r=-0.291, p<0.0001) and concomitant statin administration (rosuvastatin in 31/34 cases; r= 0.315, p<0.0001). No effect of tenofovir, patients' age, body weight or body mass index on ATV concentrations was found.

Conclusions: A significant proportion of patients treated with ATV had plasma concentrations exceeding the upper therapeutic threshold. High ATV plasma levels were significantly associated with all the main ATV-related toxicities. TDM in the day-by-day clinical practice may allow an early identification of patients at risk for untoward effects and drug dosage adjustment. Despite rosuvastatin is considered to have a low potential for drug-to-drug interactions with protease inhibitors, our data show that ATV plasma concentrations were significantly influenced by this drug.

512 Tenofovir Diphosphate Concentration-Response Relationship for HIV Prevention in Vaginal Tissue

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Background: Clinical trials with daily dosing of tenofovir (TFV) ± emtricitabine have shown disparate results for HIV protection. It is still unknown what target tissue concentrations must be achieved to confer protection. Here we describe the utility of a novel ex vivo human mucosal tissue culture model to determine the tenofovir diphosphate (TFVDP) target for protection.

Methodology: Fresh vaginal tissue was collected from 8 women undergoing surgical repair for vaginal prolapse. 5 subjects were used to characterize TFVDP formation and elimination over 96h. 3 subjects were used for HIV challenge, whereby up to 35 3mm punch biopsies (Miltex) per donor were incubated in a range of TFV concentrations (0, 0.1, 1, 10, 100 ug/mL) for 24h. TFVDP was quantified using a validated LC-MS/MS method. Remaining explants were incubated for 3h with 10^7 TCID50 HIV-1JRCSF, rinsed, and transferred to gelfoam rafts. Explants were harvested every 24h from 0-72h post-infection, with total RNA extracted using RNeasy Kit (Qiagen) and first strand cDNA synthesis performed with Superscript Vilo cDNA Synthesis Kit (Invitrogen). A quantitative RT-PCR assay measured copies of a spliced RNA variant expressed in abundance early in the transcription life cycle, and normalized for tissue weight. Infection was quantified as AUC24-72h adjusted for baseline. EC50 estimates were generated using an Emax model (Sigma Plot) and compared to estimates obtained in the TZM-bl cell line using a luciferase reporter assay.

Results: Vaginal explants phosphorylated TFV to TFVDP at a median molar conversion rate of 0.2% (range 0-2.0 %) and reached maximal conversion at 24h. TFVDP elimination half-life was 20h. Viral infection was confirmed by a peak in spliced RNA >1.5-fold baseline, and peaked at 2 days after infection. There was a poor relationship between TFV concentration and HIV protection. When normalized for TFVDP, standard error of the estimated EC50 was reduced by 4 logs. Estimated EC50 of TFVDP was 909 fmol/mg in explant tissue and 20 fmol/mg in TZM-bl cells.

Conclusions: This method uses an R5, T-cell-tropic virus to mimic the virus implicated in mucosal HIV transmission. When coupled with a novel spliced RNA assay, an Emax model of TFVDP was generated using 72h incubations. Variable phosphorylation resulted in a more reliable EC50 estimate when TFVDP (the active intracellular moiety) was used, rather than TFV incubation concentrations. Likely representing a "worst case scenario", this EC50 was ~45 times higher than a standard cellular model, but consistent with other recent clinical data. We are currently using this model to test additional drugs and drug combinations to identify target mucosal concentrations for protection against HIV infection, and determine its utility in PrEP development.

513 A Pharmacokinetic Drug-Drug Interaction Study Between Raltegravir and Atorvastatin

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Background: Dyslipidemia is highly prevalent among patients with HIV infection and contributes to an increased risk of cardiovascular disease. Atorvastatin is a potent lipid-lowering agent and is used for prevention of cardiovascular disease. A complicating factor in the concomitant use of antiretroviral agents and statins is the occurrence of drug-drug interactions.This study was designed to investigate the influence of a frequently used statin, atorvastatin, on the pharmacokinetics of the HIV integrase inhibitor raltegravir and vice versa.

Methodology: This was an open-label, cross-over, three-period phase I trial in 24 healthy volunteers. Subjects took raltegravir 400 mg BID for 7 days, atorvastatin 20 mg QD for 7 days, and the combination of atorvastatin 20 mg QD + raltegravir 400 mg BID for 7 days with 2-week washout periods in between. Treatment sequence was allocated at random. Intensive steady-state 12- and 24-hour pharmacokinetic (PK) blood sampling was performed on day 7 of each treatment period. PK parameters (AUC_{last}, C_{max}, C_{last}) were determined by non-compartmental analysis for raltegravir and the sum of atorvastatin and its active metabolites (atorvastatin-equivalents). Geometric mean ratios (GMR) of the test treatment [combination raltegravir + atorvastatin] versus the reference treatment [raltegravir or atorvastatin alone] and 90% confidence intervals (CI) were calculated after log-transformation of within-subject ratios. Fasting lipid profiles were obtained on day 1 and day 7 of each treatment period to assess short-term effect on serum low-density lipoprotein (LDL) cholesterol. To compare the change in LDL cholesterol after atorvastatin with and without raltegravir a paired t-test was performed.

Results: Twenty-four healthy volunteers, of which 11 males, were enrolled (23 Caucasian, 1 mixed race). One subject did not complete the treatment period with raltegravir alone due to reasons not related to the study. Median (range) age and BMI were 31 (18-55) years and 20.9 (18.3-28.9) kg/m^2, respectively. No serious adverse events were reported. GMR (90% CI) of raltegravir PK parameters were: 1.01 (0.68-1.51) for AUC_{0-12h}; 1.14 (0.70-1.86) for C_{max}; 0.96 (0.69-1.32) for C_{12h}. GMR (90% CI) of atorvastatin-equivalents PK parameters were: 0.98 (0.91-1.06) for AUC_{0-24h}; 1.02 (0.83-1.26) for C_{max}; 0.97 (0.87-1.10) for C_{24h}. Mean (95% CI) change in LDL cholesterol (day7 - day1) was -1.12 (-1.37;-0.87) mmol/L for atorvastatin alone compared to -1.29 (-1.50;-1.08) mmol/L for atorvastatin when combined with raltegravir (p=0.19).

Conclusions: Coadministration of raltegravir and atorvastatin does not change the pharmacokinetics of either drug in a clinically meaningfull way. The combination can be safely administered without dose adjustments.

514LB PK Study of Depot Medroxyprogesterone Acetate in HIV+ Women On Lopinavir/Ritonavir: ACTG 5283

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Background: Little is known about use of depot medroxyprogesterone acetate (MPA) with boosted-protease inhibitors (PIs), a commonly used antiretroviral treatment regimen. Interactions with boosted PIs could lead to changes in efficacy or toxicity of any of these drugs.

Methodology: We prospectively determined the effect of twice daily lopinavir (LPV) 400mg/ritonavir (RTV) 100 mg along with 2 or more nucleoside reverse transcriptase inhibitors (NRTIs) on the PK exposure of MPA through every 2 week sampling from baseline (day 0) to week 12 (AUC 0 to 12wk) (Wilcoxon rank-sum test). We also determined the effect of MPA on the PK of LPV and RTV using AUC for LPV and RTV at baseline and after 4 weeks of depot MPA using intensive PK sampling at pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 8, and 10 hours post-LPV/r dosing (Wilcoxon signed-rank test). Safety and toxicity of depot MPA and ovulation suppression (using progesterone levels of <5ng/mL) were assessed biweekly during the 12-week study, and were compared with 14 HIV+ control subjects not on HIV meds or only NRTIs, previously enrolled in A5093, who received depot MPA with identical assessments. All MPA assays were performed by PPD, Inc.

Results: 24 evaluable women on LVP/RTV were enrolled; 58% were black, 25% Hispanic and 13% white; median age 32 years; median CD4 622 cells/mm3; all had HIV RNA<400 copies/mL and negative pregnancy tests. Of the 14 historical controls, 79% were black, 14% Hispanic, and 7% white; median age 33 years. No women appeared to ovulate during the study and there were no pregnancies. MPA concentrations (median AUC0-12wk 18.08 ng*week/mL) were higher than the 14 A5093 controls (median AUC0-12wk 12.38 ng*week/mL) (p<0.001). There were no changes in the LPV/RTV levels after depot MPA (see table below). In this study, possible treatment-related toxicities occurred in 8 (33%) subjects, the most frequent being vaginal bleeding (8), and irritability (2). These side effects are similar to those described with use of DMPA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020246s036lbl.pdf).

Conclusions: MPA levels were significantly higher in HIV-infected women taking ritonavir-boosted lopinavir compared to HIV-infected women on no HIV medications or NRTIs alone. Levels of LPV and RTV were not altered by depot MPA and there was no evidence of ovulation through week 12. Depot MPA was well-tolerated despite having AUC levels 46% higher compared to historical controls, and side effects were similar to those reported in women on depot MPA.

Table 1: LPV/RTV Before and 4 Weeks After Depot MPA

	N	Median (interquartile range)	AUC0-12h, ng*h/mL	p-value
		Before DMPA injection	After DMPA injection	
LPV	24	98046 (81563, 106116)	97948 (84117, 113629)	0.782
RTV	24	5183 (4098, 7451)	5015 (3648, 6925)	0.579

515 Multi-System Investigation of the Mechanisms for Raltegravir Association With Intestinal Tissue

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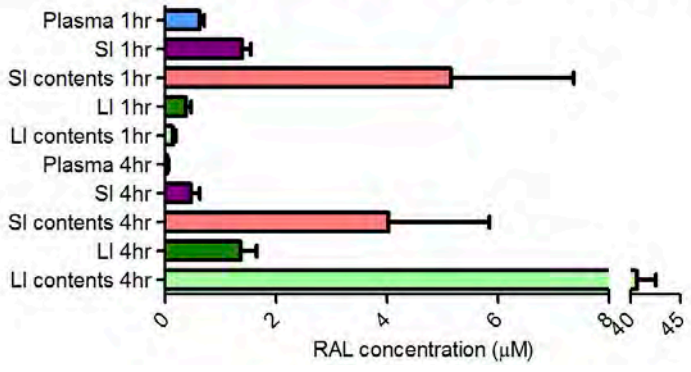
Background: Recent data have suggested that concentrations of raltegravir (RAL) in gut tissue are high after oral administration to humans, with implications for treatment and prevention. We have used in silico, in vitro, ex vivo and in vivo models to further investigate the accumulation of RAL in gut tissue.

Methodology: Gut-to-plasma affinity was predicted in silico for RAL and lopinavir (LPV) using the Poulin Theil equation. Cellular accumulation of RAL and LPV (both 1 µM) was determined at pH 5, 6, 7 and 8 in Caco-2 gut epithelial cells (15x106 cells, 37°C, 30 min). Gut-associated concentrations were determined ex vivo after incubation of 100g rat small intestine (SI) or large intestine (LI) with human plasma (3 mL, 37°C, 4 hours) containing RAL and LPV (both 50 µM). Finally, RAL concentrations in plasma, gut contents, SI and LI were determined after oral dosing (8 mg/kg) to Wistar rats with 1 and 4 hour post-dose blood/tissue sampling. In vivo samples were analysed using LC-MS/MS and other samples were analysed using scintillation counting (3H RAL and 3H LPV).

Figure 1. Concentrations of RAL in rat plasma, gut and gut contents at 1hr and 4hr post-dose



Results: Gut-to-plasma affinity ratios for RAL and LPV were predicted to be 0.53 and 6.38 in silico, respectively. Intracellular RAL in Caco-2 cells ranged from 1.41 μM (pH 5) to 0.42 μM (pH 8) and LPV ranged from 24.8 μM (pH 5) to 27.5 μM (pH 8). In ex vivo studies, RAL accumulated less than LPV in both SI (29.6 versus 65.7 μM, $p < 0.05$) and LI (34.9 versus 53.5 μM, $p < 0.05$). After oral administration to rats, RAL concentrations decreased in plasma between 1hr (0.63 ± 0.13 μM) and 4hr post-dose (0.05 ± 0.03 μM, $p < 0.05$) and in SI (1.4 ± 0.26 μM to 0.47 ± 0.27 μM, $p < 0.05$) but did not change in SI contents (5.2 ± 3.8 μM to 4.0 ± 3.2 μM, $p = 0.72$). Conversely, increases in LI (0.38 ± 0.15 μM to 1.36 ± 0.50 μM, $p < 0.05$) and LI contents (0.15 ± 0.09 μM to 40.6 ± 3.3 μM, $p < 0.05$) were observed (Figure).

Conclusions: RAL accumulated highly in gut tissue in vivo but this was not observed ex vivo or in vitro, indicating that high tissue-associated RAL concentrations in vivo were not driven by plasma-to-tissue accumulation but by high RAL concentrations in gut contents. However, given that intracellular penetration is a prerequisite for RAL activity, further study is required to preclude artefacts that may arise from contamination with gut contents. The gut is a relevant site for both pre-exposure prophylaxis (PrEP) and HIV eradication, and this screening system can be used to select for drugs with preferential accumulation in gut tissue.

516 Tenofovir DF 150 mg Once Daily in HIV-Infected Adults With Moderate Renal Impairment

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Background: Renal impairment significantly alters tenofovir pharmacokinetics. 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). New dosage strengths and formations of TDF may permit once daily dosing for these patients. We compared the pharmacokinetics of TDF 300 mg every 48 hours with 150 mg once daily in HIV-infected adults with moderate renal function impairment receiving lopinavir/ritonavir (LPV/r)-based antiretroviral therapy.

Methodology: Phase I, non-randomized, open-label pharmacokinetic study (ClinicalTrials.gov Identifier: NCT01671982). Consenting HIV-positive adults with a confirmed creatinine clearance 30 to <50 mL/min receiving TDF 300 mg every 48 hours as part of LPV/r-based HAART and an HIV-1 RNA viral load (VL) <50 copies/mL were enrolled. HBs-antigen positive adults were excluded. Intensive steady-state 48-hour blood sampling for PK assessment was performed at enrolment; 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. Immediately afterwards, the tenofovir dose was changed to 150 mg once daily. Intensive 24-hour blood sampling was repeated 2 weeks later; blood samples were drawn pre-dose, and at 0.5, 1.0, 1.5, 2.0, 4.0, 6.0, 8.0, 12, 24 hours post-dose. Subjects returned to the standard TDF dose after the PK sampling. Tenofovir plasma concentrations were determined using a HPLC assay and tenofovir pharmacokinetic parameters were calculated using noncompartmental analysis.

Results: Twenty HIV-infected adults (40% female) were enrolled. Median (range) age was 53 years (39-82), weight 49.5 kg (37.8-75.1), serum creatinine (SCr) 1.3 mg/dL (0.9-2.1), creatinine clearance (CrCL) 42.0 mL/min (31.7-49.7) and CD4 count 596 cell/mm3 (113-1063). Eighteen subjects had evaluable PK data available. With TDF 300 mg every 48 hours, the TDF AUC0-48h, Cmax and C48h were 9.61 (6.06-18.92) μg.hr/mL, 0.68 (0.44-1.31) μg/L and 0.07 (0.03-0.11), respectively. With TDF 150 mg every 24 hours, the TDF AUC0-24h, Cmax and C24h were 4.80 (2.61-9.29) μg.hr/mL, 0.42 (0.24-0.73) μg/L and 0.10 (0.05-0.20), respectively. The TDF geometric mean ratio (GMR) of AUC0-48h for every 24- versus every 48 hours dosing was 1.00 (90% CI 0.92-1.09). Tenofovir Cmax was significant lower ($p<0.01$) and Clast (i.e. C48h vs. C24h) significantly higher ($p<0.01$) with daily TDF dosing. All subjects remained virologically suppressed and no drug-related adverse events were reported.

Conclusions: Switching TDF 300 mg every 48 hours to 150 mg every 24 hours provided equivalent tenofovir exposure in patients with moderate renal function impairment receiving LPV/r-based antiretroviral therapy.

517 Tenofovir Concentrations and Prophylactic Effect in a Macaque Model of Rectal SHIV Transmission

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Background: Non-human primate (NHP) models are essential in the development and evaluation of pre-exposure prophylaxis (PrEP) strategies, but few studies have compared concentration-effect results from the NHP model with that from human PrEP trials. The objective of this study was to estimate the tenofovir-diphosphate (TFV-DP) concentration associated with 90% efficacy (EC_{90}) in the macaque rectal challenge model, and to compare it to the TFV-DP EC_{90} previously identified in the iPrEx study, a PrEP trial in men who have sex with men (MSM).

Methodology: Viably cryopreserved PBMC specimens were retrospectively analyzed from macaques PrEP studies of oral tenofovir disoproxil fumarate-emtricitabine (TDF/FTC) modalities that had different efficacies. All Rhesus macaques were challenged rectally with $SHIV_{SF162P3}$ once per week, for up to 14 weeks. One group of 6 macaques was given one TDF/FTC dose 3 days prior to each weekly virus challenge (-3 days). A second group of 6 macaques was given one TDF/FTC dose 3 days prior to, and another dose 2 hours after, each weekly virus exposure (-3 days/+2h). TDF/FTC doses were designed to match human exposures. Thirty-four control animals did not receive TDF/FTC. Viably cryopreserved PBMCs were collected at the time of virus challenges. The PBMC samples were processed and assayed for TFV-DP utilizing the same methods and procedures as the previous iPrEx analysis. The concentration-effect data were analyzed using a Cox proportional hazards model.

Results: 33/34 control animals acquired SHIV infection, 18 (55%) within the first two weekly inoculations. Five of 6 animals in the -3day group acquired SHIV, 4 (80%) after the second inoculation, and 1/6 animals in the -3 day/+2h group was infected at the 4th inoculation. In the -3 day/+2h group, the mean (SD) TFV-DP concentration accumulated approximately 2-fold, from 14.9 (5.8) fmol/10^6 cells after the first dose to 30.7 (10.1) after 4 weeks. Concentrations in the -3 day group ranged from 10.4 (2.6) fmol/10^6 after the first dose to 15.8 (7.6) after 5 weeks. No TFV-DP concentrations were below the limit of quantification. Each 5 fmol/10^6 cells of TFV-DP was associated with a 40% reduction in risk of SHIV acquisition (17% to 56%), p = 0.002. The concentration associated with 90% reduction in SHIV acquisition risk (EC_{90}) was 22.6 fmol/10^6 cells, 95% CI (13.8 to 60.8).

Conclusions: This study identified a TFV-DP EC_{90} of 22.6 (13.8 to 60.8) fmol/10^6 cells for reducing SHIV acquisition risk in a macaque rectal exposure model, which compared well with the TFV-DP EC_{90} of 16 (3 to 28) fmol/10^6 cells identified in MSM from the iPrEx study. This finding supports the use of this NHP model for PrEP studies using rectal virus challenges and oral TDF/FTC dosing.

Session P-H4 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

New Clinical and Preclinical Formulations

518 Optimisation of Intramuscular Sustained Release Nano-Formulations Using In Silico Modelling

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Background: Intramuscular (IM) sustained release antiretroviral (ARV) nano-formulations (NFs) may provide pharmacological options to simplify regimens, reduce drug costs and improve adherence. Studies are currently on-going with injectable preparations for pre-exposure prophylaxis and treatment. The aim of this study was to simulate the pharmacokinetics (PK) of IM sustained release NFs using physiologically based pharmacokinetic (PBPK) modelling. Existing ARVs were assessed for compatibility and theoretical target dose and release rate for once weekly and/or monthly administration formats were identified.

Methodology: In vitro or population PK data for 8 ARVs were integrated into PBPK models and ARV PK was simulated for 100 individuals using MATLAB, R2013b. The models included mathematical descriptions of covariance between demographics and tissue size, expression of metabolic enzymes and processes regulating absorption, distribution and elimination, which are drug-specific. The models were validated against clinical data for oral administration at standard regimens but rilpivirine (RPV) was also validated against available PK data for the 600 mg IM depot. Validated PBPK models were used for the prediction of PK following IM administration of theoretical sustained release NFs. ARV dose and release rate were optimised to obtain Ctrough values above the protein binding corrected IC95 (PBIC95) or clinical cut-offs obtained from literature sources.

Drug	IM Dose (mg)	Release rate (h^{-1})	Weekly/Monthly	AUC ($\mu g\ h\ mL^{-1}$) (Mean ± SD)	C_{max} ($ng\ mL^{-1}$) (Mean ± SD)	C_{trough} ($ng\ mL^{-1}$) (Mean ± SD)	Cut-off limit ($ng\ mL^{-1}$)
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)							
Emtricitabine	600	0.0015	**Monthly**	21.0 ± 10.9	45.8 ± 22.7	17.3 ± 10.7	14 (IC_{95})
	125	0.01	Weekly	7.2 ± 10.7	68.2 ± 79.4	14.5 ± 9.0	
Tenofovir	1500	0.001	**Monthly**	25.5 ± 17.8	56.6 ± 38.9	20.0 ± 14.0	18 (IC_{95})
	350	0.008	Weekly	6.7 ± 5.3	67.2 ± 49.1	18.7 ±13.8	
Non-Nucleoside Reverse Transcriptase Inhibitors (NRTIs)							
Efavirenz	1000	0.002	**Monthly**	190.6 ± 101.3	377.5 ± 165.6	154.0 ± 130.8	126 ($PBIC_{95}$)
	200	0.015	Weekly	34.0 ± 9.1	268.5 ± 60.9	138.1 ± 81.3	
Etravirine	225	0.011	Weekly	11.7 ± 1.8	88.6 ± 12.7	59.8 ± 16.0	52 (MEC)
Rilpivirine*	250	0.002	**Monthly**	40.2 ± 19.7	76.9 ± 33.6	35.0 ± 20.0	20.3 ($PBIC_{95}$)
	60	0.02	Weekly	8.0 ± 2.5	71.8 ± 16.4	20.7 ± 14.0	
Integrase Inhibitors (IIs)							
Dolutegravir	105	0.002	**Monthly**	91.2 ± 9.4	192.3 ± 16.6	64.3 ± 8.1	64 ($PBIC_{95}$)
	20	0.006	Weekly	12.3 ± 1.3	89.6 ± 9.5	65.5 ± 7.6	
Raltegravir	1000	0.002	**Monthly**	89.1 ± 17.9	62.8 ± 9.7	15.4 ± 2.5	15 ($PBIC_{95}$)
	225	0.007	Weekly	17.8 ± 3.4	46.8 ± 7.2	15.8 ± 2.5	
Protease Inhibitors (PIs)							
Atazanavir	600	0.009	Weekly	124.5 ± 4.1	192.1 ± 10.7	60.6 ± 2.3	60 ($PBIC_{95}$)

* Note that this dose does not apply to the existing RPV formulation. Rather, as for other listed drugs, the data represent a prediction for optimal performance of a reformulation.

Results: The simulated PK parameters for oral administration were in agreement with previously published clinical data. For validation against the existing formulation, simulated 600 mg IM RPV, mean values for AUC were 87.7 vs. 84.0 ng.h/mL, Cmax 91.7 vs. 96.7 ng/mL and Ctrough 13.3 vs. 15.7 ng/mL for simulated versus observed data with a predicted release rate of 0.0011 /h for the existing formulation. The table gives simulated PK for IM administration and a prediction of the optimal ARV dose and release rate combination. Dolutegravir, efavirenz, emtricitabine, raltegravir, tenofovir and RPV were predicted to be the suitable candidates for monthly IM formats.

Conclusions: PBPK models were used to estimate optimal dose and release rate and may be useful to inform target product profiles for sustained release NFs. Candidates with the potential for reformulation into an IM injection were identified, providing the technological complexities associated with reformulation can be overcome for these agents.

519 Macrophage Targeted Nanomedicines for Mycobacterial Infections

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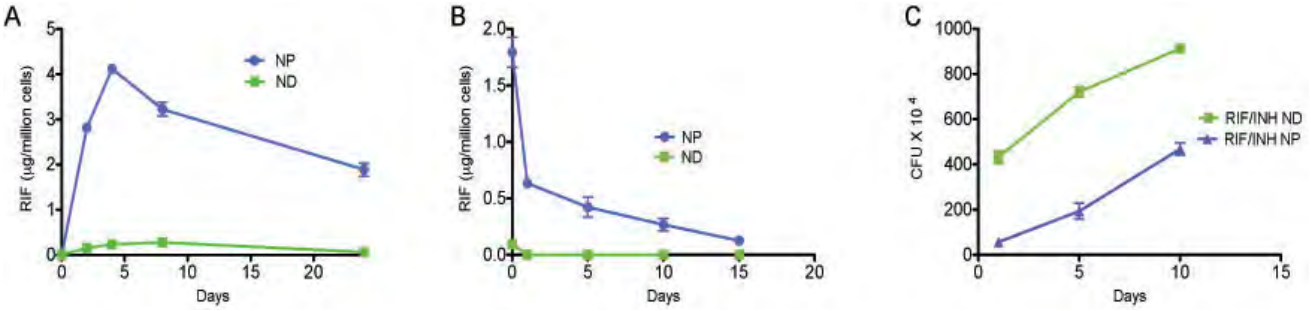
[1]University of Nebraska Medical Center, Omaha, NE, United States, [2]Pharmaceutical Science, University of Nebraska Medical Center, Omaha, NE, United States

Background: Mycobacterium tuberculosis (MTB) is a common co-morbid HIV-associated infection. Complex drug regimens and microbial resistance underlie an alarming increase of infected people that now exceeds three million worldwide. The needs for access to simplified treatment regimens are of immediate need. This can be achieved by the development of long-acting cell and tissue targeted nanoformulated MTB medicines.

Methodology: Commercially available isoniazid was derivatized to INHP. INHP and rifampin (RIF) poly-lactide-coglycolic acid (PLGA) nanoparticles were manufactured. Physical, chemical properties, cell uptake, retention, viability, trafficking and antimicrobial efficacy were determined for the nanoparticles encased drugs when compared to native drugs. Antimicrobial activities were determined in dose response tests against Mycobacterium smegmatis from one to 15 days after infection.

Results: Results: The nanoformulations displayed enhanced uptake of 4.12 µg/million cells in comparison to 0.1 µg/million cells for the native drugs (Fig. 1A). There was sustained release of the encapsulated drugs that were detectable in monocyte-derived macrophages (MDM) over 15 days; the native drugs were released within 24h (Fig. 1B). Antimicrobial activity was significantly improved up to 10-fold when the two nanoformulations were combined as opposed to native drugs (Fig. 1C). Individual drugs of both nanoformulations and native drugs showed minimum or no antimicrobial effect. We also demonstrated that the nanoformulations and M. smegmatis are trafficked into the same subcellular compartments, thereby enhancing the antimicrobial effect. These trafficking mechanisms parallel what we observed with antiretroviral drugs.

Figure 1: A comparison of drug uptake (A), retention (B) and antimicrobial efficacy study (C) between the nanoformulations (NP) and native drugs (ND)



Conclusions: In summary, we demonstrated that PLGA nanoparticles encapsulating RIF and modified isoniazid derivative improves drug uptake, retention and antimicrobial efficacy of the nanoformulations in comparison to the native drugs. Subcellular distribution study of M. smegmatis and the PLGA nanoformulations show that the drugs and the mycobacterium are trafficked into the same endocytic compartments, thereby enhancing the antimicrobial effect. It should therefore be noted that macrophage-nanoparticle delivery approach is a promising system for the management of tuberculosis in future.

520 Fluorescent Magnetic Nanoparticle as Anti-HIV Drug Carrier for Rodent Brain Targeting

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Background: HIV-1 still remains one of the leading life-threatening diseases in the world despite the introduction of Highly Active Antiretroviral Therapy (HAART). Since most of the drugs have less penetrance into viral reservoir sites such as brain, development of an active targeted drug delivery system is essential to increase the efficacy of drug targeting to the brain. In this regard, we developed a multifunctional iron oxide magnetic nanoparticle (MNP) bound to anti-HIV drug azidothymidine 5′-triphosphate (AZTTP) (MNP-AZTTP) tagged with fluroscent probe for noninvasive imaging in our lab for targeting to brain. Our initial observation on in vitro study indicated that MNP-AZTTP have significantly improved cellular uptake and drug delivery across the BBB model.

Methodology: The synthesis of MNP was prepared by reverse-phase evaporation method. MNP-AZTTP was encapsulated into liposomes with fluorescent probe incorporation. This MNP-AZTTP was further characterized with respect to particle size, polydispersity index (PDI) and surface charge. The drug dissolution study was done through dialysis at different time intervals (30 min to 2 days) measured by HPLC. The initial in vivo characterization was carried out in mice by injecting MNPs through i.v. injection and retained within the 0.2 Tesla magnetic fields for 30min, 1hr, and 2hrs with anesthesia assistance.

At the end of the treatment, mice were sacrificed and brain tissues were harvested for co-localization studies of drug and MNP by fluorescent detection on frozen section slides of brain tissue.

Results: Preliminary data showed that MNP-AZTTP are of 118±15.2 nm size with 0.15 PDI and zeta potential of the particles was 10.3 ± 2.2 mV. Further, drug dissolution study displayed significantly sustained release property over free drugs. In vivo analysis indicated that within 2hr of injection the fluorescent MNP-AZTTP reached the brain while the signal from control group was negligible. Dose dependent study has revealed that 5mg/kg of MNPs are ideal for pharmacokinetics study in mice.

Conclusions: This novel formulation will be able to deliver multiple anti-HIV drugs more efficiently to rodent brain and also help us to detect the site of drug target in a noninvasive manner through imaging process.

521LB A Novel Anti-HIV Particle Provides Sustained Plasma and Cell Drug Levels in Lymph Nodes in Primates

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Background: We have reported previously that an anti-HIV drug Indinavir bound to lipid nanoparticles (LNP) provide pH responsive release and extended plasma drug exposure and accumulation in lymph nodes in primates after subcutaneous dosing. The goal of this study is to develop and evaluate a HIV drug combination intended for a maximal suppression of residual virus. To do so we constructed an anti-HIV LNP containing two protease inhibitors [Lopinavir (LPV) and Ritonavir (RTV) and one nucleotide analogue reverse transcriptase inhibitor [Tenofovir (TNFV)] and compared the LNP versus free drug formulation for plasma time-course and intracellular drug levels in lymph nodes.

Methodology: The LNPs composed of lipids (DSPC: mPEG2000-DSPE) (8:2 m/m); and anti-HIV drugs-LPV, RTV and RNFV (115:10:5:15 lipids:LPV:RTV:TNFV m/m/m/m) were produced by solvent evaporation, followed by rehydration in buffered saline and homogenization with an Avestin Emulsiflex C5. Near-complete LNP incorporation of Lopinavir and Ritonavir and reproducible Tenofovir encapsulation (~5%) were verified. The anti-HIV LNP diameter was 50-80 nm. pH, osmolarity, and sterility were verified. Macaques (M. Nemestrina) (n=4/gp) received free or LNP drug formulation subcutaneously. Blood and peripheral blood mononuclear cells (PBMCs) were collected for 24 hours and at day-7. The inguinal lymph node was collected at 24 hours and day-7. Drug concentrations were determined by liquid chromatography tandem mass spectroscopy (LC-MS/MS-QTRAP).

Results: Primates dosed subcutaneously with anti-HIV particles composed of LPV: RTV:TNFV at 25:14:17 mg/kg provided sustained plasma drug levels for more than 7 days. In contrast, animals treated with an identical dose in free and soluble form exhibited plasma and lymph node drug levels that decline rapidly below the detection limit by 24 hrs; and exhibited significant local skin reactions that persisted for more than 2 weeks, Animals that received LNP formation did not exhibit local reaction. Treatment with anti-HIV LNP provided significant cellular drug concentrations at 24 hrs. In addition, mononuclear cells dissociated from lymph nodes also contained significant levels of LPV, RTV, and TNFV in the cells even 7 days after a single-dose anti-HIV LNP administration.

Conclusions: Anti-HIV lipid nanoparticles containing the three drugs, Lopinavir, Ritonavir and Tenofovir, demonstrated the ability of prolonged drug presence in plasma, PBMCs, and lymph node cells beyond levels achievable by free, non-particulate drug dosage form after a single subcutaneous administration in primates. Incorporation of the three drugs into LNP also reduced local side effects.

522 NanoART Facilitated HIV-1 Clearance by a Mixed-Lineage Kinase 3 Inhibitor

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Background: Antiretroviral therapy (ART) has improved life quality and longevity for infected people. However, despite ART viral replication continues, albeit at low levels. Eradication of infection remains the major goal of HIV scientists and clinicians alike. Recently, a novel mixed-lineage kinase-3 (MLK3) inhibitor (URMC-099) with promising immune and neural modulatory activities was found. Surprisingly, the drug was found to potentiate the antiretroviral activities of our nanoformulated long-acting ART

Methodology: Isobaric tag for relative and absolute quantitation (iTRAQ) was performed in URMC-099 treated monocyte-derived macrophages (MDM) seeking potential antiretroviral actions. Nanoformulated atazanavir (nanoATV) with/out dose escalated URMC-099 was tested for antiretroviral activities in HIV-1ADA exposed MDM. Viral DNA and RNA, Gag proteins and reverse transcriptase (RT) activities were assessed. Subcellular endosomal trafficking (Rab 5, 7, 8 and 14) of the ART nanoparticles were investigated by Western blot, confocal microscopy and HPLC. Humanized NOD/scid-IL-2Rγcnull (NSG) mice were infected with HIV-1ADA followed by administration of URMC-099 daily and nanoformulated atazanavir and ritonavir (nanoART/r) for three weeks beginning at 10 weeks post-infection. Peripheral viral load (VL), human CD4+ and CD8+ T cells, and lymphoid and brain tissues were investigated for virus and immune profiling.

Results: URMC-099 increased expression of the RAS-related GTP-binding proteins Rab 7, 8 and 14 in HIV-1 infected MDM. NanoATV antiretroviral activities were potentiated by URMC-099 with reductions in viral DNA and RNA, HIV-1gag and RT activity. URMC-099 increased ATV concentrations in Rab14 endosomal compartments. Highest levels of CD4+ T cells numbers were seen in infected humanized mice treated with URMC-099 and nanoATV with VL in plasma below the limit of assay detection in the mice (<500 copies/ml). Such URMC-099-ART synergy was not seen with native

drug. Histopathological tests of spleen and lymph nodes showed decreased numbers of HIV-1p24 cells with both drugs as compared to nanoATV alone. Preservation of synaptic structures was also seen. iTRAQ and tandem mass spectrometry tests were confirmed by Western blot tests showing significant Rab7 and 8 changes in HIV-1 infected MDM.

Conclusions: URMC-099 significantly potentiates nanoATV responses to restrict HIV-1 and protect CD4+ T lymphocytes. This appears to occur, in part, by sustaining ART levels in specific endosomal compartments of the cells. Such new effects of URMC-099 may represent a novel means for viral clearance.

523 A Multiple Dose Study of Raltegravir (RAL) Formulations

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Background: ISENTRESS (raltegravir) is an integrase strand transfer inhibitor indicated in combination with other anti-retroviral drugs for the treatment of human immunodeficiency virus (HIV-1) infection. ISENTRESS is currently marketed as a 400 mg oral compressed tablet (OCT) formulation of raltegravir given twice daily for a total daily dose of 800 mg. This study was conducted to characterize the steady state pharmacokinetic (PK) profile of 1200 mg formulations of raltegravir to support once daily administration.

Methodology: An open label, multiple dose, randomized, three period, three treatment, crossover study was performed in 24 healthy male and female subjects (18 to 55 years). Subjects received either 1200 mg once daily (QD) of the OCT formulation (3x400 mg tablets), 1200 mg QD of a reformulated raltegravir (rRAL) formulation (2x600 mg tablets), or 400 mg twice daily (BID) of the OCT for 5 days. Safety and tolerability were assessed. Full PK profiles in all cases were collected after administration under fasted conditions on days 1 and 5. In pursuing a model based drug development approach, a PK/PD viral dynamics model is being utilized to assess the feasibility of these 1200 mg formulations for once daily dosing and inform future study design.

Results: RAL was found to be generally well tolerated in healthy subjects. Administration of 1200 mg OCT QD in the fasted state resulted in a day 5 geometric mean (CV%) Ctrough of 83.1 nM (53%), Cmax of 14.2 µM (99%), and AUC24hr of 49.3 µM-hr (73%). Similarly, administration of a 1200 mg rRAL tablet QD in the fasted state resulted in a day 5 geometric mean (CV%) Ctrough of 81.2 nM (72%), Cmax of 20.6 µM (44%), and AUC24hr of 59.4 µM-hr (34%). Administration of 400 mg OCT BID in the fasted state resulted in a day 5 geometric mean (CV%) Ctrough of 132 nM (56%), Cmax of 3.5 µM (153%), and AUC24hr (2xAUC12hr) of 26.0 µM-hr (106%).

Conclusions: Data from this study, in combination with other recently completed Phase I studies and PK/PD viral dynamics modeling and simulation, will be utilized to further assess whether QD dosing with these formulations would have a high likelihood of exerting antiviral activity similar to that of the current BID regimen, and provide insights into the feasibility of these formulations for once daily administration.

524 In Vivo Effects of Solid Drug Nanoparticle and Conventional Efavirenz On Anxiogenesis in Rodents

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Background: Efavirenz (EFV) has variable bioavailability and induces neurocognitive side effects, including anxiety. Recently we reported an EFV solid drug nanoparticle (SDN) formulation with pharmacological benefits. Here we investigated neurocognitive disturbances in rats using the elevated plus maze (EPM) after administration of a conventional or SDN formulation. In this model, anxiety is typically demonstrated by time spent in the open arms versus the closed arms, with greater anxiety linked to less time on the open arms.

Methodology: Male Wistar rats were administered EFV (10mg/kg, 0.5% methylcellulose), SDN (10mg/kg) or vehicle control by oral gavage once daily for 5 weeks. Rats were placed in the EPM for 5 minutes weekly. Behavior was videotaped and analyzed using Ethowatcher software. Data were collected on number of entrances into the open and closed arms and time spent in the open arm, closed arm and central square (expressed as percentage of total time on EPM). Statistical analysis was performed by Mann-Whitney U test and significance was defined as $P < 0.05$. All data are given as median [IQR].

Results: No differences in behavior were observed in week 1. In week 2, the percentage of time spent on the central platform was significantly increased in the EFV group (60% [51-65%]) compared to SDN (44% [25-50%]) and control (47% [34-57%] with $P = 0.03$ and $P = 0.91$ for EFV and SDN versus control, respectively. The EFV group spent less time in the closed arm than the SDN group but this was not statistically significant. In week 3 differences in time spent on the central platform were again observed (EFV 65% [48-71%], SDN 31% [25-42%], control 46% [28-52%], with $P = 0.01$ and $P = 0.28$ for EFV and SDN versus control, respectively. Significant differences in the time spent in the closed arm were also observed (EFV 21% [13-46%], SDN 66% [47-75%], control 43% [33-71%]) with $P = 0.005$ and $P = 0.631$ for EFV and SDN versus control, respectively. Similarly in week 4, time spent by the EFV group on the closed arms was lower (EFV 34% [28-42%], control 61% [IQR 46-72%]; $P = 0.005$) and time on the central platform was higher (EFV 51% [46-57], control 30%, [26-42%]; $P = 0.001$). No statistically significant differences in behavior between any groups were observed in week 5.

Conclusions: Our experiment did not fully replicate EFV anxiogenic effects previously reported using the EPM, but did show clear behavioral effects indicative of CNS activity. Notably, a tendency of EFV to increase time spent on the central platform may be indicative of anxiogenesis. By contrast, the SDN did not consistently affect behavior in a manner that would indicate anxiogenic activity. We interpret these data as indicating the SDN may have reduced potential to induce neurocognitive disturbance, either acutely or after long-term administration.

525 Atazanavir/Cobicistat Fixed-Dose Combination Is Bioequivalent To the Separate Agents

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Background: The once-daily protease inhibitor atazanavir (ATV) boosted with low-dose ritonavir (RTV) and combined with other antiretrovirals is approved for the treatment of HIV-1 infection. Cobicistat (COBI), an alternative booster with more selective CYP3A inhibition but no antiretroviral activity or CYP induction, has similar pharmacoenhancing activity as RTV. A Phase III trial has demonstrated comparable efficacy and safety of ATV 300 mg + COBI 150 mg relative to ATV 300 mg + RTV 100 mg (85% vs 87% virologic suppression, respectively). To reduce pill and prescription burden, a fixed-dose combination (FDC) of ATV/COBI has been developed. Because ATV is recommended to be taken with food, which enhances ATV bioavailability and reduces pharmacokinetic variability, we assessed the bioequivalence of ATV and relative bioavailability of COBI in an FDC vs ATV and COBI coadministered individually after a light meal.

Methodology: This randomized, open-label, cross-over study in 64 healthy subjects assessed 48-hour ATV and COBI plasma concentration-time profiles after single doses of an FDC of ATV 300 mg/COBI 150 mg or ATV 300 mg and COBI 150 mg co-administered as individual agents (NCT01837719). Treatments were administered after a light meal and followed by a 7-day washout between each period. Pharmacokinetic (PK) parameters assessed were maximum plasma concentration (Cmax), area under the concentration-time curve to infinity and to the last time point with measurable able concentration AUC(0-T), and concentration at 24-hour post-dose (C_{24}) for ATV. Bioequivalence for ATV was established if the 90% confidence intervals (CIs) for the FDC vs individual administration geometric mean ratios (GMRs) fell within the predefined limits of 0.80-1.25 for all PK parameters.

Results: All ATV PK parameter GMR 90% CIs fell within the predefined limits indicating bioequivalence of the FDC to ATV 300 mg and COBI 150 mg coadministered individually (Table). Although not prespecified, COBI in the FDC also met the criteria for bioequivalence to coadministration of the individual agents. Not unexpectedly with ATV, 5 subjects treated per protocol had total bilirubin elevations (1.2-2.1 × ULN), which were all improving or had resolved by study discharge.

Conclusions: ATV and COBI administered in an FDC is bioequivalent to coadministration of the individual agents under fed conditions. A single dose of ATV 300 mg and COBI 150 mg was safe and well tolerated when administered either as the FDC or as individual agents.

PK Parameters of Atazanavir and Cobicistat when Coadministered Individually or as the FDC

Pharmacokinetic parameters	Adjusted geometric mean* ATV + COBI (Treatment A)	ATV/COBI FDC (Treatment B)	GMR (90% CI)* [B vs. A]
ATV, n	63†	62†‡	
C_{max} (ng/mL)	3822	4101	1.073 (1.012, 1.137)
AUC(INF) (ng.h/mL)	33475	35623	1.064 (1.011, 1.120)
AUC(0-T) (ng.h/mL)	32723	34848	1.065 (1.012, 1.120)
C_{24} (ng/mL)	415.6	450.4	1.084 (1.014,1.158)
COBI, n	63†	62†‡	
C_{max} (ng/mL)	1320	1351	1.023 (0.991, 1.057)
AUC(INF) (ng.h/mL)	9053	9225	1.019 (0.982, 1.058)
AUC(0-T) (ng.h/mL)	8745	8912	1.019 (0.983, 1.057)

*Based on a linear mixed effects model with natural logarithms of ATV or COBI as response and with treatment, period and sequence as fixed effects and subject(sequence) as a random effect. Point estimates and 90% confidence intervals (CI) for differences on the log scale were exponentiated to obtain estimates of geometric mean ratio (GMR) on the original scale. Bioequivalence was concluded if the B vs A GMR 90% CIs fell within 0.80 to 1.25 for PK parameters. †One subject excluded as accidentally given both treatments A and B. ‡One subject excluded as vomited shortly after receiving treatment B.

Session P-I1 Poster Session
Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Preclinical Studies of Novel ART Approaches: Entry

526 Non-Integrating Lentivirus Delivered CCR5-ZFNs Can Inhibit HIV-1 Infection in Humanized Mice

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Background: Zinc finger nuclease (ZFNs) technology is a powerful tool for therapeutic gene editing. CCR5 defective T cells are resistant to HIV-1 infection, so CCR5 disruption by ZFNs is a promising method for HIV-1 gene therapy. Successful clinical translation of the strategy will depend on the development of a safe and effective method for delivery of ZFNs into relevant cells. As permanent disruption of the targeted gene after a single ZFN treatment, Non-intergrating lentivirus can provide a safe vehicle for delivery to avoid toxicity and off target expression associated with long-term expression. Further, HIV envelope can be used for pseudotyping, which enables the targeting resting T cells, which are recalcitrant to transduction with conventional VSV-G pseudotyped lentivirus. Here we used non-intergrating lentivirus with either HIV or VSVG envelope delivered CCR5-ZFNs into human resting T cells or primary hematopoietic stem cells respectively and investigated the disruption of CCR5 gene and protection of HIV infection in vitro and in humanized mice.

Methodology: ZFN constructs targeting both strands of CCR5 were connected via a 2A sequence, and then inserted to a lentivirus cloning vector. Chimeric non-intergrating lentivirus (NILV) carrying CCR5-ZFNs was obtained by co-transfecting 293 T cells with intergrase-defective packaging plasmid and HIV (or VSVG) envelope plasmid. After transductions of different cell lines and primary T cells, as well as CD34+ Hematopoietic stem cells (HSCs), genomic DNAs were extracted for characterizing CCR5 disruption by CEL I assay. Thereafter, NILV transduced primary T cells or CD34+ stem cells were challenged with HIV_{BAL} to test the protection of HIV infection in vitro. Protection from HIV challenge was tested in humanized NOD-scid IL2rγc^{null} mice after adoptive transfer of NILV- transduced primary T cells (Hu/PBL model) or CD34+ stem cells (BLT model).

Results: The results showed that NILV carrying CCR5 ZFNs transduced cell lines, primary T cells and CD34+ HSCs could successfully disrupt CCR5 gene with various levels of efficacies, and that both activated and resting T cells transduced with ZFNs lentiviruses showed resistance to HIV infection in vitro. Furthermore, NILV transduced CD34+ could be reconstituted into BLT mice and, after HIV_{BaL} challenge, the CD4+ T cells count is maintained in the test group receiving ZFNs modified HSCs but not in controls. Likewise, endogenous virus replication was suppressed in NOD-scid IL2rγc^{null} reconstituted with CCR5-ZFN transduced resting T cells from a HIV seropositive patient.

Conclusions: Non-intergrating lentivirus provide a useful strategy for delivery of zinc finger nucleases for editing CCR5 and other therapeutically feasible host genes for HIV-1 gene therapy.

527 Role of Sulfhydryl in Causing Lytic Inactivation of HIV-1 by Env Targeting Peptide Triazole Thiols

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Background: We have identified peptide triazole thiol inhibitors which bind Env gp120, allosterically inhibit CD4 receptor and co-receptor surrogate mAb 17b binding, and cause both gp120 shedding and p24 release from the virus lumen. The prototype peptide triazole thiol KR-13 (R-I-N-N-I-X-W-S-E-A-M-M-βA-Q-βA-C-CONH2, X= ferrocenyltriazole-Pro) causes p24 release, however KR-13b (C-terminal SH capped by acetomidomethyl) inhibited cell infection but did not cause p24 leakage. We are investigating the mode of action by which the C-terminal sulfhydryl group causes irreversible inactivation. From a molecular dynamics simulated model of the peptide triazole-gp120 complex we know that the IXW pharmacophore of KR13 binds in the CD4 binding site. Therefore, a working model is that the thiol interferes with conserved disulfides clustered proximal to the CD4 binding site in gp120 through "disulfide exchange". These disulfides are located within gp120 at 296-331 (V3 loop), 385-418 (C4), 378-445 (C3), and 119-205 (V1/V2 loop).

Methodology: Peptide triazoles are synthesized by solid phase Fmoc chemistry, followed by click conjugation. Infectivity assays are performed with single round pseudo-typed HIV-1 BaL.01 and a luciferase gene, which is detected by chemiluminescence. p24 release was assayed using sandwich ELISA.

Results: To evaluate the importance of the spatial relationship between PT-SH and gp120 disulfide groups we synthesized truncated peptides derived from KR-13 and compared p24 release and antiviral activities. We observed a strong dependence of lysis activity on length of the linker between the IXW pharmacophore and SH group. We also examined the ability of KR13 to cause p24 release after HIV-1 treatment with Ellman's reagent, a disulfide exchange inhibitor. These results demonstrate that release of p24 induced by KR13 is significantly inhibited by Ellman's reagent. Additionally, we have shown that 2G12, a conformational antibody which binds to a glycosyl group near the V3 loop, competes with the p24 release of virolytic peptides in a dose dependent manner.

Conclusions: We have shown that there is a discontinuous relationship between virolysis and peptide length, indicating that a minimal length is required for efficient virolysis. Our findings suggest that virolytic peptides disrupt the stable conformation of Env by interfering in disulfide exchange within gp120, thus sensitizing the viral membrane to rupture. Furthermore, our data implicates the V3 loop disulfide as a potential site that triggers this disulfide exchange cascade. We currently plan to investigate the functional cross-talk between the fusion mechanism and events leading to virolysis as well as examine the importance of specific Env disulfides that may be involved in disulfide exchange.

528 eCD4-Ig Is a Highly Potent HIV-1 Entry Inhibitor

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Background: Soluble CD4 and its more bioavailable form, CD4-Ig, neutralize HIV-1 less potently than most broadly neutralizing antibodies (bNAbs) because they bind the HIV-1 envelope glycoprotein with lower affinity and promote infection when cellular CD4 is limiting.

Methodology: We generated a fusion of CD4-Ig and a small CCR5-mimetic sulfopeptide (eCD4-Ig) and compared this fusion with CD4-Ig and the broadest and most potent bNAbs. We also investigated its properties *in vivo*.

Results: eCD4-Ig overcomes both shortcomings of CD4-Ig: It bound the envelope glycoprotein with higher avidity than CD4-Ig and its sulfopeptide inhibited infection promoted by CD4-Ig. eCD4-Ig efficiently neutralized a diverse panel of antibody-resistant tier 2 and tier 3 isolates without exception and with IC_{50}s ranging from 0.002 to 1.137 µg/ml (0.02-11 nM) – values comparable to or better than those of the best HIV-1 bNAbs. Because it binds only conserved regions of the HIV-1 envelope glycoprotein, it is also broader than any bNab. Underscoring this breadth, it neutralized all forty isolates resistant to CD4-binding site bNAbs NIH45-46 and 3BCN117, as well as HIV-2 and antibody resistant SIV isolates, with IC_{50}s from 0.001 to 1.453 µg/ml. eCD4-Ig also induced markedly more efficient antibody-dependent killing of HIV-1- or SIV-infected cells than did CD4-Ig and protected humanized mice from an HIV-1 challenge. Further, it retained its efficacy when delivered as an adeno-associated virus vector to three rhesus macaques, without eliciting an anti-eCD4-Ig antibody response.

Conclusions: eCD4-Ig is a highly potent, exceptionally broad, and mechanistically distinct inhibitor of HIV-1 entry that can be used to prevent or treat an HIV-1 infection.

529 Computational Design of Novel Potent Inhibitors of HIV-1 Entry

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Background: The process of HIV-1 entry is key to the replication of the virus. It is one of the most attractive targets in the search for new drugs to treat HIV-1 infection as entry inhibitors would have utility in both pre- and post-exposure prophylaxis, including woman-controlled microbicides. In the HIV-1 entry field, two main inhibitor chemotypes predominate (BMS-377806- and NBD-556-type compounds) with the BMS-377806 analogues demonstrating superior potency. However, the BMS-377806 analogues suffer from poor solubility and oral bioavailability. Therefore, given the enormous potential of small molecule entry inhibitors, we have designed and tested a series of novel compounds that function as entry inhibitors and have better predicted ADME/PK properties.

Methodology: To identify novels compounds that function as entry inhibitors, we performed a high-content pharmacophore virtual screen using Blaze v10 (Cresset, UK) and a pharmacophore derived from templating BMS-377806, BMS-488043, and BMS-626529 using FieldTemplater v3.0 (Cresset, UK). 50 compounds were purchased for testing in the single round infection assay against HIV-1 pseudotyped with HIV-1 Env and AMLV Env. Spark v10 (Cresset, UK) and StarDrop v5.2 (Optibrium Ltd, UK) were employed to design a series of next generation compounds with novel scaffolds. Next generation compounds were synthesized and tested for potency and specificity in the single round infection assay.

Results: Assessment of the antiviral potencies and specificity of 50 commercially available screening compounds identified 5 novel compounds previously undescribed in the literature. However, each hit contained a core piperazine; a moiety that is shared by the BMS-377806-type inhibitors. Replacement of the core piperazine with a dipyrrolidine yielded a novel inhibitor with high micromolar potency. Sequential replacements of a terminal acenaphtene ring, with varying azaindole groups resulted in an inhibitor with low nanomolar potency. However, predicted ADME/PK properties remained poor. Replacement of the dipyrrolidine with a pyrrolo-3,4-pyrazole afforded a compound with improved predicted ADME/PK properties and that retained nanomolar potency.

Conclusions: Using a combination of high-content pharmacophore virtual screening, coupled with scaffold hopping by bioisoteric replacements, and consideration of predicted ADME/PK properties, we have designed a new small molecule entry inhibitor with a novel scaffold, nanomolar potency, and improved predicted drug-like properties. This new chemotype may provide a blueprint for the future development of small molecule entry inhibitors, whilst characterization of its mechanism of action will yield important basic information about the process of HIV-1 entry.

530 Cenicriviroc Achieves High CCR5 Receptor Occupancy at Low Nanomolar Concentrations

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Background: Cenicriviroc (CVC) is a novel, once-daily, potent, CCR5 and CCR2 antagonist that has completed Phase 2b evaluation for the treatment of HIV-1 infection in treatment-naïve adults (NCT01338883). The aims of this study were to evaluate in vitro receptor occupancy and biology after treatment with CVC, BMS-22 (TOCRIS, a CCR2 antagonist) and an approved CCR5 antagonist, Maraviroc (MVC).

Methodology: PBMCs from 5 HIV+ and 5 HIV- subjects were incubated with CVC, BMS-22 or MVC, followed by either no treatment or treatment with a RANTES (CCR5 ligand) or MCP-1 (CCR2 ligand). The capacity of each drug to inhibit CCR5 or CCR2 internalization was evaluated. Cell-surface expression of CCR5 and CCR2 was assessed by flow cytometry, and fluorescence values were converted into molecules of equivalent soluble fluorescence (MESF).

Results: Both CVC and MVC, in the absence of RANTES, increased cell-surface expression of CCR5. This effect was seen to a much greater degree in HIV-negative subjects (CD4+ and CD8+ T cells). CVC prevented RANTES-induced CCR5 internalization at lower effective concentrations than MVC. The effective concentration at which saturation of CCR5 was reached for CVC was 3.1 nM for CD4+ and 2.3 nM for CD8+ T cells (~91% and ~90% receptor occupancy, respectively). MVC reached saturation at 12.5 nM for both CD4+ and CD8+ T cells, representing ~86% and ~87% receptor occupancy, respectively. CVC and MVC achieved high but incomplete saturation of CCR5, an effect that may be amplified by the observation of increased CCR5 expression with both agents in the absence of RANTES. In the absence of MCP-1, CVC induced CCR2 internalization and decreased cell-surface expression on monocytes. BMS-22 slightly increased CCR2 cell-surface expression. CVC prevented MCP-1-induced CCR2 internalization at lower concentrations than BMS-22. Saturation of monocyte CCR2 was reached at 6 nM of CVC, representing ~98% CCR2 occupancy. To reach >80% receptor occupancy, an average of 18 nM of BMS-22 was required, compared to 1.8 nM of CVC.

Conclusions: CVC more readily prevented RANTES-induced CCR5 internalization (at lower concentration) than MVC in vitro, indicating CVC more be more effective at preventing cellular activation by RANTES than MVC in vivo. Baseline CCR5 expression levels in treated subjects may be a determinant of CCR5 antagonist activity in vivo. CVC achieved ~98% receptor occupancy of CCR2 on monocytes at low nanomolar concentrations in vitro, and reduced CCR2 expression on monocytes in the absence of MCP-1. High saturation of CCR2 by CVC paired with reduced expression may explain the potent CCR2 blockade observed with CVC in the clinic. CVC has potent immunomodulatory activities in vitro, and may be an important combined immunotherapeutic and anti-retroviral in chronic HIV infection.

Session P-I2 Poster Session
Tuesday March 4, 2014, 2:30 PM–4:00 PM Exhibit Hall B
Preclinical Studies of Novel ART Approaches: Post-Entry

531 Identification of a Novel HIV-1 Inhibitor Targeting Vif-Dependent Degradation of Human APOBEC3G

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Background: APOBEC3G (A3G) is a cellular cytidine deaminase that restricts HIV replication by inducing G-to-A hypermutation in viral DNA and by deamination-independent mechanisms. Vif overcomes this innate antiviral activity by binding to A3G and targeting it for proteasomal degradation and by inhibiting its incorporation into virions. The interaction of Vif with A3G is essential for viral replication; as such, it represents a potential therapeutic target. Currently, there are no antivirals targeting Vif or its interaction with A3G.

Methodology: To identify compounds that inhibit interaction between A3G and HIV Vif in a high-throughput format, we developed a homogeneous time-resolved fluorescence resonance energy transfer (TR-FRET) assay. This assay detects the interaction between GST-Vif residues 1-94, which contains the A3G binding site, and a peptide consisting of A3G residues 110-148, a surrogate for the Vif binding site. A 307,520 compound library from the NIH Molecular Libraries Small Molecule Repository (MLSMR) was screened and 3686 hits were identified. To validate hits and eliminate false-positives, we employed a second TR-FRET-based assay and counter screen assays to evaluate dose response performance and off-target effects.

Results: In these primary and secondary screens, 310 hits were identified and then tested for antiviral activity against HIV-1Ba-L virus replication in human PBMC and in a cell-based screen for their ability to inhibit Vif-dependent degradation of A3G. These studies identified 3 compounds that demonstrated both antiviral activity against HIV replication in PBMC and attenuation of Vif-dependent degradation of A3G. One compound, N.41, showed antiviral activity in H9 T cells (A3G+) but not in SupT1 T cells (A3G-) and had an IC50 = 8.4 μM and TC50 >100 μM when tested against HIV-1Ba-L replication in PBMC. N.41 increased levels of A3G and its incorporation into virions in virus-producing cells, attenuated infectivity of single-round viruses in a Vif-dependent manner, and inhibited Vif-A3G interaction in co-immunoprecipitation assays. N.41 increased human but not African green monkey A3G levels in virus-producing cells in a Vif-dependent manner, and increased endogenous A3G levels in CEM T cells. Preliminary structure-activity relationship (SAR) studies suggested that a hydroxyl moiety located at the phenylamino group is critical for N.41 activity. Importantly, we identified several N.41 analogs with improved antiviral activities.

Conclusions: In this study, we identified a new lead compound that attenuates HIV replication by increasing A3G innate antiviral activity via liberating it from Vif regulation. SAR studies suggest that N.41 is a potential lead for further development as an antiviral.

532 Drugging HIV Vif as a Rational Approach To Eradication

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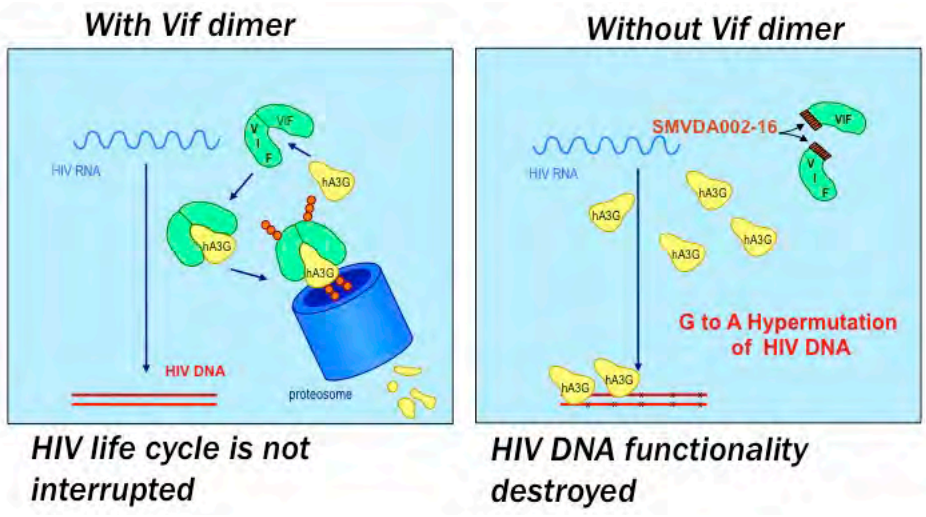
Background: The HIV auxiliary protein known as viral infectivity factor (Vif) enables HIV to overcome cellular APOBEC host-defense factors by binding to these proteins as a substrate receptor, thereby ensuring their ubiquitination and degradation through the 26S proteasome. Vif-Vif interaction through the PPLP domain has been shown to be 'druggable' in living cells using peptide mimetics. Disruption of Vif dimers inhibited live virus in spreading infection assays by protecting A3G from Vif-dependent degradation and enabled A3G incorporate in viral particles (Miller et al., (2007) Retrovirology 4:81-91).

Methodology: Live cell FRET for Vif dimerization in high throughput screening together with medicinal chemistry have identifying a small molecule Vif dimerization antagonist (SMVDA002-16) with low cytotoxicity and nM antiviral efficacy.

Results: Inhibition of HIV infection showed strict dependence on the expression of Vif and APOBEC3G. SMVDA002-16 enabled A3G antiviral activity by protecting A3G from Vif-dependent degradation, enhanced virion incorporation of A3G and inhibited viral replication. Analysis of integrated viral genomes for mutations in the pol gene in these studies following 48 hrs and 7 days of infection revealed extensive G to A hypermutation with numerous sense and nonsense codon



changes. Infection of PBMC by 17 HIV isolates covering the 9 major HIV subtypes along with 8 drug resistant HIV strains was suppressed following a single dose of SMVDA002-16.

Conclusions: Compounds that bind to Vif and inhibit Vif dimerization can be effective antivirals due to their ability to enable APOBEC3G host defense. There is a clear imperative to aggressively pursue this target for first-in-class therapeutics, prophylaxis and a potential functional cure.

533 A Novel Class of Multimerization Selective Inhibitors of HIV-1 Integrase

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Background: The quinoline-based compounds are promising leads for the development of clinically useful HIV-1 integrase (IN) inhibitors, however published studies with these quinoline-based compounds have highlighted the following deficiencies: i) the A128T mutation in IN has been shown to readily develop and confer marked resistance to this class of compounds; ii) the multifunctional nature of quinoline compounds to inhibit the IN-LEDGF/p75 binding and promote allosteric IN multimerization with similar IC50 values presents significant limitation for exploiting these inhibitors as investigational probes to study HIV-1 molecular biology.

Methodology: We exploited the available X-ray crystal structures of quinoline compounds bound to HIV-1 IN catalytic core domain (CCD) to rationally modify existing quinoline compounds. In particular, we have compromised the quinoline moiety and made a series of modifications to enhance the inhibitor potency specifically for allosteric IN multimerization without significantly affecting the IN-LEDGF/p75 binding.

Results: We have developed a new class of compounds that potently and selectively inhibits HIV-1 replication by allosterically modulating IN multimerization. In sharp contrast from quinoline compounds, our most promising multimerization selective inhibitor, PB-20 was about 60-fold more selective for IN-multimerization (IC50 of 89 nM) compared with IN-LEDGF/p75 binding (IC50 of 5,030 nM). The X-ray crystal structure of PB-20 bound to HIV-1 IN CCD elucidated structural basis for high selectivity of PB-20 for IN multimerization. PB-20 potently (EC50 of ~30 nM) inhibited HIV-1 replication when added to producer cells, whereas this compound was ~5,000-fold less effective in target cells (EC50 of ~50,900 nM). Such markedly reduced activity of PB-20 in target cells could be explained by the fact that PB-20 is not an effective inhibitor of IN-LEDGF/p75 binding during viral ingress, whereas the inhibitor could potently induce aberrant IN multimerization during the late stage HIV-1 replication. The A128T substitution, which is sufficient to effectively confer resistance to archetypal quinoline-based compounds, was not observed with PB-20. Instead triple substitution at the PB-20 binding site was identified as the main phenotype suggesting an increased genetic pressure by PB-20. These findings indicate the critical feasibility of our rational modification approaches to improve existing compounds.

Conclusions: We provide a first demonstration of an HIV-1 IN inhibitor PB-20 that potently and selectively inhibits the late stage HIV-1 replication via selectively modulating the multimeric state of IN.

534 PF74 Inhibits Multiple HIV Capsid Functions Independent of Host Cyclophilin A and CPSF6

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Background: HIV capsid (CA) is an emerging target for antiretroviral treatment. PF-3450074 (PF74) is a small-molecule CA binder that has been proposed to inhibit reverse transcription (RT) by accelerating HIV core uncoating. PF74 antiviral potency can depend on cyclophilin A (CypA) binding to CA in some cells and it shares a CA binding site with the host nuclear transport factor CPSF6, which restricts HIV infection when mislocalized to the cell cytoplasm. Here we further interrogate the mechanism of action (MOA) for PF74 in human T cells and clarify its potential dependence on CypA and CPSF6.

Methodology: HIV reporter viruses were produced in HEK293T cells and used to infect MT2 cells and primary CD4+ T cells to determine the antiviral effect of PF74. Compound exposure was controlled by staggered addition and cell washing at various times post-infection. DNA products of infection were analyzed by qPCR. CypA and CPSF6 levels were varied in MT2 cells by overexpression and shRNA knockdown. CA (P90A, N74D) and CPSF6 ($FG_{321}AA$) mutations were used to eliminate CypA or CPSF6 binding to the viral capsid. CPSF6 binding to CA was tested using a CA-NC pulldown assay.

Results: PF74 efficiently inhibited late (EC_{50} = 795 nM) and early (EC_{50} =264 nM) post-entry stages of HIV-1 replication in single-round infectivity assays and stabilized CA-NC polymers *in vitro*. Stable CypA knockdown or mutation of the CypA binding site of CA (P90A) had no effect on HIV infectivity or PF74 antiviral potency in T cells. CypA-independence of PF74 MOA was confirmed in PBMCs using HIV isolates unable to bind CypA due to CA polymorphisms. Drug washout studies showed that at high concentrations (100x EC_{50}), PF74 inactivates cell-free virus via core disassembly and also acts concomitant with the RT step in infected cells. At 10x EC_{50}, however, PF74 acted post-RT and was not virucidal, suggesting antiviral mechanism(s) beyond capsid destabilization. In time-of-addition studies, PF74 (10x EC_{50}) remained active when added after RT but before vDNA integration, and normal levels of late-RT products but reduced 2-LTR circles were observed under these conditions. In contrast, reduced late-RT products were detected at higher compound concentrations. Although PF74 did compete with CPSF6 binding to CA *in vitro*, it remained active against the N74D mutant virus that does not bind CPSF6, suggesting a CPSF6-independent MOA.

Conclusions: Although PF74 can accelerate viral capsid disassembly at high concentrations, our results indicate that this compound primarily acts after the RT step, but prior to 2-LTR circle accumulation in human T cells, via a CypA- and CPSF6-independent MOA. We propose that by directly stabilizing the viral capsid at lower drug concentrations, PF74 may interfere with nuclear targeting of the pre-integration complex.

536 Recent Progress in Developing Potent and Broadly Active HIV-1 Maturation Inhibitors

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Background: A betulinic acid-based compound, bevirimat (BVM), the first-in-class HIV-1 maturation inhibitor, acts by blocking a late step in protease-mediated Gag processing: the cleavage of the capsid-spacer peptide 1 (CA-SP1) intermediate to mature CA. BVM was shown in multiple clinical trials to be safe and effective in reducing viral loads in HIV-1-infected patients. However, single-amino-acid polymorphisms in the SP1 region of Gag resulted in variable response in BVM-treated patients, leading to the discontinuation of BVM's clinical development.

Methodology: We carried out an extensive medicinal chemistry campaign to develop BVM derivatives that demonstrate not only increased potency against consensus clade B strains of HIV-1 but also that are active against isolates with polymorphisms in SP1 and primary, non-clade B isolates. Compound activity was tested in assays that measure CA-SP1 processing by radioimmunoprecipitation, single-cycle infectivity, cell-cell transmission, and virus replication kinetics. Long-term selection experiments were performed to identify mutations that confer resistance to these novel compounds. Compound binding to Gag was tested directly by using a tritium-labeled derivative. The effects of the compounds on virion morphology were examined at high resolution by cryo-electron tomography

Results: We identified a set of BVM derivatives that are not only more potent than BVM against WT HIV-1 but also show robust antiviral activity against SP1 polymorphic strains and clade C isolates. These second-generation inhibitors are structurally similar to BVM with C28 heteroatom modifications. The best of these analogs displayed ~3-log improved potency against polymorphic HIV-1 relative to BVM. Selection experiments identified a panel of resistant mutants that contain substitutions in Gag. The resistance mutations were analyzed for their effect on viral assembly, viral fitness, CA-SP1 processing, compound binding, and particle morphology. Cryo-electron tomography analysis demonstrated that HIV-1 maturation inhibitors act not only by blocking CA-SP1 processing but also by stabilizing the immature Gag lattice.

Conclusions: This study identifies a panel of C28 BVM derivatives that display marked improvements relative to BVM in their potency and breadth of activity. Biochemical, virological, and structural analyses performed with these compounds provide novel insights into the target and mechanism of action of HIV-1 maturation inhibitors. The results of this study provide novel insights into the structure of the maturation inhibitor-binding site and the role of SP1 in virus assembly and maturation. Finally, these findings suggest that clinical development of HIV-1 maturation inhibitors should resume.

Session P-J1 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

RCTs in Second-Line ART and Virologic Failure

537 Mortality Among HIV+ Participants Randomized To Omit NRTIs vs. Add NRTIs in OPTIONS (ACTG A5241)

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Background: OPTIONS enrolled treatment experienced participants with virologic failure who then started a new regimen after randomization to omit or add NRTIs. In the primary week 48 analysis, we found that omitting NRTIs was not inferior to adding NRTIs (CROI 2013, 153LB). In this analysis, we examined all-cause mortality.

Methodology: A5241 enrolled 360 subjects who had PI, NNRTI and NRTI experience and/or viral resistance. Personalized regimens with 3-4 ARVs (excluding NRTIs) having >2 active drugs, and NRTI combinations were selected; subjects were then randomized to add or omit NRTIs with the new regimen. All subjects were followed for 96 weeks for outcomes including mortality. Since mortality events were rare, exact logistic regression models using one covariate estimated exact odds ratios (eOR).

Results: During the screening process, when all subjects continued the failing NRTI-containing regimen (median duration 51 days), the mortality rate was 4.15/100 patient-years [p-y] (3 deaths). Following study entry and initiation of study treatment, there was only 1 death (0.31/100 p-y) among those omitting NRTIs (n=177); this participant died of trauma and pneumonia. Among those adding NRTIs (n=180), there were 10 deaths (3.1/100 p-y); these occurred at <24 wks (3), 24-48 wks (2), 48-72 wks (2), 72-96 wks (3) after study entry. Causes of death (with contributing factors) included heart failure (lymphoma) (1), cardiac disease (2), E. coli sepsis (liver failure, acute renal failure, HCV+) (1), cirrhosis (intra-abdominal bleed, HCV+) (1), listeria meningitis (1), pneumonia (2), PML (1) and renal failure (IRIS, hepatitis, autoimmune enteropathy) (1). All 10 add NRTI participants had initial virologic response to treatment.

Ability to identify factors associated with death is limited due to the rarity of events, especially by arm. VACS mortality index using baseline values was a significant predictor of mortality (eOR=1.9 per 10 unit increase, 95% CI = 1.3-2.8), whereas individual components of the index were not significantly associated: age (p=.17), hemoglobin (p=0.25), creatinine clearance (p=0.11), CD4 (0.91), HIV RNA (p=0.18), Hepatitis C (p=0.12).

Conclusions: In a randomized study that omitted vs. added NRTIs to new regimens, an unexplained imbalance in mortality was observed with only one death in the omit NRTI arm. Interpretation of the mortality difference is difficult because of the small number of events (11) and the potential for unmeasured confounders. The VACS mortality index was useful in predicting mortality in this treatment experienced population.

538 Partner-Based Intervention for Adherence To Second-Line ART: A Multinational Trial (ACTG A5234)

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Background: Adherence is a fundamental determinant of antiretroviral therapy (ART) success. Some programs require patients to identify a support partner to enhance adherence. However, evidence supporting this strategy's effectiveness is lacking.

Methodology: We conducted a 1:1 randomized trial of a treatment partner-based intervention compared with usual care for second-line ART at 9 low and middle income sites. Eligible patients were failing a non-nucleoside-based first-line regimen with HIV RNA >1000 copies/mL and had a willing support partner. The second-line regimen included lopinavir/ritonavir (400/100 mg) twice daily and emtricitabine/tenofovir disoproxil fumarate (200/300 mg) once daily. The intervention included one standardized partner training session focused on adherence support strategies and the partner observing and documenting one ART dose daily > 5 days/week for 24 weeks. Experimental partners were trained to implement adherence strategies and/or telephone the site for help if they observed non-adherence. Control partners received general HIV health information at entry with no additional support. The primary outcome was virologic failure (confirmed HIV RNA >400 copies/mL) at or prior to week 48; secondary outcomes included virologic failure at 24 weeks and adherence measured using electronic monitors (MEMS) summarized as % of doses taken quarterly (Q). The proportion of participants with failure was compared between groups using Fisher's exact tests. Median adherence per quarter was compared using Wilcoxon rank sum tests.

Results: We enrolled 129 patients in the intervention and 128 in usual care, 130 (51%) males, 204 (79%) of African origin, 52 (20%) Latino, with a median age 38 years (interquartile range 33-45). Partners were parents (57, 22%), spouses (55, 21%), siblings (50, 19%), friends (41, 16%), and other (54, 21%). The proportions experiencing virologic failure at week 24 were 19% in the experimental arm vs.13% in the control arm, (p=0.31) and at week 48 were 26% in the experimental arm vs. 18% in the control arm, (p=0.13). Adherence by MEMS was similarly high [Q1: 96% vs. 96%, Q2: 91% vs. 94%, Q3: 90% vs. 93%, Q4: 91% vs. 93%] in experimental and control arms, respectively (all p>0.3).

Conclusions: We found no intervention effect on virologic responses or adherence. Potential reasons include control partners providing sufficient support without specific training, our single session being insufficient to significantly enhance skills, the study visits serving as a co-intervention that resulted in high adherence in the controls, or selection bias by enrolling highly adherent motivated volunteers. Continuing work is needed to identify interventions that can improve adherence in persons failing first line therapy.

539 Predictors of Late Virological Failure After Initial Successful Suppression On EFV-Based ART

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Background: There are practical issues, including high cost, in implementing virologic monitoring of patients on antiretroviral therapy (ART) in resource-limited settings. We evaluated factors that might guide less frequent virologic monitoring after successful virologic suppression on efavirenz (EFV)-based ART in such settings.

Methodology: HIV-1 RNA was measured every 8 weeks in antiretroviral naive participants with nadir CD4 counts <300/mm^3 who were randomized to EFV with lamivudine/zidovudine or emtricitabine/tenofovir in the international ACTG A5175/PEARLS trial, and who achieved HIV-1 RNA <1000 c/mL at 24 weeks without prior virologic failure or new AIDS event. Predictors of late virologic failure (late VF: confirmed HIV-1 RNA ≥1000 c/mL after 24 weeks) were evaluated by multivariate Cox models using stepwise selection from among the following variables: demographic; pre-ART CD4, HIV-1 RNA, AIDS, TB, hepatitis B, laboratory test results and body mass index; ART regimen; occurrence of Grade ≥3 laboratory results and signs/symptoms, ART change, self-reported adherence before week 24; and week 24 CD4 change and HIV-1 RNA (≤400 vs 401-999).

Results: 911 of 1045 subjects (87%) had HIV-1 RNA <1000 at 24 weeks. During median follow-up of >3yr after week 24, 82 of the 911 (9%) experienced late VF. VF rate appeared higher between 24 to 48 weeks (2.4%) but was reasonably constant thereafter (~1.25% every 24 weeks). In multivariate analysis, increased late VF risk was significantly associated with lower pre-ART hemoglobin (adjusted hazard ratio [AHR]=1.18 per 1g/dL lower; 95% CI: 1.04, 1.33; p=0.008), and both self-reported imperfect ART adherence (55/516 [10.7%] vs 27/413 [6.8%] for perfect adherence; AHR=1.72; CI: 1.08, 2.72; p=0.022) and absence of Grade ≥3 laboratory results prior to week 24 (77/800 [9.6%] vs 5/111 [4.5%] for those with Grade ≥3 results; AHR=2.53; CI: 1.02, 6.29; p=0.046). Sensitivity analyses restricted to subjects who did not change ART regimen, and to those without Grade ≥3 laboratories, prior to week 24 showed similar results. In time-updated analysis, self-reported imperfect adherence was a significant predictor of increased late VF risk.

Conclusions: In this clinical trial setting, the rate of late VF after successful suppression on EFV-containing ART was very low suggesting that virologic monitoring strategies involving infrequent (eg annual) measurements, possibly targeting subjects reporting imperfect adherence and those with lower pre-ART hemoglobin, might be considered; the implications of this for accumulation of resistance mutations needs evaluating. The unexpected finding that subjects without Grade ≥3 laboratory results before 24 weeks had higher risk of late VF needs evaluating further in a larger study.

540 Raltegravir Non-Inferior To Standard of Care in SECOND-LINE Therapy Over 96 Weeks

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Background: A regimen of lopinavir/ritonavir (LPV/r) and raltegravir (RAL) demonstrated non-inferior efficacy relative to a regimen of LPV/r with nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTIs) in primary analysis at 48 weeks. In this analysis we aim to assess durability of effect over 96 weeks.

Methodology: A total of 541 HIV-1 infected adults virologically failing first-line NNRTI+2N(t)RTI were randomised to receive RAL+LPV/r (RAL) or 2-3 N(t)RTI+LPV/r (N(t)RTI) in an open-label trial at 37 sites in Africa, Asia, Australia, Europe and Latin America, . Eligibility criteria included no previous exposure to protease inhibitors (PI) and integrase strand transfer inhibitors (InSTI) and no active hepatitis B infection. Genotypic antiretroviral resistance testing (GART) was permitted. Differences between the proportion of participants with HIV-1 RNA (pVL) <200 copies/mL and <50 copies/mL by intention to treat were compared using chi-square statistics with a non-inferiority margin of -12%. Differences in biochemical, haematological and metabolic changes were assessed using T-tests.

Results: Participants were 55% male; 42% Asian; 36% African; and14% Hispanic. At randomisation mean (sd) age was 38.8 (8.8) years, mean (sd) duration of 1st-line ART, 4.1 (2.8) years, mean (sd) plasma HIV-1 RNA, 4.2 (0.9) log copies/mL, and mean (sd) CD4+T-cells, 211 (157) cells/mm^3. 3.7% patients withdrew or were lost to follow-up by week 96 (5.5% N(t)RTI vs. 1.9% RAL arm) and19 patients died (11 in N(t)RTI arm vs. 8 in the RAL arm). In both arms 83% of participants remained on the randomized regimen through 96 weeks. pVL was< 200 copies/mL at 96 weeks in 80.4% in the RAL arm and 76.0% in the N(t)RTI arm (difference: 4.4 [95% confidence interval -2.6, 11.3]) and met non-inferiority criteria. Mean increases in CD4+ cell count (cell/mm^3) were similar in both arms. There were no differences in number of participants experiencing an adverse event or a serious adverse event; the RAL arm was associated with a significantly higher mean change in haemoglobin, lymphocytes, total cholesterol, HDL-cholesterol and LDL-cholesterol (Table 1).

Conclusions: At 96 weeks, an N(t)RTI-sparing second-line regimen of LPV/r+RAL continued to demonstrate similar efficacy, safety and tolerability compared to a regimen containing LPV/r+2-3N(t)RTIs. These results support the use of a combination PI and InSTI regimen as an option following failure of 1st line NNRTI+2N(t)RTIs.

Efficacy and safety outcomes summarized by randomised arm					
		RAL (N=270)	N(t)RTI (N=271)	Difference [RAL-N(t)RTI] (95%CI)	P
HIV-1 RNA proportion below threshold	<200 copies/mL	80.4 (217/270)	76.0 (206/271)	4.4 (-2.6, 11.3)	0.22
	<50 copies/mL	70.0 (189/270)	67.5 (183/271)	2.5 (-5.3, 10.3)	0.54
Mean change from baseline to week 96	CD4 (cells/mm^3)	229	202	27 (-5, 59)	0.10
	Haemoglobin (g/dL)	8.3	5.5	2.9 (-0.1, 5.7)	0.05
	Lymphocytes (10^9/L)	0.7	0.5	0.2 (0.0, 0.3)	0.0.02
	Total cholesterol (mg/dL)	36.0	14.9	21.0 (12.7, 29.3)	<0.01
	HDL cholesterol (mg/dL)	3.6	-0.2	3.8 (1.3, 6.3)	<0.01
	LDL cholesterol (mg/dL)	19.1	6.6	13.0 (6.8, 19.2)	<0.01
	Glomerular filtration rate (mL/min per 1.73 m^2)	-5.2	-5.5	0.3 (-2.5, 3.1)	0.83
Proportion experiencing Adverse Events	Serious events	14.8(40/270)	12.2 (33/271)	2.6 (-3.1, 8.4)	0.37
	Any events	85.9 (232/270)	89.7 (243/271)	-3.7 (-9.3, 1.8)	0.18

541LB Randomized Comparison of Three Second Line ART Regimens in Africa: The 2 Lady/ANRS/EDCTP Study

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Background: Access to antiretroviral therapy (ART) has increased significantly in the last decade: 9.7 million people were on ART at the end of 2012, 2.9% only on second line. WHO recommends the use of a ritonavir boosted Protease Inhibitor (PI/b) containing regimen in patients failing a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)-based first line, but evidence for the choice of combination is lacking.

Methodology: A 48 weeks, randomized, open label, non-inferiority trial in 3 African cities (Yaoundé - Cameroon, Bobo Dioulasso - Burkina Faso, Dakar - Senegal) comparing efficacy and safety of 3 second line regimens:

Arm A: tenofovir (TDF)/emtricitabine (FTC) + lopinavir/ritonavir (LPV/r), reference arm,

Arm B: abacavir (ABC) + didanosine (ddI) + LPV/r,

Arm C: TDF/FTC + darunavir/ritonavir (DRV/r).

Patients were eligible if above 18 years, failed a first line NNRTI based ART (confirmed HIV-1 RNA≥1 000 copies/mL), showed good adherence (≥80%) and signed informed consent. Efficacy was defined as a HIV-1 RNA <50 copies/mL at 48 weeks and was analysed in both intention to treat (ITT-FDA snapshot) and per protocol (PP). Sample size was calculated for a power of 80% to show non inferiority with a margin of 15% and two-sided 95% confidence intervals.

Results: From January 2010 to October 2012, 454 patients were randomized. Participants were mainly women (72%), had been on ART for a median duration of 49 months (IQR 33- 69), had a median CD4 count of 183 cell/mm3 (IQR 87 - 290) and a median plasma HIV-1 RNA (VL) of 4.5 log10 (IQR 4 - 5.1). All but 6 had resistance to at least one first line drug and 95% to 2 classes.

At week 48 (cf table), 294 (65.2%) of the 451 analysed participants had an HIV-1 RNA<50 copies/mL, while 275 (83.2%) and 410 (90.9%) had a VL below 200 and 1 000 copies/mL respectively.

Primary results in ITT showed a difference of 5.6% (IC95% -5.1; 16.4) and 6.1% (IC95% -4.5; 16.7) between the reference arm A and arms B and C respectively, excluding non-inferiority. In multivariate analysis, VL ≤ 100 000 copies/ml at baseline was independent predictor of viral suppression.

No difference among arms was observed in median CD4 gain (+127 cells/uL), mortality or severe adverse events. No Protease mutations were observed in patients failing second line.

Conclusions: Despite multiple NRTI mutations, PI/b based second line regimens showed satisfactory results. However, results for patients with high viral load at switch to second line are of special concern. The WHO recommended regimen remains a valid option.

Results for different VL thresholds and arm comparisons (with 95% CI)						
	A, n (%)	B, n (%)	C, n (%)	Total n (%)	B-A, % (95% CI)	C-A, % (95% CI)
ITT, Total	152	145	154	451		
HIV-1 RNA < 50 copies/mL	105 (69.1%)	92 (63.4%)	97 (63.0%)	294 (65.2%)	5.6% (-5.1 ; 16.4)	6.1% (-4.5 ; 16.7)
HIV-1 RNA < 200 copies/mL	130 (85.5%)	118 (81.4%)	127 (82.5%)	375 (83.2%)	4.1% (-4.3 ; 12.6)	3.1% (-5.1 ; 11.3)
HIV-1 RNA < 1000 copies/mL	142 (93.4%)	129 (89.0%)	139 (90.3%)	410 (90.9%)	4.5% (-2.0 ; 10.9)	3.2% (-3.0 ; 9.3)
PP, Total	149	135	148	432		
HIV-1 RNA < 50 copies/mL	105 (70.0%)	92 (68.2%)	97 (65.5%)	294 (68.1%)	2.3% (-8.4 ; 13.1)	4.9% (-5.7 ; 15.5)
HIV-1 RNA < 200 copies/mL	129 (86.6%)	117 (86.7%)	127 (85.8%)	373 (86.3%)	-0.1% (-8.0 ; 7.8)	0.8% (-7.1 ; 8.6)
HIV-1 RNA < 1000 copies/mL	141 (94.6%)	128 (94.8%)	139 (93.9%)	408 (94.4%)	-0.2% (-5.4 ; 5.0)	0.7% (-4.6 ; 6.0)

Session P-J2 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

RCTs in First-Line ART in Treatment Naive Patients

542 First-Line Therapy With LPV/r vs NVP and 2 NRTIs in a Developing Country: W144 of a Randomized Trial

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Background: In resource-limited countries, NNRTI-based regimen, as recommended by WHO, may result in emergence of more HIV drug resistance, because of a low genetic barrier.**The purpose of the trial is** to compare the efficacy and tolerance of LPV/r and NVP-based regimens and 2 WHO nucleoside backbones in naive HIV infected patients (p.).

Methodology: Naive p. from 5 clinics in Lubumbashi (Congo-RDC) were randomized to receive LPV/r tablets versus NVP combined with TDF/FTC or ZDV/3TC. VL and CD4 were performed at baseline (BL) and every 24 weeks (W). The primary endpoint was the % of p. with therapeutic failure defined as clinical and virologic failures (VL>1000 c/ml) (missing data=failure), assessed at W48 and 96. We present here the results of 144 W of follow-up.

Results: 425 Black African p. (72% female; median (md) age 38 years, md CD4 165/µL; md VL 5.2 log c/ml) were randomized (216 in LPV/r, 209 in NVP). BL characteristics were comparable. In the ITT analysis, previous results (abstract 88LB, CROI 2012) showed no difference between LPV/r and NVP

treatment arms at W96 except a higher proportion of virologic failure (VF) in p. on NVP-based regimens. W144 ITT analysis showed a significant difference on endpoints between LPV/r (94/216) and NVP (111/209) (p=0.0479) and persistence of a significant difference in VF rate (20/216 vs 37/209 for LPV/r and NVP, respectively) (p= 0.015). BL genotypes showed NNRTI mutations (mt) in 3/31 NVP-failing p. and no PI mt in LPV/r-failing patients. At time of failure, NNRTI mt were seen in 23/26 NVP-failing p. and 0/13 primary PI mt in LPV/r failing patients. NRTI mt were seen in 19/26 p. in NVP arm (including K65R in 7 p. and M184V in 18 p.) vs 3/13 p. in LPV/r arm (M184V in 3 p.).

Md CD4 change from BL was significant higher in LPV/r arm (251 cells/μL [interquartile range (IQR) 153;384]) compared with NVP arm (174 cells/μL [IQR 102-330]) (p= 0.0093). There was no difference in adherence > 95% between groups (73.6 vs 74.4 for LPV/r vs NVP).

The discontinuation rate for toxicity was low: 2 p. (0.9%) in LPV/r and NVP groups. Hypersensitivity reactions were more frequent in the NVP (8/209) vs LPV/r (0/216) groups (p=0.0032). Diarrhea, nausea and vomiting were predominant with LPV/r (p=<0.0001).

Md change from BL in estimated GFR was significant higher for NVP +20.5 ml/min [IQR 6.3;38.9] vs LPV/r +11.5[IQR -1;28.5] (p=0.0044) without significant difference between backbones.

Compared to BL, total cholesterol, LDL, HDL cholesterol, triglycerides and haemoglobin increased over time, but without significant difference between treatment groups.

Conclusions: In a resource-limited setting after 144 weeks of follow-up NNRTI-NRTI first-line regimen is associated with more virologic failure, more drug resistance mutations and a lower immunologic response than a PI-based regimen.

543 Dolutegravir Regimen Statistically Superior To Tenofovir/Emtricitabine/Efavirenz: 96-Wk Data

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Background: At the primary 48-Week analysis, Dolutegravir (DTG) 50 mg + abacavir (ABC)/lamivudine (3TC) once daily was superior to Tenofovir (TDF)/ Emtricitabine (FTC) /Efavirenz (EFV) in treatment-naive HIV-1 patients, with 88% vs. 81% suppressed virologically (plasma HIV <50c/mL by snapshot algorithm [P=0.003]); safety/tolerability was favorable for DTG + ABC/3TC. In order to access durability we now present 96 week final results.

Methodology: SINGLE (ING114467) is an ongoing Phase III, randomized, multi-center, double-blind, double-dummy study comparing the efficacy and safety of DTG plus ABC/3TC fixed dose combination (FDC) to TDF/FTC/EFV (ATR) in treatment-naïve HIV patients. Randomization was stratified by baseline plasma HIV-1 RNA (≤ vs >100,000 c/mL) and CD4 cell count (≤ vs > 200 cells/mm3).

Results: 833 subjects were enrolled and treated (84% males; 32% non-white); treatment groups were similar at baseline. Through Week 96, 80% of DTG+ABC/3TC subjects and 72% of ATR subjects achieved <50 c/mL plasma HIV-1 RNA based on the FDA snapshot algorithm (difference 8.0%, 95% CI: +2.3%, +13.8% based on Cochran-Mantel-Haenszel analysis adjusted for strata), achieving pre-specified statistical superiority (P= 0.006). Differences in efficacy were primarily driven by a higher rate of discontinuation due to adverse events (AEs) in ATR recipients (11%), vs. 3% with DTG + ABC/3TC; most occurred prior to Week 48 (10% vs. 2%). Differences in time to viral suppression (28 vs 84 days; p< 0.0001, generalized Wilcoxon test) and the change from baseline in CD4+ cells over 96 weeks (325 vs. 281 cells/mm3, p = 0.004, adjusted repeated measure model) both favored the DTG + ABC/3TC arm. DTG+ABC/3TC was better tolerated than ATR, with nervous system (23 vs. 50%, p< 0.001) and psychiatric disorders AEs (32 vs. 40%, p=0.021) being more frequent with ATR, while insomnia was more frequent with DTG+ABC/3TC (17 vs. 11%, p=0.021, Fisher's exact test). Few subjects experienced protocol defined virologic failure between Week 48 and 96 (occurrence increased from 4 to 6% of subjects in both arms). No treatment emergent primary integrase inhibitor (INI) or nucleoside reverse transcriptase inhibitor (NRTI) resistance mutations were observed through 96 weeks for subjects receiving DTG+ABC/3TC, while EFV and NRTI primary resistance mutations were observed in six and one patient respectively in the ATR group.

Conclusions: The DTG+ ABC/3TC regimen resulted in potent and durable suppression of viral replication over 96 weeks, which was statistically superior to an ATR regimen. DTG+ ABC/3TC maintained a favorable AE profile, with no treatment emergent primary INI or NRTI resistance mutations and a low rate of discontinuation due to virologic failure through 96 weeks.

544LB A Randomized, Placebo-Controlled, Double-Blind Study of VM-1500 in HIV-Naïve Patients

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Background: VM-1500 is the pro-drug of the active compound VM-1500A, a potent, highly selective NNRTI. Its antiviral profile is superior to that of efavirenz and other currently marketed NNRTIs. The PK profile suggests once daily dosing. Together with minimal side effects, VM-1500 may be a good NNRTI to be started in HIV treatment.

Methodology: A randomized, placebo-controlled, multiple dose, double-blind study for 7 days in patients with HIV infection who are antiretroviral therapy-naïve with HIV-1 RNA > 5,000 copies/ml and CD4 > 250 cells/mm3. Eight patients were randomized to VM-1500 (20 mg) or placebo (7:1). After positive DSMB review the dose was escalated from 20 mg to 40 mg. A second cohort of 8 patients was randomized to VM-1500 (40 mg) or placebo (7:1).

Results: Seven patients who received 20 mg of VM-1500 for 7 days the average HIV-1 RNA decreased from 82,944 copies/ml to 2,133 copies/ml while one patient who received placebo, HIV-1 RNA was 303,000 copies/ml at day 1 and 248,000 copies/ml at days 8. The average CD4 increased from 551 cells/mm3 to 592 cells/mm3 in VM-1500 group and the CD4 of one patient in placebo arm was 492 cells/mm3 at day 1 and 517 cells/mm3 at day 8. For the second cohort with VM-1500 40 mg, 7 patients who received 40 mg of VM-1500 for 7 days the average HIV-1 RNA decreased from 93,671 copies/ml to 1,316 copies/ml while one patient who received placebo, HIV-1 RNA was 126,000 copies/ml at day 1 and 116,206 copies/ml at days 8. The average CD4 increased from 471 cells/mm3 to 525 cells/mm3 in VM-1500 group and the CD4 of one patient in placebo arm was 424 cells/mm3 at day 1 and 388 cells/mm3 at day 8. For the side effects, 3 patients in the first cohort (20mg) had mild dry mouth and polyuria, 1 patient had mild headache. However, patients in the second cohort (40mg) had no side effects for the whole seven days of VM-1500 treatment.

Conclusions: VM-1500 showed excellent activity with a 1.8 log reduction in HIV-1 RNA after 7 days of treatment with only minimal side effects. VM-1500 is a good once daily candidate NNRTI to treat HIV-infected patients.

Patients' characteristics, CD4, and HIV-1 RNA									
Group and Patient's number	HIV-1 RNA Day-1 copies/ml	HIV-1 RNA Day-8 copies/ml	CD4 Day 1 cell/mm3	CD4 Day 8 cell/mm3	Group and Patient's number	HIV-1 RNA Day-1 copies/ml	HIV-1 RNA Day-8 copies/ml	CD4 Day 1 cell/mm3	CD4 Day 8 cell/mm3
Group I VM-1500 20 mg	83,800	681	448	416	Group I VM-1500 40 mg	8,664	226	678	694
Group II VM-1500 20 mg	46,200	1,940	632	642	Group II VM-1500 40 mg	21,557	611	606	522
Group III VM-1500 20 mg	198,000	7,590	576	577	Group III VM-1500 40 mg	47,336	757	324	386
Group IV VM-1500 20 mg	17,200	281	908	1,103	Group IV VM-1500 40 mg	314,191	4,686	226	297
Group V VM-1500 20 mg	40,600	755	377	456	Group V VM-1500 40 mg	7,640	129	440	513
Group VI VM-1500 20 mg	188,000	3,390	491	528	Group VI VM-1500 40 mg	154,276	2,169	543	594
Group VII VM-1500 20 mg	6,810	294	424	424	Group VII VM-1500 40 mg	102,000	634	480	671
Group VIII VM-1500 20 mg	303,000	248,000	492	517	Group VIII VM-1500 40 mg	126,000	116,206	424	388

545 The Oral Exam: A Simple Tool To Identify HIV-Infected Patients in Need of Antiretroviral Therapy

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Background: Oral mucosal lesions that are associated with HIV infection can play an important role in monitoring the progression of disease, and can guide the decision to initiate antiretroviral therapy (ART). The discrepancies in the incidence of oral lesions, including AIDS-defining oral lesions, as a function of the timing of ART initiation has not been well characterized in the developing world. This information would be invaluable in better understanding how a simple clinical tool, the oral exam, can be used to predict the need for ART in resource-poor settings in which frequent CD4 T cell counts are not easily obtained.

Methodology: A randomized controlled clinical trial was conducted at the GHESKIO Center in Port-au-Prince, Haiti between 2004 and 2009. 816 HIV-infected ART-naïve participants with CD4 T cell counts between 200 and 350 cells/mm3 were randomized to either immediate ART initiation (early arm; N=408) or ART initiation when CD4 T cell count was less than or equal to 200 cells/mm3 (delayed arm; N=408). Every 3 months, all participants

underwent a comprehensive physical exam including an oral exam. All oral lesions were documented using Oral HIV/AIDS Research Alliance (OHARA) case definitions of oral disease endpoints.

Results: The frequency of oral disease endpoints in the delayed ART initiation arm was 2.98 times greater (N=164/408) than in the early arm (N=55/408). There was a significantly higher incidence of oral candidiasis, angular chelitis, oral hairy leukoplakia and herpes labialis in the delayed arm. Recurrent intra-oral herpes simplex was twice as frequent in the delayed arm (N=8), and the average number of recurrences per patient was 2.5, as compared to 2 in the early arm. Of note, 8 patients in the delayed arm presented with AIDS defining oral conditions. Oral warts occurred 15 times in the delayed arm, but of these 66.7% occurred after ART initiation and the median time on ART was 177 days (range 110 to 738 days).

Conclusions: In our cohort, 40% of patients that delayed ART initiation developed an oral disease endpoint; this included 8 patients who presented with an AIDS-defining oral condition. In developing world settings, a routine oral exam is a simple and useful tool for identifying patients in need of initiating ART.

546 Efficacy of First-Line ARV Regimens: An Exploratory "Target Not Detected" Analysis

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Background: Antiretroviral regimens aim to achieve undetectable HIV-1 RNA <50 copies/mL (c/mL). Below 50 c/mL, the Amplicor HIV-1 RNA v1.5 assay provides qualitative results, either "< 50 c/mL (ie, HIV-1 RNA detected but not quantified), or "<50 c/mL, No HIV-1 RNA Detected", referred to as "target not detected" (TND). Efficacy and TND of three first-line INSTI, NNRTI, and PI-based regimens in two phase 3 randomized, double-blinded clinical trials in HIV-1-infected, treatment-naïve adults were explored.

Methodology: Study 102: Elvitegravir/cobicistat/emtricitabine/tenofovir DF (EVG/COBI/FTC/TDF) vs. efavirenz/FTC/TDF (EFV/FTC/TDF); Study 103: EVG/COBI/FTC/TDF vs. ritonavir-boosted atazanavir with FTC/TDF (ATV+RTV+TVD). Plasma HIV-1 RNA levels were assessed at all study visits through Week (W) 144 using the Roche COBAS Amplicor HIV-1 Monitor Test v1.5. All subjects in the ITT population from both studies were evaluated (n=1,408). Achievement of TND by treatment group and baseline characteristics was evaluated. P-values by two-sided Fisher's Exact Test < 0.05 were statistically significant.

Results: Statistically more EVG/COBI/FTC/TDF subjects achieved TND than EFV/FTC/TDF from W2-W16 and from W2-W24 for ATV+RTV+TVD. However, after these time periods, TND levels were similar between treatment groups through W144 (Table 1). TND at W144 for all treatment groups was more frequent in subjects with baseline HIV-1 RNA ≤100,000 copies/ml and having adherence ≥95%. Consistent and reproducible TND results were achieved and maintained at all visits from W48-W144 in approximately 15% of patients regardless of treatment group.

Conclusions: Subjects treated with EVG/COBI/FTC/TDF achieved HIV-1 RNA TND more rapidly than those treated with EFV/FTC/TDF or ATV+RTV+TVD. By W48 and through W144, TND was similar for all treatment groups. The clinical significance of achieving TND is uncertain. TND was associated with early initiation of treatment as suggested by lower HIV-1 RNA, consistent with recent treatment initiation guideline recommendations.

Table 1. HIV-1 RNA at Week 144, % (n)

<50 copies/mL at Week 144 by Treatment Group (Missing=Failure Analysis)				
Study 102	EVG/COBI/FTC/TDF 82.2% (286/348) EFV/FTC/TDF 78.1% (275/352)			p=0.1858
Study 103	EVG/COBI/FTC/TDF 81.0% (286/353) ATV+RTV+TVD 78.9% (280/355)			p=0.5116
<50 TND at Week 144 by Treatment Group (TND Exploratory Analysis)				
Study 102	EVG/COBI/FTC/TDF 63.2% (220/348) EFV/FTC/TDF 61.9% (218/352)			p=0.7549
Study 103	EVG/COBI/FTC/TDF 63.2% (223/353) ATV+RTV+TVD 59.7% (212/355)			p=0.3550
<50 TND at Week 144 by Baseline Characteristic (All Treatment Groups Combined)				
	Study 102		Study 103	
HIV-1 RNA ≤100,000 c/mL HIV-1 RNA >100,000 c/mL	65.9% (307/466) 56.0% (131/234)	p=0.0129	68.1% (284/417) 51.9% (151/291)	p<0.0001
Adherence ≥95% Adherence <95%	69.4% (359/517) 44.4% (79/178)	p<0.0001	66.2% (329/497) 50.7% (106/209)	p=0.0001

547 Randomized Comparison of Anthropometric Outcomes On EFV-Based Antiretroviral Therapies

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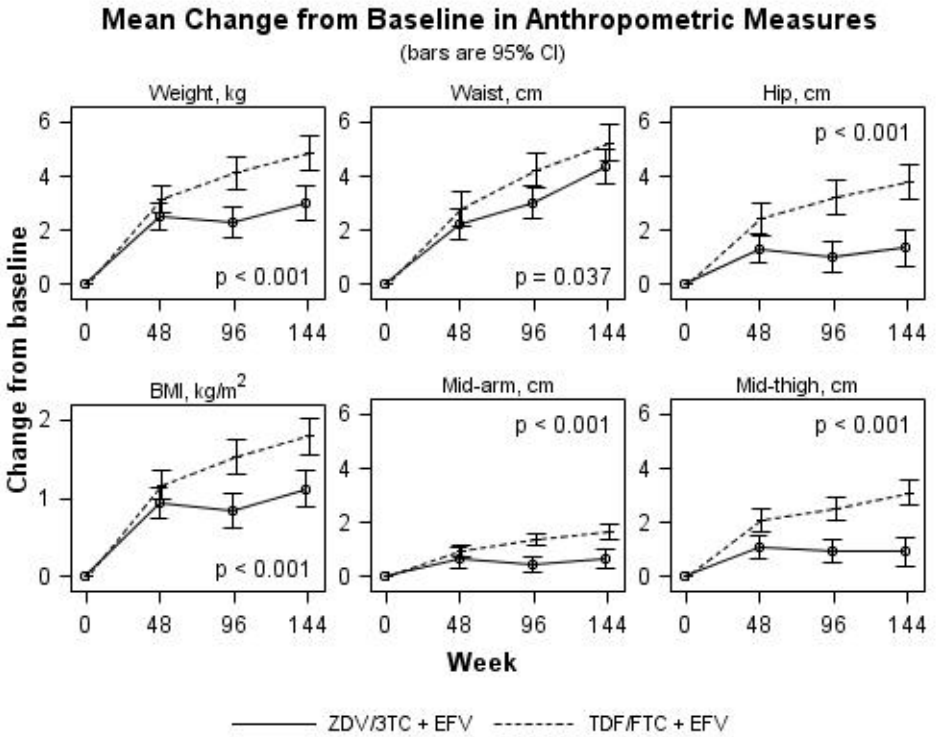
Background: ACTG A5175/PEARLS was a randomized trial undertaken in diverse geographic settings that showed similar outcomes for the primary endpoint of time to virologic failure, new AIDS event or death in the comparison of tenofovir/emtricitabine or zidovudine/lamivudine with efavirenz (TDF/FTC+EFV or ZDV/3TC+EFV). We present results for a secondary objective comparing the effects of these regimens on anthropometric outcomes.

Methodology: Antiretroviral naïve subjects with nadir CD4 counts <300/mm^3 were enrolled in Brazil, Haiti, India, Malawi, Peru, South Africa, Thailand, United States and Zimbabwe, and randomized to TDF/FTC+EFV (n=526) or ZDV/3TC+EFV (n=519). We compared changes in weight, body mass index (BMI), and mid-arm, waist, hip and mid-thigh circumferences, from baseline to 48, 96 and 144 weeks using repeated measures intent to treat analysis

Results: 46% of subjects were female; median age, CD4 count and HIV-1 RNA were 34y, 159/mm^3 and 5.0 $\log_{10}$ c/mL. Mean (sd) baseline anthropometric measures were: weight kg: 63 (14); BMI kg/m^2: 23 (4); circumferences, cm: mid-arm 28 (4), waist 80 (10), hip 92 (10), mid-thigh 48 (7). 9% had BMI<18.5 (underweight); 26% had BMI≥25 (overweight). At weeks 48, 96 and 144: n=973, 941 and 902 had measurements; 35 subjects died and 106 were lost to follow-up before week 144. In both arms, there were significant increases in all anthropometric measures at each of weeks 48, 96 and 144 (figure). The increases from baseline were, however, significantly larger for TDF/FTC+EFV vs ZDV/3TC+EFV (repeated measures p<0.001 except p=0.037 for waist) with mean change at week 144: weight kg: 4.8 vs 3.0; BMI kg/m^2: 1.8 vs 1.1; circumferences, cm: mid-arm 1.7 vs 0.7, waist 5.2 vs 4.3, hip 3.8 vs 1.4, mid-thigh 3.1 vs 0.9. Difference in mean BMI change between arms did not vary significantly by baseline BMI: at week 144, -0.3 vs -0.8 kg/m^2 for baseline BMI <18.5, 1.0 vs 0.7 for BMI 18.5-<25; 3.1 vs 2.1 for BMI≥25. There were 7 clinical diagnoses of lipoatrophy in the ZDV/3TC+EFV arm but none in the TDF/FTC+EFV arm.



Conclusions: Although the primary efficacy outcome was similar for TDF/FTC+EFV and ZDV/3TC+EFV, increases in weight, BMI and body circumferences were larger for TDF/FTC+EFV. While these findings and the lower rate of clinical lipoatrophy for TDF/FTC+EFV support current guideline recommendations for TDF/FTC+EFV as initial therapy, the greater BMI increases and hence potential for increased cardiovascular risk among overweight subjects needs consideration.

548 NEGR1 Genetic Variants and Risk for Virological Failure With Genotypic Resistance in Botswana

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Background: Access to antiretroviral therapy (ART) in sub-Saharan Africa has expanded due to a large number of national initiatives. Published findings from the Tshepo study previously demonstrated that NNRTI-assigned ART had no effect on the development of virological failure with genotypic resistance (VF/r) when evaluating persons randomized to receive nevirapine versus efavirenz-based ART. Here, we explore for the first time the impact of host genetic factors on the development of VF/r among ART-treated adults in Botswana.

Methodology: The Tshepo study is a 3-year randomized clinical study following 650 ART-naïve adults (69.4% female) from Botswana who initiated first-line NNRTI-based ART. 48 out of 650 (7.4%) enrolled study participants developed VF/r. We conducted a large-scale gene-centric association study on participants with sufficient DNA using the Illumina Human CardioMetabolo chips enriched in markers for metabolic and cardiovascular genes (198K), including mitochondrial, ADME, renal, and immune response genes. After quality control, 133,822 SNPs were tested for association with VF/r in 46 cases

vs. 522 participants who did not develop VF/r. Logistic regressions in an additive model were performed and adjusted for gender, age, CD4, HIV-RNA, and BMI at baseline, as well as for the first two eigenvectors from the population stratification analysis.

Results: One chr1 SNP reached the Bonferroni study-wide significance level (OR=8.6, P=2.4x10-7), and 10 additional SNPs from the same locus met the suggestive significance threshold (P<10-5). These markers are all located in the introns of NEGR1, a gene previously associated with obesity, BMI, hemostatic factors, SLE, asthma and Wilm's tumor. We tested for a potential role of BMI in VF/r: mean BMI was similar among patients with VF/r (21.9) and patients without (22.2); and little change in ORs or P values was seen in models with and without BMI as a covariate.

Conclusions: This study provides compelling evidence that variation in NEGR1 is associated with the development of VF/r among ART-treated adults in Botswana, independently from BMI. This is the first report to identify a non-HLA gene associated with VF/r. The role of NEGR1 in development of HIV drug resistance warrants replication and functional exploration.

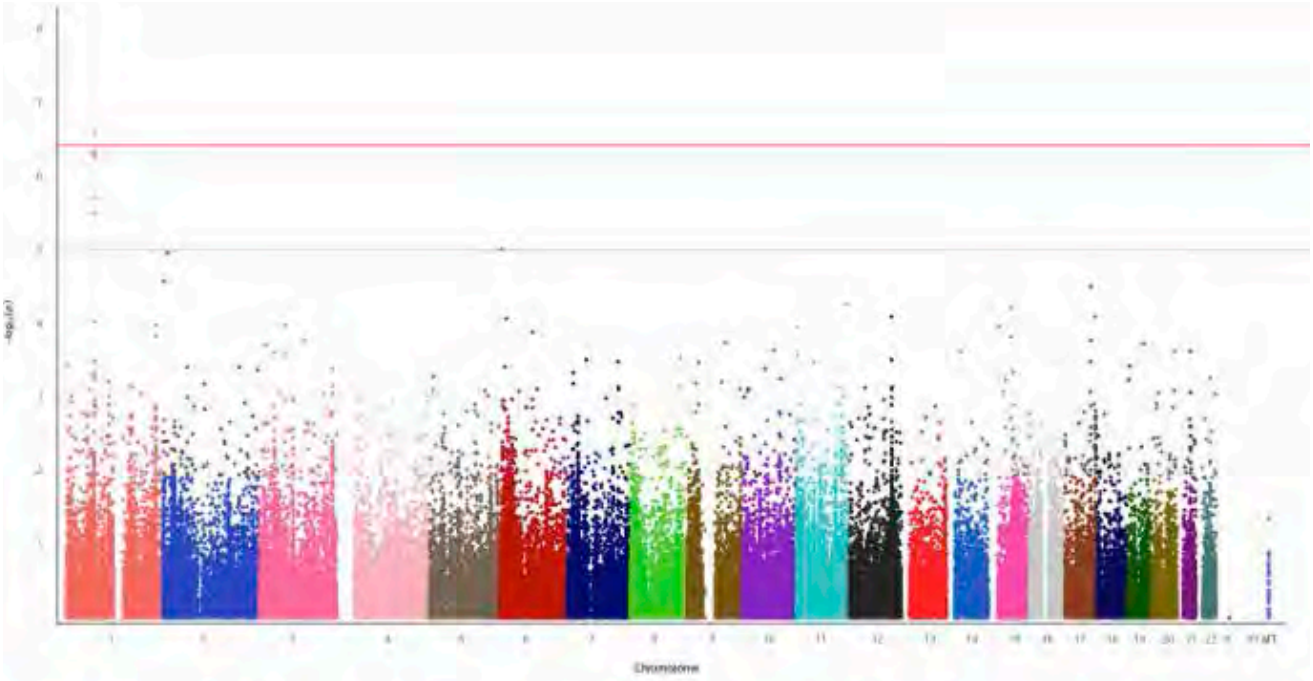

Figure 1: Manhattan plot. Distribution along the chromosomes of $-\log_{10}$(P-values) obtained for the virological failure association study. The red line marks the Bonferroni study-wide significance threshold ($P=3.7\times10^{-7}$), and the blue line marks the suggestive significance threshold ($P=10^{-5}$).

Session P-J3 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

ART Simplification, Intensification, and Switch Studies

549LB Paradoxical Impact of Maraviroc/Raltegravir Added To HAART in Acute HIV Infection: ANRS 147 Trial

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Background: Early HAART in acute HIV infection (PHI) is recommended at this period of generalized activation, the addition of maraviroc to boost CD4 increase and raltegravir for his potent antiviral effect should reduce HIV reservoirs and immune damage. The randomized multicenter OPTIPRIM-ANRS-147 trial was designed to evaluate the impact of an early 24-month treatment on total PBMC-associated HIV-DNA levels of raltegravir, maraviroc, darunavir/r and Truvada® (emtricitabine/tenofovir) (arm 1) compared to darunavir/r and Truvada® (arm 2).

Methodology: Inclusion criteria were: HIV-1 western-blot (WB) ≤4 antibodies and positive HIV-RNA, and CD4<500/mm3 in case of asymptomatic PHI. The primary endpoint was the between-arm difference in HIV-DNA level changes at M24. Clinical evaluation, HAART tolerance, CD4 count and activation, plasma HIV-RNA (VL) and HIV-DNA were analysed. At M24 HAART interruption was recommended if VL<50 cp/mL and CD4 ≥500/mm3 or ≥30%. Treatment resumption was further recommended if VL≥50 000 cp/mL or CD4<500/mm3 and <30%.

Results: 90 patients were randomized 1/1 during 2010-2011, median age 35.5 years, 92% male; 96% had PHI symptoms (median time from symptoms onset 20 days [IQR:13-28]); 43% had HIV1 WB ≤1 Ab. At enrolment, median CD4, HIV-RNA, HIV-DNA values were 472 cells /mm3 [IQR: 368-640], 5.4 log10 cp/ml [4.9-5.8] and 3.7 log10 cp/106PBMC [3.4-4.0], respectively. Two treatment-related serious adverse effects occurred in arm 2 (pancreatitis,

lipodystrophy). At M24, a high impact of HAART on reservoir in arm 2 was observed, with an HIV-DNA change from baseline of -1.44 [-1.77; 1.03] log. However, the addition of raltegravir and maraviroc in arm 1 did not induce a higher decrease: -1.43 [-1.61; 1.23] (p=0.80); CD4 increase was similar in both arms. A paradoxical kinetic of VL was observed, with a higher decrease in arm 1 until M3 than arm 2 (60%<50cp/ml vs 31%, p=0.01) and conversely a significantly worse viral control in arm 1 vs arm 2 from M6 to M18: 71% vs 89%, 78% vs 96%, 82% vs 96% at M6, M12, M18, respectively. At M24, % of VL<50 cp/ml was similar in both arms, 91% vs 93%. We observed a trend towards lower decrease until M3 in CD4 activation (CD4/CD38+HLADR+): -1.7% arm 1 vs -2.9% vs arm 2 (p=0.09). The same difference was observed in patients with VL<50 cp/mL at M6. Lastly, 2 patients (1/arm) maintained VL<400 cp/ml1 year after treatment interruption, defining them as Post Treatment Controllers (PTC).

Conclusions: We report a strong impact of HAART on HIV-reservoirs in acute PHI patients, with 2 cases of PTC, but no additional benefit of this pentatherapy compared to guideline-recommended 3-drug therapy. Our hypothesis is that the versatile effects of maraviroc on immune cellular trafficking led to low level of viral replication thus limiting HIV reservoir decrease.

550LB Randomised Controlled Trial of a PI Monotherapy Switch Strategy for Long-Term HIV Management

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Background: Previous randomised trials show patients switching to PI monotherapy maintain high rates of viral load (VL) suppression over 48-96 weeks, sometimes meeting VL non-inferiority criteria. However, longer-term resistance and toxicity risks are uncertain and the place of PI monotherapy in long-term management therefore remains controversial.

Methodology: The Protease Inhibitor Versus Ongoing Triple-therapy (PIVOT) trial was a pragmatic 5-year prospective, randomised, controlled, open-label strategy trial in HIV-positive adults taking a stable NNRTI or PI-based regimen who had no previous VL failure and had VL<50 c/ml for ≥6months at trial entry. Patients were randomised to maintain ongoing triple therapy (OT) or switch to a PI monotherapy strategy (*PIm*) using a (physician selected)ritonavir-boosted PI with prompt reintroduction of NRTIs if unable to maintain VL suppression <50 c/ml. VL was measured every 12 weeks, with resistance testing for all confirmed VL rebound ≥50 c/ml. Primary outcome was *loss of future drug options*, defined as new intermediate/high level resistance to ≥1 drug to which the patient's virus was considered to be sensitive at trial entry. Secondary outcomes included serious disease complications (AIDS, serious non-AIDS, all-cause death), total grade 3/4 adverse events and neurocognitive function change (annual 5-test battery). All analyses were by ITT; non-inferiority margin 10%.

Results: We randomised 587 patients (77% male, 68% white, 53% on NNRTI regimen at baseline) at 43 UK sites. Median (maximum) follow-up was 44 (59) months; 2.7% withdrew or were lost-to follow up. In PIm, 80% selected DRV/r, 14% LPV/r, 7% other PI/r. VL rebound was much more common in PIm; all rebounds on monotherapy re-suppressed either spontaneously or with NRTI reintroduction. Sequences were obtained for 83% of confirmed VL rebounds, but few new resistance mutations were seen in either arm. PIm was non-inferior on the primary outcome of loss of future drug options and there were no significant differences in serious disease complications, adverse events or neurocognitive function between the arms. 58% in PIm remained on monotherapy at the end of trial and overall drug costs were substantially lower in this arm.

Conclusions: PI monotherapy, with prompt reintroduction of NRTIs for VL rebound, was a successful long-term management strategy, preserved future treatment options, was safe and well tolerated, and may be considered for more widespread use in long-term HIV care.

Table 1: Number of patients with event, mean change in CD4 count or neurocognitive function, and mean costs - all during period from baseline to end of follow up.

	OT (n=291)	PIm (n=296)	Difference PIm–OT (95% CI)	p-value
VL rebound ≥ 50 copies/ml, confirmed - n (%) [1]	8 (3.2%)	95(35.0%)	31.8% (24.6 to 39.0%)	<0.001
Loss of future drug options [by 36 months] - n (%) [2]	2 (0.7%)	6 (2.1%)	1.4% (-0.4 to 3.4%)	0.15
Loss of future drug options [by end of trial] - n (%) [2]	4 (1.8%)	6 (2.1%)	0.2% (-2.5 to 2.6%)	0.85
By drug class - n				
NRTI	3	1	-	-
NNRTI	3	2	-	-
PI	1	3	-	-
CD4 change, cells/mm^3 mean (SE) [3]	+91 (9)	+108 (9)	+17 (-10 to +43)	0.21
Serious disease complication n (%)	8 (2.8%)	15 (5.1%)	2.3% (-0.8% to 5.4%)	0.15
Grade 3/4 adverse event n (%)	62 (21.3%)	72 (24.3%)	3.0% (-3.8 to 9.8%)	0.38
Neurocognitive function [NPZ-5] change -mean (SE) [3]	+0.51 (0.04)	+0.50 (0.04)	-0.01 (-0.11 to +0.09)	0.86
Cost of ART drugs, £ mean (SE) [4]	30,230 (860)	21,260 (700)	-8970 (-6,790 to -11,160)	–

Notes: [1] Kaplan-Meier estimates; [2] Kaplan-Meier estimates with bootstrap confidence interval for difference; [3] change to last measurement adjusted for baseline value; [4] standard UK formulary price, individual drugs

551LB Simplification of PI+RTV+FTC/TDF To E/C/F/TDF Maintains HIV Suppression and Is Well Tolerated

Jose Arribas[1], Gilles Pialoux[2], Joseph Gathe[3], Giovanni Di Perri[4], Jacques Reynes[5], Pablo Tebas[6], Thai Nguyen[7], Ramin Ebrahimi[7], Kirsten White[7], David Piontkowsky[7]

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Background: Antiretroviral (ARV) regimen simplification can improve treatment adherence and quality of life. We report the Week (W) 48 results of a prospective, randomized, open-label, ongoing Phase 3b trial of a regimen simplification to the single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF (E/C/F/TDF) from ritonavir-boosted protease inhibitor (PI+RTV) plus emtricitabine/tenofovir DF (FTC/TDF) regimens.

Methodology: Virologically suppressed subjects on PI+RTV + FTC/TDF regimens for ≥ 6 months were randomized (2:1) to switch to E/C/F/TDF or remain on their baseline PI regimen (i.e. PI). Eligibility criteria included CrCl ≥ 70 mL/min, no documented resistance to FTC and TDF, exposure to no more than 2 prior ARV regimens, and no history of virologic failure. The primary endpoint was the proportion of subjects who maintained HIV-1 RNA < 50 c/mL at W48 by FDA snapshot algorithm (12% noninferiority margin). If noninferiority was established, then superiority would be tested per a prespecified sequential testing procedure.

Results: A total of 433 subjects (86% male, 19% non-white, 18% age ≥ 50 years) were randomized and treated (293 E/C/F/TDF; 140 PI). At randomization, RTV-boosted atazanavir (40%) and RTV-boosted darunavir (40%) were the most common PIs used; median years since first ARV use was 3; 19% were on their second ARV regimen. Baseline characteristics were similar between the two groups. At W48, 94% of subjects on E/C/F/TDF maintained HIV-RNA < 50 c/mL compared to 87% on PI (difference 6.7%, 95% CI +0.4% to +13.7%; p=0.025). Rates of virologic failure were low (0.7% E/C/F/TDF vs 1.4% PI) with no emergent resistance in either group. The safety and tolerability profiles of E/C/F/TDF were consistent with those reported in previous studies. Grade 2-4 drug-related adverse events (AEs) were 3.8% E/C/F/TDF vs 1.4% PI. AEs leading to drug discontinuation were low, 2.0% vs 2.9% respectively. At W48, median changes in CrCl (mL/min) were -7.5 and 0.4, respectively, with no cases of proximal renal tubulopathy in either group. There was a larger decrease from baseline in fasting triglycerides for E/C/F/TDF compared to PI (median: -16 vs +3 mg/dL; p =0.001) and no change in other lipid parameters.

Conclusions: Switching to E/C/F/TDF compared to continuing PI+RTV+FTC/TDF resulted in significantly higher rates of virologic suppression without emergence of resistance. E/C/F/TDF was well-tolerated with a favorable safety profile. Switching to E/C/F/TDF from a multiple-tablet, PI-based regimen may be an option for patients wishing to simplify their ARV therapy.

552LB Effect of Selenium Supplementation On CD4 Depletion in Rwandan HIV Patients: A Randomized Trial

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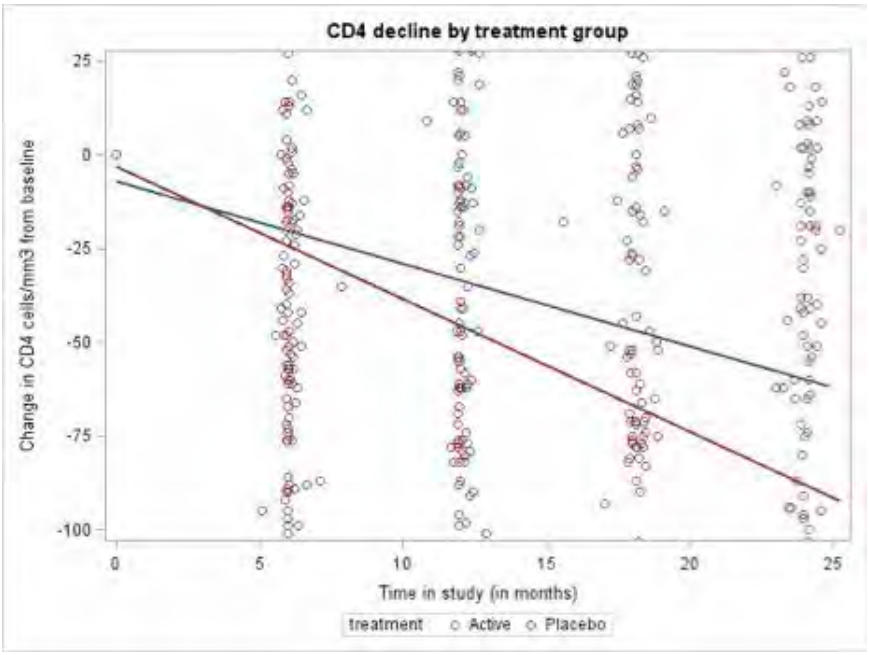
Background: Micronutrient deficiencies occur early in human immunodeficiency virus (HIV) infection and are associated with accelerated disease progression. We aimed to determine if long-term selenium supplementation is effective and safe in delaying CD4 T-cell decline and disease progression when implemented early in adults infected with HIV who are antiretroviral therapy (ART) naïve in Rwanda.

Methodology: We randomized patients in a multi-centre, patient and provider-blinded, randomized, placebo-controlled clinical trial involving ART naive HIV-infected patients. We recruited patients ≥ 21 years of age with documented HIV infection and CD4 cell count of 400-650 cells/mm3, and not yet on ART. Patients received selenium 200 mcg per day or matching placebo. The primary outcome is change in CD4 T-cell status between groups. Secondary outcomes include a composite of CD4 depletion to 350 cells/, or start of ART, or the emergence of a documented CDC-defined AIDS-defining illness; viral suppression; mortality; and



adverse events. We applied an intent-to-treat analysis. Linear regressions with generalized estimating equations and effect modification was used for the primary outcome.

Results: 151 patients received selenium and 149 placebo arm, with an average baseline CD4 of 555 cells/mm3. Seventeen patients were lost to follow-up. One non-AIDS death occurred in each group. Twenty-three women were time censored due to pregnancy and placed on ART. The rate of CD4 depletion was reduced by 43.8% among patients receiving selenium (95% confidence interval [CI]: 7.8-79.8% reduced). Figure 1 displays the CD4 change over 24 months. Average declines in CD4 over the trial period were 54 cells among the selenium arm and 95 cells among the placebo arm. In total, 96 events for the composite outcome were observed, with 45 (47%) in the treatment arm. We found no treatment effect for the composite outcome (hazard ratio 1.00, 95% confidence intervals [CIs] 0.66 - 1.54) or viral suppression (odds ratio, 1.18, 95% CI 0.71 - 1.94). We found no significant differences between groups for adverse events.

Conclusions: In ART-naive HIV-infected adults, 24-month selenium supplementation was safe and significantly decreased the rate of measured immune decline. Selenium supplementation may be an inexpensive and effective intervention when started in the early stages of HIV disease.

553LB Switch From NNRTI plus FTC/TDF To E/C/F/TDF Maintains HIV Suppression and Is Well Tolerated

Anton Pozniak[1], Martin Markowitz[2], Anthony Mills[3], Hans-Juergen Stellbrink[4], Antonio Antela[5], Pere Domingo[6], Pierre-Marie Girard[7], Keith Henry[8], Will Garner[9], Bill Guyer[9]

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Background: Concerns with current and/or long-term side effects or dosing complexity of antiretroviral (ARV) regimen may prompt patients to request ARV switches. We report the Week (W) 48 results of a prospective, randomized, open-label, ongoing Phase 3b trial of a regimen switch to the single-tablet regimen (STR) elvitegravir/cobicistat/emtricitabine/tenofovir DF (E/C/F/TDF) from non-nucleoside reverse transcriptase inhibitor (NNRTI) + emtricitabine/tenofovir DF (FTC/TDF) regimens in virologically-suppressed HIV-1 subjects.

Methodology: Subjects suppressed on NNRTI + FTC/TDF regimens for ≥ 6 months were randomized (2:1) to switch to E/C/F/TDF or remain on their baseline NNRTI regimen (i.e. NNRTI). Eligibility criteria included CrCl ≥ 70 mL/min, no documented resistance to FTC and TDF, exposure to no more than 2 prior ARV regimens, and no history of virologic failure. The primary endpoint was the proportion of subjects who maintained HIV-1 RNA < 50 c/mL at W48 by FDA snapshot algorithm (12% noninferiority margin).

Results: A total of 434 subjects (93% male, 22% non-white, 22% age ≥ 50 years) were randomized and treated (291 E/C/F/TDF; 143 NNRTI). At randomization, 78% of subjects were on an efavirenz (EFV)-based regimen (74% on STR EFV/FTC/TDF); median years since first ARV use was 3; and 31% enrolled in the study due to concern with current or long-term side effects of their ARVs. Baseline characteristics were similar between the two groups. E/C/F/TDF was noninferior to NNRTI regimens, as 93% and 88% respectively maintained HIV-1 RNA < 50 c/mL at W48 (difference 5.3%, 95% CI -0.5%, +12.0%). Virologic failure rates were 1% with no emergent resistance detected in either group. The safety and tolerability profiles of E/C/F/TDF were consistent with reports from previous studies. Grade 2-4 drug-related adverse events (AEs) occurred in 5.5% E/C/F/TDF and 1.4% NNRTI. AEs leading to discontinuation were low (2.1% E/C/F/TDF vs 0.7% NNRTI). Median changes in CrCl (mL/min) at W48 were, as expected, -11.6 and -0.2 respectively. Small decreases from baseline in total, LDL, and HDL cholesterols were experienced by those switching from EFV-based regimens. Decreases from baseline at W48 in rates of neuropsychiatric symptoms, e.g. vivid dreams (-15%, $p < 0.001$), dizziness (-11%, $p < 0.001$), anxiety (-9%, $p = 0.008$), and insomnia (-10%, $p = 0.004$), were reported after switching to E/C/F/TDF [HIV Symptom Index]. HIV Treatment Satisfaction scores were higher for subjects who switched to E/C/F/TDF ($p < 0.001$) [HIV Treatment Satisfaction Questionnaire].

Conclusions: Switching to E/C/F/TDF from NNRTI + FTC/TDF regimens was associated with high rates of virologic suppression, no resistance development, and favorable tolerability with improved treatment satisfaction.

Session P-K1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Viral Set Point and Elite Controllers

554 Blunted Response To cART in Elite Controllers

Faroudy Boufassa[1], Jerome Le Chenadec[2], Laurence Meyer[3], Dominique Costagliola[4], Peter W. Hunt[5], Florecia Pereyra[6], Steve Deeks[5], Gianfranco Pancino[7], Olivier Taulera[8], Mathias Lichterfeld[9], Pierre Delobel[10], Asier Saez-Cirion[7], Olivier Lambotte[11]

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Background: HIV Elite Controllers (ECs) spontaneously control viral load. Some EC however initiate anti-retroviral treatment (cART), due to loss of viral control or CD4 T cell (CD4Tc) decrease. The CD4Tc dynamics in Controllers on cART has been poorly described. Here we studied the CD4Tc dynamics after cART initiation among 34 EC followed in US and Europe cohorts, compared to viremic infected patients (VIRs).

Methodology: ECs were defined as having ≥ 5 viral load (VL) measurements <400 copies/mL over ≥5 years while never having received ART and were identified from the French ANRS CO18 Cohort, the US SCOPE Cohort, the International HIV Controllers study and the European CASCADE collaboration. VIRs were selected from the ANRS COPANA Cohort which enrols ART-naïve recently-diagnosed (<1 year) HIV-1-infected adults. Dynamics of CD4Tc counts after cART initiation were modelled by piecewise mixed linear models.

Results: In VIRs, CD4Tc increase after cART initiation followed a 2-stage pattern: an initial rapid increase over the first 3 months (+0.63 sqrt(CD4)/month), followed by a slower increase of +0.19 sqrt(CD4)/month. This contrast with treated ECs where no such rapid first slope was observed: the CD4 increase was moderate and similar to the second slope observed in VIRs. For a patient starting cART at 300 CD4Tc, mean gain in the first 12 months were 139 for VIRs vs. only 80 for ECs (p=0.048).

Conclusions: This is the largest series of treated ECs. ECs who initiate cART experience an increase in CD4Tc counts, although lower than that achieved by VIRs.

555 Viral Set Point After Cessation of Antiretroviral Therapy Initiated in Acute Primary HIV Infection

Christine Durier[1], Cécile Goujard[2,3], Caroline Roussillon[4,5], Isabelle Fournier[1], Catherine Fagard[4,5], Isabelle Charreau[1], Gilles Pialoux[6,7], Bruno Hoen[8,9], Christine Rouzioux[10,11], Jean-Pierre Aboulker[1], ANRS 100 PRIMSTOP & ANRS 112 INTERPRIM study groups

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Background: Antiretroviral therapy (ART) is increasingly offered to persons with primary HIV infection (PHI) to improve the course of HIV disease. To identify among individuals treated during PHI those who will be able to control viral replication after cessation of ART is important from the dual perspective of clinical management and identification of mechanisms of viral control.

Methodology: Data from 112 participants in ANRS 100 (n=26) and ANRS 112 (n=86) trials who received 18-month ART initiated in acute PHI and underwent a scheduled treatment interruption were pooled for analysis. Logistic regressions were used to identify factors associated with a plasma HIV-1 RNA (VL) level <1000 cp/mL 6 months after cessation of therapy (viral set point). Median (interquartile range) results are presented.

Results: Median age was 34 years (29-41); 13 (12%) were women. Before treatment initiation, CD4 T cell count was 425 cells/mm3 (299-607), VL and total cell associated HIV-1 DNA levels were 5.7 log10 cp/mL (5.0-5.9) and 3.5 log10 cp/10^6 PBMC (3.0-3.7), respectively and number of Western blot antibodies was 2 (1-3). At completion of 72-84 weeks of treatment, VL was <50 cp/mL in 83/108 (77%) patients, CD4 T cell count had increased to 682 cells/mm3 (556-852) and HIV DNA decreased to 2.3 log10 cp/10^6 PBMC (1.8-2.7). Six months after ART interruption, median VL was 3.9 log10 cp/mL (3.0-4.3). VL was <1000 cp/mL in 26 patients (23%, 9/13 women and 17/99 men) and <50 cp/mL in 7 patients (6.2%, 4/13 women and 3/99 men, p=0.003 Fisher's exact test). Female sex and a low baseline VL were significantly associated to a low viral set point; a high CD4 T cell count at baseline showed a trend. Patient's age, trial, number of Western-blot antibodies, CD8 T cell count at baseline, HIV DNA level at baseline and at treatment interruption were not associated with viral set point. In multivariate analysis, female sex was the only variable significantly associated to an increased likelihood of VL <1000 cp/mL (p=0.02). Considering men only (n=99), 17% achieved a VL <1000 cp/mL 6 months after interruption and no predictive factor of viral set point was identified among CD4 T cell count, VL or HIV DNA level at initiation or at 18 months of treatment.

Conclusions: Women were more likely to control viral replication than men. After adjustment on sex, no other pretreatment or end-of-therapy characteristic was identified in this population to predict a low or undetectable VL 6 months after cessation of ART. This difference between men and women deserves further investigation.

556 HIV Elite Controllers Are Hospitalized More Often Than Persons With Medically Controlled HIV

Trevor A. Crowell[1], Kelly A. Gebo[1], Joel N. Blankson[1], Baligh R. Yehia[2], Richard M. Rutstein[3], Stephen A. Berry[1]

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Background: We compared hospitalization rates and causes for persons with elite control (EC) to those for persons with medical control (MC) and uncontrolled (UC) HIV RNA but high CD4.

Methodology: Among adults engaged in care 2005-2011 at 12 HIV Research Network sites, we identified person-years (PY) with CD4 consistently >350 cells/mm3 and categorized each PY as EC, MC, or UC. EC was defined by ≥3 undetectable HIV RNA values over ≥12 months in the absence of antiretroviral therapy (ART). MC required the same HIV RNA parameters with use of ART. All other PY were considered UC. Progression out of EC or MC status occurred with HIV RNA increase or CD4 decline. Negative binomial regression with GEE was used to assess factors associated with hospitalization. ICD-9 codes were used to assign hospitalizations into diagnostic categories.

Results: Of 26,741 patients with CD4 >350, there were 224 elite controllers contributing 475 EC PY; 10,148 persons contributing 29,020 MC PY; and 22,968 contributing 47,288 UC PY. Compared to the MC and UC groups, the EC group was older (median age 46, 45, and 42 years for EC, MC, and UC, respectively), higher percentage female (46%, 26%, 28%) and Black (51%, 43%, 49%) and had higher median CD4 (745, 466, 480 cells/mm3).

Unadjusted hospitalization rates were consistently higher among the EC group (mean 22.1/100 PY) than in the MC (10.6) or UC groups (13.0, figure). Compared to MC, the EC (aIRR 1.67 [1.09-2.57]) and UC (1.30 [1.21-1.39]) groups had higher hospitalization incidence after adjustment for year, demographics, HIV risk factor, CD4, insurance, and clinical site.

A greater percentage of EC admissions were for cardiovascular (23% for EC, 16% MC, 11% UC) and pulmonary causes (20%, 5%, 5%) and less were for non-AIDS defining infections (4%, 21%, 29%).

Conclusions: Elite control is associated with higher hospitalization rates than medical control of HIV infection. Underlying mechanisms need to be explored and studies are needed to investigate whether ART might reduce hospitalizations among elite controllers.

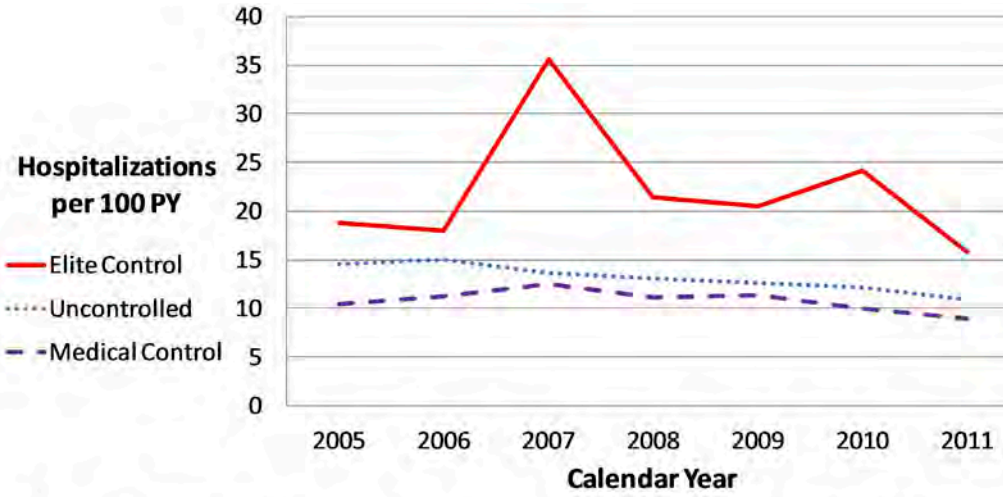

Figure. All-cause hospitalization rates among patients with CD4 >350 by HIV control status

Session P-K2 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

ART Initiation, Monitoring, and Outcomes

557 CD4 Cell Count Monitoring Frequency Among HIV+ Persons in New York City (NYC), 2007-2011

Julie E. Myers[1,2], Qiang Xia[1], Lucia V. Torian[1], Mary K. Irvine[1], Blayne H. Cutler[1], Graham Harriman[1], Kent A. Sepkowitz[3], Colin W. Shepard[1]

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Background: National guidelines advise CD4 testing every 6-12 months in clinically stable HIV+ patients with suppressed HIV viral load (VL), while some quality management protocols require CD4 monitoring every 6 mos. To determine whether some patients could be safely tested less often, we used NYC surveillance data to explore CD4 testing among stable patients in NYC, 2007-2011.

Methodology: We constructed a population-based, retrospective open cohort analysis of NYC HIV Surveillance Registry data. HIV+ patients aged ≥13 years with stable viral suppression (≥1 VL in the previous calendar year; all measurements <400 copies/mL) and stable immune status (≥1 CD4 in the prior calendar year; all measurements ≥200 cells/mm^3) entered the cohort the following year beginning on January 1, 2007. Each subsequent year, patients who were eligible and not previously enrolled entered the cohort on January 1. Patients were followed through 2012, and censored at first VL≥400 copies/mL or the last CD4/VL. The primary outcome was the probability of maintaining CD4≥200 cells/mm^3. A multivariate Cox model was used to identify factors associated with maintenance of CD4≥200 cells/mm^3.

Results: During a median 2.5 (interquartile range: 1.2, 4.7) years of observation, 58,691 stable patients entered the cohort (168,769 person-years of observation). Mean annual number of CD4 measurements among stable patients was 2.8 (standard deviation: ±1.3) and varied little by year or characteristic. Two years after entering, 66.9%, 91.9% and 97.8% of those with initial CD4 200-349 cells/mm^3, 350-499 cells/mm^3, and ≥500 cells/mm^3, respectively, maintained CD4≥200 cells/mm^3. Compared to those with initial CD4≥500 cells/mm^3, those with CD4 200-349 cells/mm^3 (adjusted hazard ration [AHR] = 13.6, 95% confidence interval [CI], 12.7, 14.6) and CD4 350-499 cells/mm^3 (AHR = 3.3, 95%CI: 3.1, 3.6) were more likely to have a CD4<200 cells/mm^3, controlling for sex, race, age, HIV risk group, and diagnosis year.

Conclusions: In a population-based cohort with well-controlled HIV, initial CD4 at cohort entry was an independent predictor of maintaining CD4≥200 cells/mm^3; the probability of maintaining CD4≥200 cells/mm^3 for at least 2 years was >90% among those with initial CD4≥350 cells/mm^3. These findings suggest that limited CD4 monitoring in individual patients is appropriate, especially among those with CD4≥350 cells/mm^3, as additional testing is unlikely to require clinical action. At the New York State Medicaid rate of US$64.93 for a CD4 test in 2013, NYC would save approximately US$1.3 million or US$3.0 million annually, if CD4 monitoring were limited to twice yearly or once yearly, respectively, for stable patients with CD4≥350 cells/mm^3.

558 Value of Viremia Copy Years in Deciding Optimal Timing of ART Initiation in Adults With HIV

Ashley Olson[1], **Sarah Walker**[1], Amitabh Suthar[2], Caroline Sabin[3], Heiner Bucher[4], Inma Jarrin[5], Santiago Moreno[6], Santiago Perez-Hoyos[7], Kholoud Porter[1], Deborah Ford[1], CASCADE Collaboration in EuroCoord

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Background: Time updated VL levels and CD4 counts are routinely used to monitor HIV positive adults but fail to capture cumulative HIV exposure. Viremia copy years (VCY) is such a measure and has been shown to be predictive of AIDS/death, although it is unclear of its use in deciding when to start ART. We aimed to assess the impact of initiating vs. deferring ART on risk of AIDS/death by levels of VCY both independent of and within two CD4 strata, <350 and ≥350 cells/mm3.

Methodology: Using CASCADE data on HIV seroconverters, we created a series of nested cohorts corresponding to consecutive months starting month 5 post seroconversion (SC) for individuals ≥16 years at SC after 1997, had ≥1 VL measured 4-12 months post SC, were ART naïve and AIDS free prior to end of baseline month. Time to AIDS/death was compared in those initiating vs. deferring ART in the baseline month using Cox models adjusted for time independent factors: country, sex, risk group, SC year; and time dependent factors prior to the baseline month: age, time since last VL, and current CD4, VCY and VL (excluding the first 4 months post SC) and mean number of previous CD4/VL measurements/year. Robust variance was used to adjust for individuals contributing ≥1 baseline visit. We repeated analyses using CD4 strata <500 and ≥500 cells/mm3.

Results: Of 6497 individuals contributing ≥1 baseline month, 3089 (48%) initiated ART and 293 (5%) acquired AIDS/died. Median (IQR) CD4 at ART initiation was 322 (249, 419) cells/mm3. Pooling CD4 strata, hazard ratios (HR) of AIDS/death associated with initiating vs. deferring ART reduced as VCY increased, suggesting a stronger benefit of ART in those with higher VCY. Trends by VCY were different when stratifying by CD4; in patients with CD4<350 cells/mm3, there was an overall reduction in the HR of AIDS/death in all VCY groups (all HR < 1) with no evidence that this benefit varied by VCY (p=0.78). At CD4 ≥ 350 there was a trend for increasing benefit of initiation with increasing VCY, with the largest benefit seen in the VCY ≥ 100,000 c/mL group (HR, 95% CI= 0.56, 0.35-0.90); no evidence of benefit if VCY was < 20,000 c/mL. Results were qualitatively similar for CD4 strata ≥ 500 cells/mm3.

Conclusions: Although we cannot rule out the possibility of unmeasured confounding, it appears that limiting the cumulative HIV burden to < 100,000 VCY in individuals with CD4 ≥ 350 cells/mm3 through ART reduces the hazard of clinical outcomes by 44%.

Estimated HR (95% CI) for the benefit of initiating vs. deferring ART by VCY strata						
VCY Strata	CD4<350	het p	CD4≥350	het p	Independent of CD4	het p
VCY < 10,000	0.55 (0.19, 1.60)	0.78	1.49 (0.79, 2.81)	0.16	1.27 (0.74, 2.17)	0.001
VCY (10,000-20,000)	0.63 (0.27, 1.47)		1.18 (0.55, 2.57)		1.10 (0.62, 1.95)	
VCY (20,000-50,000)	0.35 (0.15, 0.80)		0.65 (0.34, 1.22)		0.51 (0.31, 0.85)	
VCY (50,000-100,000)	0.29 (0.11, 0.79)		0.81 (0.43, 1.51)		0.49 (0.29, 0.85)	
VCY ≥100,000	0.39 (0.27, 0.59)		0.56 (0.35, 0.90)		0.37 (0.27, 0.50)	

559 Expansion of ART and Progressive Declines in All-Cause Mortality in British Columbia, Canada

Christopher Cheung[1], Erin Ding[2], Julia Zhu[2], Benita Yip[2], Lillian Lourenco[2], Rolando Barrios[2], Julio Montaner[1, 2], Robert S. Hogg[2, 3], Viviane Lima[1, 2], **David M. Moore[1, 2]**
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Background: Expansion of ART programs in recent years has been promoted as a means to reducing the further spread of new HIV infections. We examined the effect of such an expansion in British Columbia (BC), Canada on all-cause and cause specific mortality among participants in the provincial HIV/AIDS Drug Treatment Program (DTP).

Methodology: We analyzed data from participants aged ≥18 in the BC DTP to measure two-year mortality and causes of death from January 1, 2001to December 31, 2012. Deaths were identified through record linkages with the BC Vital Statistics Agency and we used ICD-10 codes for the underlying cause of death. We conducted tests of trend and compared DTP participant characteristics by dividing the study time into two-year time periods for the entire study period. We used Cox proportional hazard models to determine the risk of death for participants who had received ART for at least 3 months. Participants initiating ART in the final two-year period were excluded from the latter analysis.

Results: A total of 3933 new participants initiated ART and a total of 8221 received ART during the study period (Table). Overall mortality in the DTP declined from 256/4028 (6.4%) of DTP participants in 2001-2002 to 219/6258 (3.5%) in 2011-2012 (p=0.018 for test of trend). HIV-related deaths decreased (3.8% to 0.9% of DTP participants, p=0.022) and similar decreases were observed in deaths due to chronic liver disease, cardiovascular disease, and suicides (p=0.008, 0.022, and 0.002; respectively). There were no trends with respect to deaths from non-AIDS infections or cancers or respiratory causes. Multivariate models, adjusted for age, gender, history of injection drug-use and adherence to therapy demonstrated that the risk of mortality was independently associated with ART initiation in 2003 - 2004 (adjusted hazard ratio [AHR] 0.74; 95% CI 0.56 - 0.98); 2005 - 2006 (AHR = 0.58; 95% CI 0.42 - 0.80); 2007-2008 (AHR=0.49; 95% CI 0.34 - 0.71) and 2009-2010 (AHR = 0.42; 95% CI 0.25- 0.72) in comparison to 2001 - 2002(reference).

Conclusions: We observed decreases in overall mortality and reductions in HIV-related deaths among participants in the BC DTP over the study period. However, we also observed declines in cardiovascular, liver-related deaths and suicides. These changes parallel a secondary expansion of ART in BC which suggests broad clinical benefits to HIV treatment expansion beyond classically-defined HIV-related conditions.

Reported causes of death by two-year time period among BC HIV/AIDS DTP participants								
Two-year time period	2001-2002	2003-2004	2005-2006	2007-2008	2009-2010	2011-2012	Total (2001-2012)	p value
N of program participants	4028	4281	4589	5072	5676	6258	8221	--
Deaths – all causes (%)	256 (6.4)	294 (6.9)	318 (6.9)	241 (4.7)	228 (4.0)	219 (3.5)	1556 (18.9)	0.018
HIV related (%)	154 (3.8)	175 (4.1)	208 (4.5)	137 (2.7)	93 (1.6)	55 (0.9)	822 (10.0)	0.022
Other infectious and parasitic disease (%)	4 (0.1)	9 (0.2)	5 (0.1)	6 (0.1)	3 (0.05)	3 (0.05)	30 (0.3)	0.158
Cancer (non-AIDS) (%)	12 (0.3)	20 (0.5)	18 (0.4)	18 (0.4)	36 (0.6)	20 (0.3)	124 (1.5)	0.639
Cardiovascular disease (%)	16 (0.4)	16 (0.4)	15 (0.3)	19 (0.4)	8 (0.1)	5 (0.08)	79 (1.0)	0.022
Chronic respiratory diseases (%)	3 (0.07)	1 (0.02)	3 (0.07)	5 (0.1)	5 (0.09)	4 (0.06)	21 (0.3)	0.486
Chronic Liver Disease (%)	13 (0.3)	12 (0.3)	10 (0.2)	7 (0.1)	4 (0.07)	8 (0.1)	54 (0.7)	0.008
Unintentional Injuries (%)	6 (0.2)	9 (0.2)	2 (0.04)	5 (0.1)	9 (0.2)	0 (0)	31 (0.4)	0.230
Suicide (%)	31 (0.8)	25 (0.6)	21 (0.5)	25 (0.5)	13 (0.2)	0 (0)	115 (1.4)	0.002
Other causes of death (%)	17 (0.4)	27 (0.6)	36 (0.8)	19 (0.4)	57 (1)	124 (2.0)	280 (3.4)	0.076

560 Higher CD4 at ART Initiation Predicts Greater Long Term Likelihood of CD4 Normalization

Frank J. Palella[1], Carl Armon[2], Joan S. Chmiel[3], John T. Brooks[4], Rachel Debes[2], Richard Novak[5], Bienvenido Yangco[6], Kathy Wood[2], Marcus Durham[7], Kate Buchacz[8]

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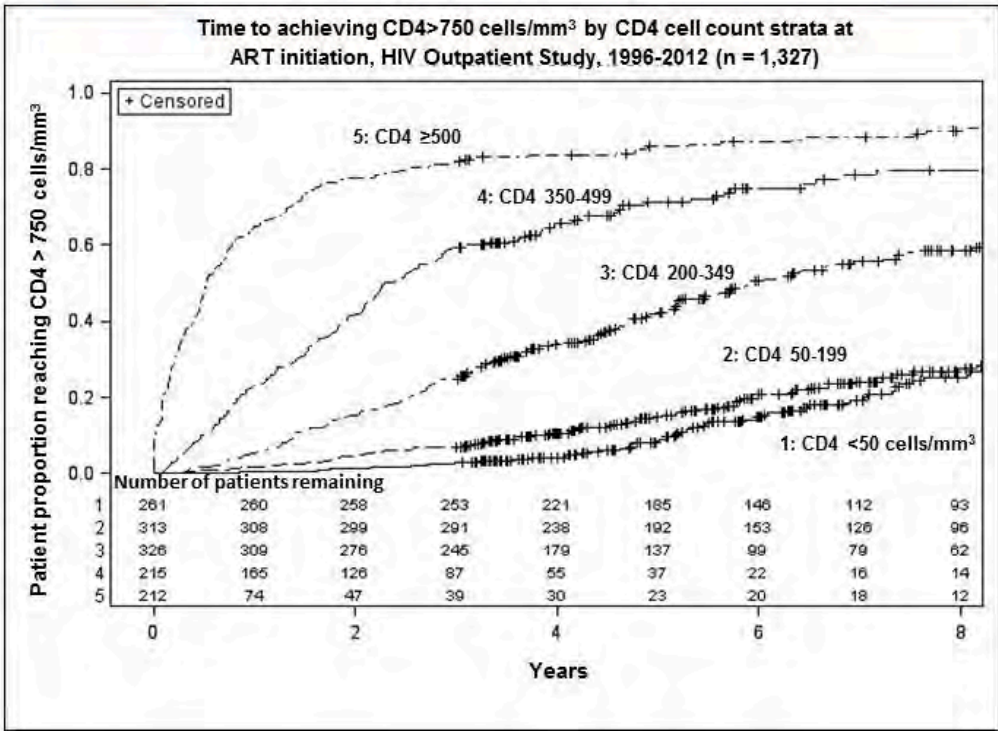
Background: Higher plasma CD4 cell counts per mm^3 at ART initiation (AI-CD4) improve long-term CD4 responses and survival. Recent data suggest attaining CD4 > 750 is a clinically significant threshold for AIDS-related illness reduction and immune "normalization". We evaluated the effect of AI-CD4 on chances of achieving CD4 > 750 and mortality risk.

Methodology: Among HIV Outpatient Study patients seen during 1996-2012 for three or more years after AI, we analyzed CD4 trajectories and mortality rates per 100 persons-years (MR) by AI-CD4, and the association of AI-CD4 with achieving CD4 > 750 using Kaplan-Meier methods and Cox proportional hazards models.

Table: Characteristics of Eligible Patients in HOPS by AI-CD4 (N = 1327)

AI-CD4 Range (cells/mm^3)	Crude mortality rates per 100 persons-years (n = 1327)	CD4 closest to death, mm^3 (n = 64)	Median peak CD4 count, mm^3 (n = 1327)	% Patients with peak CD4 > 750 mm^3 (n = 1327)	Hazard ratio [95% Confidence Interval, CI) for achieving CD4 > 750 mm^3 (n = 1327)
≥ 500	0.4	436	1127	90	14.1, [10.5-18.9]
350-499	0.3	516	924	73	6.70, [4.97-9.03]
200-349	0.3	257	776	54	3.09, [2.31-4.13]
50-199	0.9	188	552	26	1.19, [0.85-1.66]
< 50	0.8	216	531	23	(Referent)



Results: Of 1327 eligible patients followed a median of 7.9 years, > 85% received HAART ≥ 75% of follow-up time, and 64 died. Higher AI-CD4 was associated with increased median peak CD4 ($p < 0.001$ for trend; see Table). Maximal CD4 response and benefit appeared to plateau at eight years, but differences by AI-CD4 strata persisted ($p < 0.001$ for trend; see Figure). Lower crude MRs ($p = 0.005$ for trend) and higher CD4 closest to death ($p = 0.013$ for trend) were associated with higher AI-CD4. Increases in median CD4 for persons with AI-CD4 < 50 and 50-199 seemed to converge by eight years after AI (< 50% achieved CD4 > 750) whereas patients with AI-CD4 > 350 normalized by eight years (> 80% of patients). In multivariable analyses, higher AI-CD4 was the only factor independently associated with achieving a CD4 > 750 during follow-up through last HOPS contact.

Conclusions: Progressively higher AI-CD4 predicted greater long-term CD4 gains, greater chances of achieving CD4 > 750 ("normalization"), increased crude survival rates, and higher CD4 at death. CD4 gains and chances of reaching CD4 >750 peaked at eight years after AI. Most persons with AI-CD4 >350 eventually achieved CD4 normalization while less than half of persons with AI-CD4s < 50 and 50-199 did. AI-CD4 ≥ 500 optimized the likelihood of CD4 normalization. These data confirm the hazards of delayed AI and support AI at CD4 ≥ 500.

561 Is CD4 Monitoring Needed Among Ugandan Clients Achieving Virologic Response To Treatment?

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Background: Immunologic monitoring with CD4 counts every 6 months is commonly performed for individuals receiving antiretroviral therapy (ART). In the setting of immunologic and virologic response to ART (CD4>=200 cells/ul and HIV viral load (VL) <400 copies/ml), it is unclear whether ongoing CD4 monitoring is necessary. We investigated the proportion of clients who achieved a virologic and immunologic response who had a subsequent decline in CD4 (<200 cells/ul) despite virologic suppression.

Methodology: Clients receiving ART through the Rakai Health Sciences Program in Uganda between June 2004-May 2013 were eligible for this analysis. We evaluated clients who had achieved a CD4>=200 cells/ul and a VL<400 copies/ml and had at least 3 pairs of sequential CD4 and VL measurements occurring within 390 days (a sequence). A CD4 count decline was defined as a drop in CD4 count to <200cells/ul during a period of viral suppression. Survival analysis was used to estimate time to first CD4 sequence and CD4 decline. A cox proportional hazards model was used to identify factors associated with a CD4 decline.

Results: A total of 1553 clients were included, 68% females, mean (sd) age of 35.5 years (8.3), median (IQR) baseline CD4 count 183 cells/µl (106-224). A total of 1482 (95.4%) clients had at least one sequence of CD4/VL measurements, while 71(4.6%) had more than one sequence. On average, clients acquired a sequence after 8.3 months on ART (6.9-14.2). In a per-client analysis, 43 clients (2.8%) developed CD4 declines, the majority occurring among individuals whose initial CD4 was <300 cells/ul (table 1). Of the 43 clients who developed declines, 24 had an additional CD4 measurement and 20/24 (83%) achieved a CD4>=200 cell/ul on their next measurement (median 285; IQR 220-365). CD4 declines were significantly greater among those with lower CD4 at sequence initiation, adjusted hazard ratio (AHR) 4.3 (95% CI 2.1, 9.0) CD4 200-249 versus >=350. A 50 cell/µl increase in the baseline CD4 count was associated with a reduced hazard of CD4 count decline, AHR 0.8 (95% CI 0.71, 0.96).

Conclusions: Clients who achieved a CD4 count >=200 cells/ul and a VL <400 copies/ml on ART were unlikely to experience a CD4 count decline to <200 cells/ul and among those who did experience a decline, the majority were transient in nature. As access to VL monitoring expands in resource limited settings, decreasing the frequency of CD4 count monitoring among virally suppressed clients may reduce costs.

CD4 Declines					
Initial CD4 in Sequence	All	200-249	250-299	300-349	>=350
Per-client analysis	1553	294	299	254	706
CD4 maintained at >=200 cells/ul	1510 (97.2)	275 (93.5)	286 (95.7)	245 (96.5)	704 (99.7)
CD4 declines	43 (2.8)	19 (6.5)	13 (4.3)	9 (3.5)	2 (0.3)

562 Long Term Effects of Treatment Interruptions in Adults and Children

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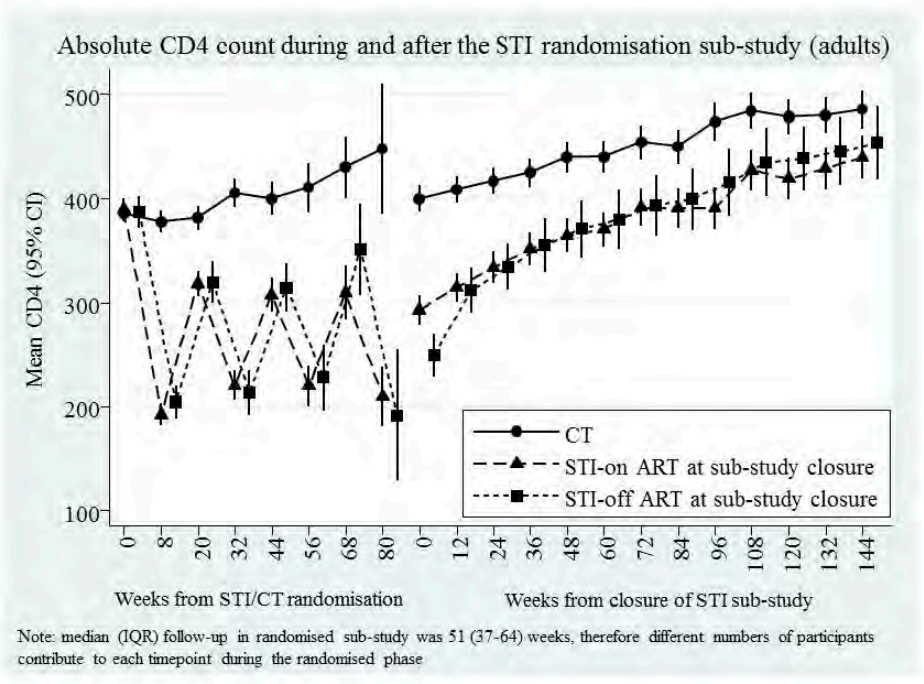
Background: Stockouts are relatively common in large ART programmes and cause treatment interruptions, but their long-term impact is rarely assessed. We investigated this using long-term follow-up of a structured treatment interruption (STI) randomization 12 weeks on/off in a large adult trial (DART), and data on unplanned treatment interruptions (UPTIs) in this and a parallel paediatric trial (ARROW).

Methodology: The DART STI randomisation stopped early; patients returned to continuous therapy (CT) and were followed for a further 3 years. Random effects models were used to assess differences in CD4s between those randomized to STI vs CT over the long-term back on ART. Linear regression was used to assess the impact of total time off ART on CD4 4 years (adults) or 3 years (children) after ART initiation. The impact of time-updated cumulative time off ART on mortality was assessed using Cox models. All models adjusted for sex, centre and pre-ART CD4/CD4% and age.

Results: DART STI patients had >100 cells/mm^3 lower CD4 when restarting CT (Figure). Subsequently STI patients gained 48 (95% CI 43-54) cells/year, significantly faster than the 31 (25-36) in CT patients (p<0.001). Extrapolating forward, those randomized to STI would have similar CD4 to those on CT 4-5 years after restarting ART. 32% (1055/3316) adults had total 1955 UPTIs lasting ≥4 days, vs 23% (281/1206) children (p<0.001) with 536 UPTIs, with median total 17 days (7-49) off treatment in adults vs 13 (7-34) in children. In both adults and children most UPTIs occurred in the first year on ART (p<0.001). The most common reason for UPTIs was inability to attend clinic (61% adults, 50% children). Adverse events were a more common reason in adults (22%, 1% children) and patient/carer decision in children (17%, 5% adults). For every extra cumulative month off ART (STIs+UPTIs) in adults CD4 4 years after ART initiation was 6 cells/mm^3 lower (95%CI 2-8, p<0.001); in children CD4% 3 years after ART initiation was 2% lower (1-3%, p=0.001). Having ever interrupted ART increased mortality risk in adults (HR=3.0 [95% CI 2.1-4.2] p<0.001) with similar non-significant trend in children (HR=2.6 [0.7-10.4] p=0.18). There was no evidence of independent effects of cumulative time off ART in adults (HR=1.1 per doubling [1.0-1.2] p=0.26) or children (1.6 [0.9-2.8] p=0.11).



Conclusions:

TIs lead to lower CD4 counts over the long-term even after returning to ART, highlighting the importance of avoiding ART interruption in programmes in resource limited settings.

563 Failure of Initial HAART in Caribbean, Central and South America

Carina Cesar[1], Bryan E. Shepherd[2], Cathy A. Jenkins[3], Beatriz Grinsztejn[4], Marcelo Wolff[5], Jean W. Pape[6], Denis Padgett[7], Juan Sierra Madero[8], Eduardo Gotuzzo[9], Pedro E. Cahn[1], CCASANet

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Background: Access to highly active antiretroviral therapy (HAART) is expanding in Latin America (LAC). The aim of this study was to identify factors associated with failure of initial HAART.

Methodology: Antiretroviral-naïve adults who started their first HAART on or after January 1, 2000 at participating CCASAnet sites were included. Cumulative incidence of virologic failure and major regimen change was estimated considering death as a competing event. Hazard ratios (HR) were computed using univariate and multivariable Cox models. Secondary models with major regimen change as the outcome included Haiti (excluded from the primary analysis due to lack of viral load [VL] data).

Results: 13,954 HAART initiators met inclusion criteria (867 from Argentina, 1817 from Brazil, 1075 from Chile, 6468 from Haiti, 917 from Honduras, 811 from Mexico, and 1999 from Peru). Median follow-up was 3.7 years (interquartile range [IQR] 1.8 to 5.9). Nearly 60% of patients were male; the median age at HAART initiation was 37 years (IQR 30 to 44); median CD4 count was 152 cells/mm3 (IQR 60 to 249), and median VLwas 5 log10 copies (IQR 4.5 to 5.4 log10); 39% with AIDS (ranging from 8% in Argentina to 58% in Mexico); median frequency of VL measurement was 3.1 per year; 26% of patients from Honduras did not have VL available; this proportion was less than 2% for the other sitesMost patients at all sites started an NNRTI-based regimen. The cumulative incidence of virologic failure was 9.5%, 18.8% and 27.2% at 1, 3 and 5 years after HAART initiation, respectively. The cumulative incidence of a major regimen change across all sites including Haiti was 2.4%, 7.9% and 13.8% at 1, 3 and 5 years after HAART initiation, respectively.

Virologic failure was associated with younger age (adjusted hazard ratio [aHR]= 1.94 for 20 vs. 40 years; 95% CI 1.61-2.34; p<0.001); prior AIDS (aHR=1.31; 95% CI 1.16-1.47; p<0.001); HAART start in earlier calendar years (aHR 1.34 for 2002 vs. 2006; 95% CI 1.21-1.50; p<0.001); non-NNRTI-based regimen (PI-base regimen aHR=1.29; other regimen aHR=1.47; p<0.001).

Similarly, younger age and AIDS were both associated with a major regimen change. In contrast, earlier year of first HAART was associated with a decreased risk of regimen change (aHR=0.80 for 2002 vs. 2006). Predictors of major regimen change were similar between Haiti and the Latin American sites.

Conclusions: This is the first study to evaluate rates of virologic failure and major regimen change throughout Latin America. Rates were moderate/high, but similar to those seen in North America and Europe. Trends along time may reflect availability of second line drugs. Failure was more likely among younger patients, suggesting the need to design specific strategies for these patients.

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564 The HIV Treatment Cascade: Is There More To the Story?

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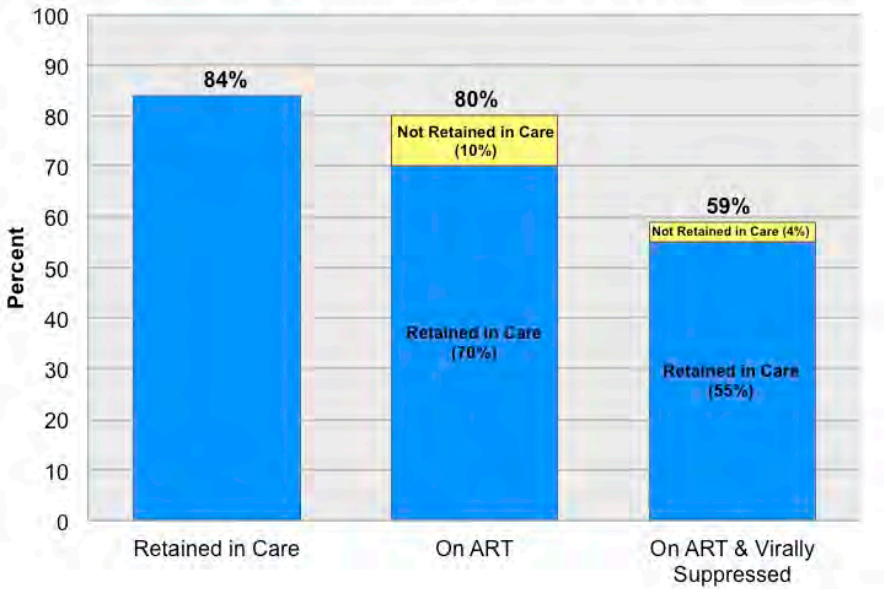
Background: The HIV treatment cascade is an effective framework for improving the delivery of care to people living with HIV (PLWH). Steps in the cascade are calculated in a conditional manner, with the number of persons completing the prior step serving as the base population for the next step. However, this approach may underestimate use of ART and viral suppression by excluding persons not meeting standard definitions of retention in care.

Methodology: Using 2010-2012 data from 13 HIV Research Network clinics, we calculated the proportion of patients completing the final two steps of the cascade: (1) use of ART for ≥6 months in the calendar year, and (2) viral suppression (HIV RNA <400 copies/mL) at the last measure in the 2nd half (Jul-Dec) of the year among those on ART. Cascade steps were stratified by retention in care (≥2 primary HIV visits separated by ≥90 days in the year). Multivariable regression compared characteristics of patients retained vs. not retained among those who were (1) on ART and (2) on ART and virally suppressed, adjusting for age, sex, race, HIV risk factor, insurance, initial CD4 count, and calendar year.

Results: A total of 28,569 adults (≥18-years-old) contributed 58,088 person-years (PY) to the analysis. Overall, patients were retained in care in 84%, on ART in 80%, and virally suppressed in 59% of PY. Following the standard cascade, 84% were retained in care, 70% were retained and on ART, and 55% retained, on ART, and virally suppressed. Therefore, we identified 10% of PY where patients did not meet retention criteria, but were on ART; and 4% of PY where patients did not met retention criteria, but were on ART and achieved viral suppression. (Figure) Among patients on ART, those with heterosexual and IDU risk (vs. MSM) and lower CD4 counts were less likely to be retained; whereas older patients, Hispanics (vs. whites), and persons with public insurance (vs. private) were more likely to be retained (p-value <0.05). Similar associations were observed for patients on ART and virally suppressed, except CD4 count was no longer significantly associated with retention.

Figure: Treatment Cascade for HIV-Infected Adults by Retention in Care Status



Conclusions: Excluding patients not retained in care from the HIV treatment cascade underestimates the proportion on ART by 10% and the proportion with viral suppression by 4%. These patients may receive care at outside clinics or have excellent self-management skills; thus not meeting retention criteria. Better understanding of how PLWH use outpatient HIV services may improve how we assess and design HIV care delivery.

565 Cumulative Viral Load Predicts All-Cause and AIDS-Related Mortality After Initiation of ART

Michael J. Mugavero[1], Andrew O. Westfall[2], M. John Gill[3], Michael Saag[1], Sophie Abgrall[4, 5], Gerd Fätkenheuer[6], Peter Reiss[7], Suzanne M. Ingle[8], Margaret T. May[8], Jonathan A. C. Sterne[8], on behalf of ART-CC

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Background: The prognostic value of cross-sectional viral load (VL) measures for clinical events following ART initiation is well established but the best way to quantify their association with clinical events and death over time is unclear.

Methodology: Treatment-naïve patients starting ART between January 2000 and December 2009 in one of 17 cohorts participating in the ART Cohort Collaboration (ART-CC) were included. Time-updated viremia copy-years (VCY) following ART initiation ("baseline"). VCY estimates the cumulative plasma viral burden based on the area under the VL curve and was calculated daily for each patient. We assumed a lower limit of detection of 500 copies/ml: values <500 were set to 250 for calculation of VCY). Procedures for standardized coding of deaths were adapted from the CoDe protocol. We used Cox models to estimate associations (hazard ratio [HR], 95% CI) of baseline and time-updated viral load, and time-updated VCY, with all-cause,

AIDS-related, and non-AIDS-related mortality. All models were adjusted for baseline age, sex, transmission risk group and cohort, and time-updated CD4 count.

Results: Among 33563 patients (mean age 39 years, male 71%, mean baseline CD4 217 cells/μL), a mean 13 viral load measures were available during mean 3.2 years following ART initiation. 1341 patients died, including 503 AIDS-related deaths, 614 non-AIDS-related deaths, and 224 unclassifiable/ unknown deaths. All viral load measures predicted all-cause mortality, but time-updated VCY remained strongly predictive when adjusted for the other viral load measures. Similar patterns, with stronger associations, were observed for AIDS-related mortality. Associations with non-AIDS mortality were modest, with little evidence that any of the three VL measures independently predicts non-AIDS mortality.

Conclusions: Cumulative plasma viral burden following ART initiation better predicts all-cause and AIDS-related mortality than most recent VL, independent of time-updated CD4 count. None of the VL measures considered was clearly associated with non-AIDS mortality.

Table. Hazard ratios (95% CI) for associations of viral load measures with all-cause mortality, after adjusting for other prognostic factors.

			HR (95% CI) for all-cause mortality		HR (95% CI) for AIDS-related mortality	
	Person-years	Deaths	Adjusted for other prognostic factors	Additionally adjusted for other VL measures*	Adjusted for other prognostic factors	Additionally adjusted for other VL measures*
Baseline VL (copies/ml)						
<100,000	51093	506	1	1	1	1
>=100,000	55832	835	1.23 (1.09-1.37)	1.09 (0.95-1.25)	1.21 (1.00-1.46)	0.95 (0.75-1.20)
Time-updated VL (copies/ml)						
<500	85461	738	1	1	1	1
500-9,999	7868	148	1.50 (1.25-1.81)	1.37 (1.13-1.66)	1.58 (1.17-2.14)	1.34 (0.98-1.83)
10,000-100,000	8277	178	1.25 (1.04-1.50)	1.15 (0.95-1.39)	1.37 (1.03-1.82)	1.14 (0.84-1.54)
>100,000	5317	277	1.45 (1.22-1.73)	1.12 (0.92-1.37)	1.53 (1.18-1.98)	0.99 (0.73-1.35)
Time-updated viremia (VCY) (copy-years/ml)						
<10,000	47417	444	1	1	1	1
10,000-100,000	49456	611	1.23 (1.08-1.39)	1.14 (0.98-1.33)	1.40 (1.13-1.74)	1.45 (1.12-1.89)
100,000-350,000	8368	196	1.75 (1.45-2.11)	1.56 (1.24-1.96)	2.08 (1.51-2.86)	2.18 (1.46-3.26)
>350,000	1683	90	2.00 (1.52-2.63)	1.74 (1.27-2.39)	3.40 (2.23-5.20)	3.64 (2.17-6.10)

* other VL measures are the other two viral load measures listed in the table

Session P-K3 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

ART: Adherence and Retention

566 Measures of ART Adherence Associated With Virological Failure in Rakai, Uganda

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Background: Adherence is a major predictor of antiretroviral therapy failure; however, viral load monitoring, which is the gold standard for monitoring the efficacy of HIV treatment and measuring validity of adherence reports, is often not feasible in resource limited settings. Simple adherence measures are available in the ART program in Rakai, Uganda, including measures based on pharmacy refill (PR), appointments and pill count. We examined whether these measures were associated with the occurrence of first virological failure(VF).

Methodology: We analyzed ART adherence and virological failure in 2710 patients aged 15 years or older who initiated ART from 2004 to 2012 in Rakai, Uganda. Adherence was measured using pill counts, pharmacy-refills and appointment attendance based on visits scheduled at two weeks during the first 3 months, then once per month for the first year, and once every two months after the first year. Viral load assays were done at six month intervals. We defined adherent patients as individuals who had at least 95% of pill count, appointment attendance or Pharmacy refills during the 6 months prior to viral load (VL) monitoring. The primary outcome was the occurrence of first VF using WHO's 2013 criterion >=1000copies/ml. Three types of adherence measures (AM) were considered, based on 1) Pill count: ((Dispensed-Returned pills)/ (Pills prescribed during the 6 months))*100%; 2) Appointments: ((total appointments attended with no delay)/ (total expected appointments over a 6 months interval))*100%.; and 3) Pharmacy refill: ((Dispensed medication)/ (pills prescribed during the 6 months))*100%. Multivariate proportional hazards Cox model adjusted for age at VL visit, baseline regimen, WHO stage, CD4, Year of initiating ART and ART experience, was used to examine whether each AM was associated with time from ART initiation to first VF.

Results: The median follow-up time was 46.4 months; IQR 23.8-69.5 months. VF during follow-up was observed in 16% patients (n=426) and 6% (n=27) of these persons subsequently died. The hazard ratios (HR) adherent to non-adherent associated with VF were: pill count (HR: 0.50, 95%CI 0.38-0.67), appointment (0.46, 95%CI 0.37-0.58) and pharmacy-refill adherence (HR: 0.29, 95%CI 0.22-0.37). Younger age (15-29) was associated with a two-fold significant increase in VF. The CBV/EFV regimen combination and the later year of initiating ART were associated with a significant reduction in risk for VF.

Conclusions: All adherence measures were predictive of VF. Because monitoring appointments requires the least effort in clinical settings, it may be a preferred method of assessing adherence in resource-poor settings and early detection of VF.

567 Measures of Retention in HIV Care Differ in Their Associations With Clinical HIV Outcomes

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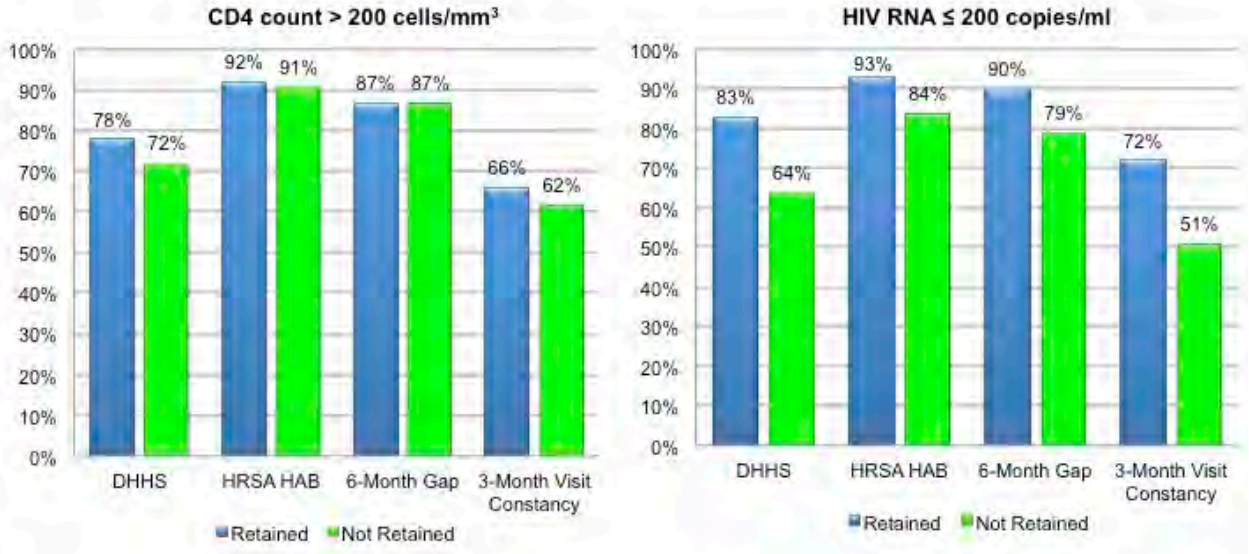
Background: Retaining HIV-infected persons in care is important to receiving antiretroviral therapy (ART) and suppressing viral load. Multiple measures of retention are currently in use with no clear gold standard. Identifying which measures are most closely associated with favorable clinical outcomes may inform how we monitor retention in HIV care.

Methodology: We conducted a serial cross-sectional analysis of 22,261 adults (≥18-years-old) in 14 NA-ACCORD clinical cohorts between 2006 and 2010. Patients contributed one year of data during their first full calendar year of observation (subsequent to their year of entry into the cohort). Four measures of retention were calculated for each patient in this year: (1) US Department of Health and Human Services (DHHS), ≥1 visit in each half (Jan-Jun and Jul-Dec); (2) Health Resources and Services Administration (HRSA), ≥2 visits separated by ≥90 days; (3) 6-month gap, ≥6 months between sequential visits, with retention defined as no gap; and (4) 3-month visit constancy, number of 3-month intervals with ≥1 visit. Outcomes were: (1) CD4 >200 cells/mm3 and (2) HIV RNA ≤200 copies/mL at the last measurement in the year. Poisson regression examined the association between retention measures and the outcomes, adjusting for age, sex, race, HIV risk factor, initial CD4 count, use of ART, and calendar year.

Results: Overall, 75% of patients met the DHHS measure, 89% the HRSA, 85% did not have a 6-month gap, and 63% had visits in 3-4 quarters of the year; 84% had CD4 >200 cells/mm3 and 54% had HIV RNA ≤200 copies/mL. Retention measures varied in their associations with the outcomes. (Figure) The DHHS measure was the only metric significantly associated with CD4 >200 cells/mm3 (adjusted prevalence ratio 1.09, 95% CI 1.05-1.13). All measures were significantly and positively associated with HIV RNA ≤200 copies/mL: DHHS (1.31, 1.25-1.37), HRSA (1.25, 1.16-1.34), 6-month gap (1.19, 1.12-1.27), and 3-month visit constancy (1.20, 1.12-1.29 for 2 quarters; 1.36, 1.27-1.45 for 3 quarters; 1.42, 1.33-1.52 for 4 quarters). Comparisons across measures indicate that the DHHS measure was the strongest predictor of both CD4 >200 cells/mm3 and HIV RNA ≤200 copies/mL ($p<0.05$).

Conclusions: Even though prior studies have shown that retention measures are strongly correlated, we demonstrate that measures vary in their association with clinical outcomes early in the course of patients' care. The DHHS indicator may be the most useful measure to monitor retention in HIV care.

Figure. Percent of HIV-Infected Patients with CD4 Count >200 cells/mm^3 and HIV RNA ≤ 200 copies/ml by Retention Measure



Note: To facilitate comparison with other measures, retention in care for the 3-month visit constancy measure was defined as having visits in 3-4 quarters of the year.

568 Immune, Virologic and Adherence Measures as Time-Dependent Predictors of Loss To Follow-Up

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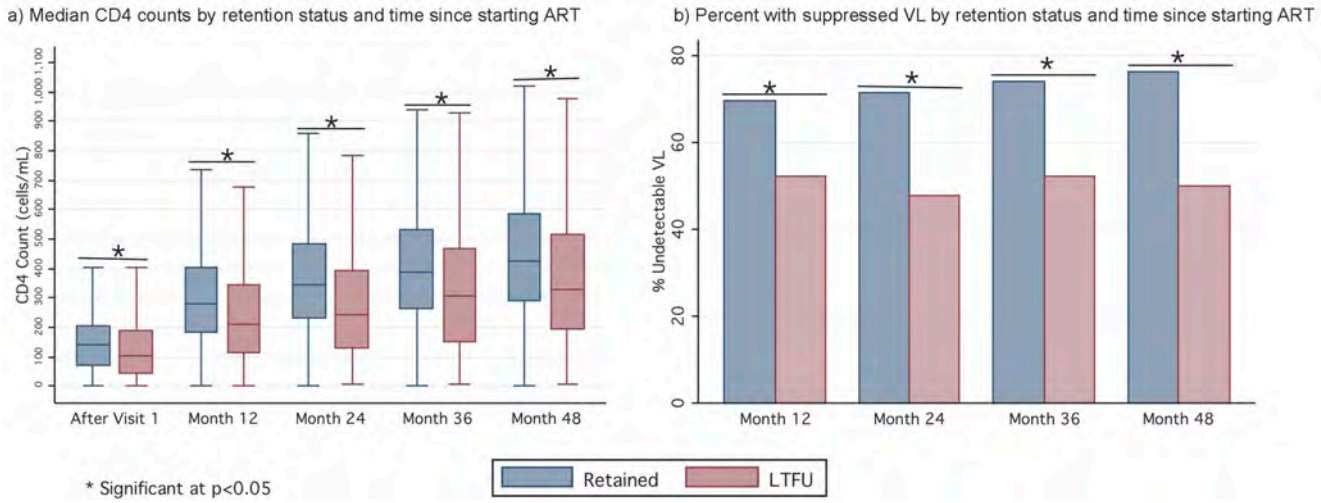
Background: For programs supporting large numbers of patients on ART, loss to follow-up (LTFU) and inadequate adherence pose major obstacles in achieving successful outcomes. In preliminary analyses examining patterns and predictors of attrition, we found that baseline CD4+ cell counts, baseline viral loads and early adherence patterns were associated with overall LTFU. In this evaluation, we further characterized the association of CD4+ cell counts, viral loads (VL), and treatment gaps on LTFU in a time-dependent fashion.

Methodology: From 2004-2012, Harvard/APIN received PEPFAR funds (HRSA #U51HA02522) to support and develop a sustainable HIV prevention, care and treatment program across multiple clinical centers in Nigeria. All patient ART-related data were collected and stored electronically. LTFU was defined as ≥60 days since the last scheduled refill date. For the analyses on CD4 counts and VL, we examined LTFU in 6-month increments, evaluating the CD4+ cell counts and VL taken at the prior visit as a predictor of loss in a time-dependent fashion. For the evaluation on large early treatment no LTFU, the gap was defined as a contiguous ≥90 days between refill dates during the first 6 months of treatment (i.e., "+90 gap"). Logistic regression methods were used to evaluate the association between +90 gap and LTFU.

Results: Between 2004-February 2011, the Harvard/APIN PEPFAR program enrolled 64,372 previously ARVnaive ART patients. Of those, 35% were eventually LTFU. In evaluating the association of CD4+ cell counts and VL suppression rates in a prior visit for months 6, 12, 18, 24, 30, 36, 42, and 48, we found that CD4+ cell counts and VL at prior visits remained significant predictors of attrition ($p<0.05$; Figure 1). Additionally, patients with the +90 gap were more likely to become LTFU beyond 6 months than those that did not have the gap ($p<0.05$). Patients with the +90 gap were less likely to have VL suppression and had a lower CD4 count increase by month 12 versus those without the gap ($p<0.05$).

Conclusions: The majority of analyses on LTFU focus on baseline measures as predictors of attrition. In this evaluation, we were able to show that time-dependent CD4+ cell counts and viral loads are continuous predictors of loss at 6-month time points starting at ART initiation extending to month 48 and that early large gaps in treatment were associated with LTFU within the first year of ART initiation. These data highlight additional indicators that should trigger counseling to ensure low rates of attrition.

Figure 1. CD4 Counts and Viral Loads Predict LTFU in Time-Dependent Manner



Session P-K4 Poster Session
Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Second-Line ART

569 Virologic Suppression With Second-Line Therapy: Does the Initial Regimen Matter?

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Background: In those experiencing virologic failure (VF) on first-line antiretroviral therapy (ART), the impact of the initial drug regimen on the rate of subsequent virologic suppression (VS) is unknown.

Methodology: We describe the outcomes of second-line therapy in those experiencing VF in the AIDS Clinical Trials Group A5202 trial, a randomized study comparing tenofovir/emtricitabine or abacavir/lamivudine with either efavirenz or atazanavir and ritonavir in treatment-naïve individuals. Following VF, subjects underwent resistance testing and were managed according to standard-of-care at the study sites. Subjects' first-line regimen was defined as that taken at VF and was categorized as containing either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a ritonavir-boosted protease inhibitor (PI/r). Subjects were classified as not taking ART at VF if they had not been on therapy for ≥ 8 weeks at the time of VF. VS on second-line ART was defined

as an HIV RNA < 200 copies/mL at 24 weeks following confirmed VF. We compared VS between those who failed NNRTI- versus PI/r-based therapy using a Fisher's exact test and a logistic regression model adjusting for age, sex, and HIV RNA, CD4 count, and resistance at VF, limiting the analysis to subjects with complete follow-up data.

Results: Of 1,857 subjects, 269 (14.5%) experienced VF; 94 (34.9%) and 134 (49.8%) failed their NNRTI- or PI/r-based first-line regimens, respectively, and 41(15.2%) were not taking antiretrovirals at VF. Of subjects with genotype data at VF, resistance was detected in 71 of 92 (77.2%) failing NNRTI, 21 of 133 (15.8%) failing PI/r, and 17 of 41 (41.5%) not on ART. Therapy modifications following VF are shown in the table. At 24 weeks after confirmed VF, 141 of 155 (91.0%) subjects who had failed first-line NNRTI or PI/r therapy remained in the study on ART and had HIV RNA values available. VS was achieved on second-line ART in 42 of 56 (75.0%) subjects failing NNRTI and in 55 of 85 (64.7%) failing PI/r (unadjusted P=0.265, adjusted P=0.602); in a missing=failure sensitivity analysis, 44.7% failing NNRTI and 41.0% failing PI/r achieved VS (unadjusted P=0.590, adjusted P=0.741).

Conclusions: Among those with follow-up data, therapy was changed more often following failure of NNRTI- versus PI/r-based first-line regimens, likely due to increased resistance. However, subsequent virologic suppression on second-line ART at 24 weeks did not differ significantly between the initial drug regimens.

TABLE: Regimen modifications and subsequent virologic suppression following VF on first-line NNRTI- or PI/r-based treatment

First-line at initial VF / At confirmed VF + 24 (±6) weeks		NNRTI (N=94) n (%)	PI/r (N=134) n (%)	Not on ART (N=41) n (%)	Total (N=269) n (%)	P Values*
Subjects on ART		**67**	**88**	**16**	**171**	
Regimen modifications	No change	22 (32.8)	64(72.7)	3 (18.8)**	89 (52.1)	<0.001[a]
	Only changed NNRTI or PI/r	15 (22.4)	7 (8.0)	0	22 (12.9)	<0.001[b]
	Only changed NRTIs	3 (4.5)	9 (10.2)	0	12 (7.0)	
	Changed NRTIs + NNRTI/PI/r	27 (40.3)	8 (9.1)	13 (81.3)†	48 (28.1)	
Virologic suppression	Yes	42 (75.0)	55 (64.7)	12 (80.0)	109 (69.9)	0.320[a]
	No	14 (25.0)	30 (35.3)	3 (20.0)	47 (30.1)	0.265[b]
	No HIV RNA available	11	3	1	15	0.233[c]
						0.590[d]
Subjects not on ART/missing information		**27**	**46**	**25**	**98**	
	Not on ART	11	11	16	38	
	Completed study	4	13	3	20	
	Lost to follow-up or death	12	22	6	40	

NNRTI: Nucleotide/nucleoside reverse transcriptase inhibitors
* P values from Fisher's exact tests comparing across groups [a, c]; between NNRTI versus PI/r-based first-line regimen groups only [b, d]; excluding subjects with missing data [a, b]; and treating subjects with missing data as not attaining virologic suppression [c, d]
** Subjects restarted the most recent regimen they had been taking prior to stopping ART.
† Changes from the most recent regimen subjects had taken for ≥ 8 weeks prior to VF

570 Favorable Long-Term Outcomes of 2nd-Line ART Despite Drug-Resistant HIV-1 in Sub-Saharan Africa

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Background: With the expansion of antiretroviral therapy (ART) in resource-limited settings, the number of people with treatment failure and need for 2nd-line regimens will increase. We assessed the long-term effectiveness of boosted protease inhibitor (bPI)-based 2nd-line ART in 13 African settings, in patients with and without extensive nucleoside reverse transcriptase inhibitor (NRTI) resistance mutations at the time of regimen switch. Additionally, we explored the accumulation of protease resistance mutations.

Methodology: In an observational cohort, HIV-RNA and genotypic resistance testing was performed in adults who switched to bPI-based 2nd-line regimens at 13 clinical sites in Kenya, Nigeria, South Africa, Uganda, Zambia and Zimbabwe. Genotypic sensitivity score (GSS) was calculated using the Stanford algorithm. Associations between mutations present at the time of switch and virological failure (VF) after 12 or 24 months of ART were assessed using chi-square tests.

Results: Of 243 patients who started 2nd-line ART, 54% harbored drug resistant HIV with a GSS < 3, leading to a partially active 2nd-line regimen. After 12 and 24 months, 88% and 79% of patients were retained in care, respectively (Figure). After 12 months, 29 out of 206 (14%) patients with available viral load (VL) had VF, compared to 27 out of 177 (15%) after 24 months (p=0.745). Of 29 patients with VF at 12 months, 10 (35%) also had VF at 24 months, 10 (35%) were re-suppressed, and the remainder was lost to follow-up, died or switched to 3rd-line ART. A partially active 2nd-line regimen at the time of switch

was not significantly associated with VF at 12 or 24 months of follow-up (p=0.586 and p=0.897, respectively). At 12 and 24 months, 53% and 75% of patients with genotypic test results harbored drug resistant HIV, respectively. Protease mutations were present in 1 (6%) and 6 (30%, p=0.097) sequences at 12 and 24 months. Protease mutations were M46I (n=5), V82A (n=4) and I84V (n=1), and occurred in combination with NRTI mutations 5 out of 6 times (p=0.095). A partially active regimen at the time of switch was not significantly associated with protease resistance development (p=0.354).

Conclusions: Favorable virological response to 2nd-line bPI-based ART was maintained over 2 years, despite extensive NRTI resistance at the time of switch. While still infrequent by month 24, increasing protease resistance over time may become a barrier to successful long-term bPI-based ART in resource-limited settings.

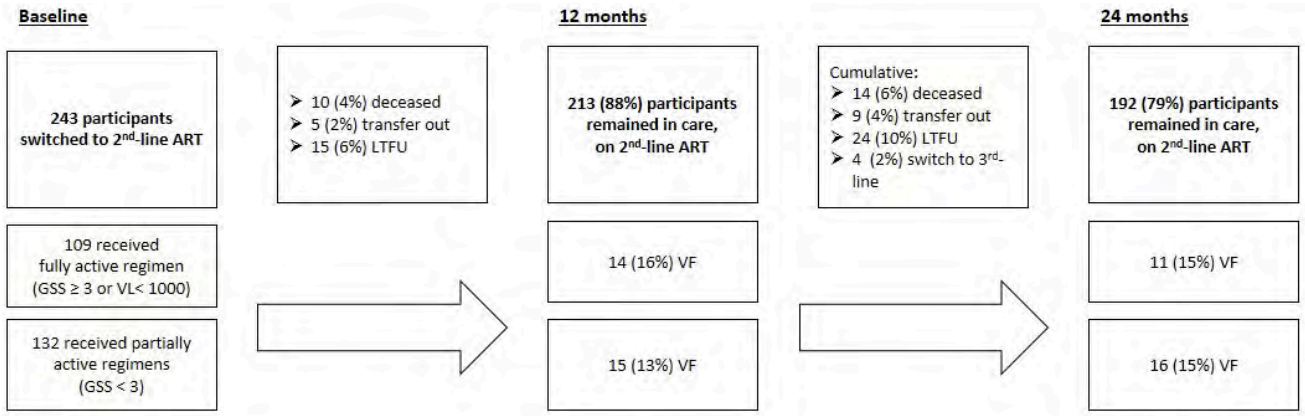

Figure of participants on second-line antiretroviral therapy after first-line failure.
ART = antiretroviral therapy; LTFU = lost-to-follow-up; GSS = genotypic sensitivity score, calculated using the Stanford algorithm; VL = viral load; VF = virological failure (viral load > 400 cps/ml)

571 Predictors of Time To Switch To Second Line ART After First Line Failure in Johannesburg South Africa

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Background: Many patients with documented virologic treatment failure on first line antiretroviral therapy (ART) need to be switched to a second line regimen. In South Africa, national treatment guidelines state that patients with two consecutive failing viral load measurements on non-nucleoside reverse transcriptase inhibitor first line treatment should be switched to a protease inhibitor based regimen. Yet, there are often long delays in switching if it occurs at all. To better understand why delays occur, we explored whether clinic attendance or disease progression was more likely to explain delays in second line initiation.

Methodology: We conducted an observational cohort study using data from Themba Lethu Clinic in Johannesburg, South Africa, a large, public sector HIV clinic. We included all adult patients initiating first line ART since April 2004 with virologic failure (date of 2nd consecutive viral load ≥ 1,000 copies/mL) at least 1 year before the end of the study period in 2013. We looked for demographic, clinical, and visit adherence predictors of time to switch to second line ART after first line failure using Cox proportional hazards regression to adjust for confounders.

Results: 16825 patients initiated first line ART, of which 1578 (9.4%) failed after a median (IQR) of 22.8 (13.7-38.6) months. Of the 1578 who failed 60% were female. At time of failure, mean (SD) age was 39.2 (9.1) years, mean (SD) CD4 count was 244 (183) cells/mm^3, and median (IQR) viral load was 8700 (2728-41000) copies/mL. 69% (1086) of failing patients switched to second line ART in a median (IQR) of 2.8 (1.0-6.6) months. A faster rate of switching was seen in

Table. Cox proportional hazard ratios predicting shorter time to second line switch from first line failure.

Predictor	Crude HR (95% CI)	Adjusted HR (95% CI)
Male	1.08 (0.96, 1.22)	1.14 (0.98, 1.32)
Viral load (copies/mL) at failure:		
1,000 to 9,999	Reference	
10,000 to 59,999	1.49 (1.29, 1.71)	1.32 (1.11, 1.57)
60,000+	1.64 (1.41, 1.92)	1.44 (1.18, 1.76)
CD4 count (cells/mm^3) at failure:		
0-99	1.24 (1.01, 1.53)	1.04 (0.82, 1.31)
100-250	1.31 (1.12, 1.54)	1.18 (1.00, 1.40)
>250	Reference	
Time on first line treatment before failure:		
0-1 years	1.59 (1.29, 1.97)	1.40 (1.06, 1.85)
1-2 years	1.25 (1.04, 1.51)	1.14 (0.88, 1.46)
2-3 years	1.18 (0.95, 1.46)	1.16 (0.88, 1.52)
3-4 years	1.13 (0.89, 1.44)	1.02 (0.74, 1.41)
4+ years	Reference	
Visits missed before treatment failure by >7 days:		
<10%	1.10 (0.94, 1.29)	1.19 (0.98, 1.46)
10-20%	1.01 (0.84, 1.21)	1.06 (0.84, 1.32)
>20%	Reference	

patients with higher viral load, lower CD4 count and shorter duration on first line ART prior to failure (Table). We found some evidence that differences in clinic attendance after failure explained how quickly switches occurred; a smaller proportion of patients who switched by 6 months had missed visits in the first 6 months after failure (31%) than those who did not switch by 6 months (45%).

Conclusions: We found that disease severity at first line failure predicted faster switching, with patients with higher viral load levels and lower CD4 counts being switched to second line more quickly. Lack of visit adherence before failure had a minimal effect on delaying second line ART, and the majority of patients did not miss visits within the 6 months following failure, indicating delay in second line ART initiation is not solely explained by patients missing visits.

Session P-K5 Poster Session
Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

HIV-2

572 Dolutegravir in the French Early Access Program in Integrase HIV-2-Resistant Infected Patients

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Background: Dolutegravir (DTG) is a second generation integrase inhibitors (INSTI), active in patients harboring first-generation INSTI resistant virus. In France, DTG is currently available in early access program (EAP) in salvage therapy. DTG has shown in vitro activity on HIV-2 isolates. We report preliminary safety and efficacy data of DTG containing regimens in HIV-2 infected patients with virological failure.

Methodology: Data from all HIV-2 infected patients with virological failure to raltegravir, receiving DTG 50 mg bid with optimized background antiretroviral (OB ARV) regimens were included in EAP. Plasma HIV-2 RNA (pVL) was performed at time of DTG initiation (baseline), Month 3 (M3) and M6. Cumulative genotypic resistance tests (current and historical) were interpreted according to the last version of ANRS algorithm (v23). ARV plasma concentrations (C12h) were determined using LC-MS/MS. Demographic, biological and therapeutic characteristics were recorded. Medians (IQR) were presented.

Results: A total of 13 HIV-2 infected patients (sex ratio M/F 11:2) aged 51 years, with 15 years infection duration and having received 16 previous ARV prescriptions had been included in EAP. Median follow up was 9 months (min: 3 - max: 15). HIV-2 groups were: A (n=9), B (n=3) and H (n=1). HIV-2 tropism was R5 in 3 patients. Baseline median pVL and CD4 cells count values were 4548 cp/mL (885-21,199) and 97 cells/mm3 (62-157), respectively. Available integrase genotypic resistance patterns were: Y143R (n=6), Y148R/S (n=2), N155H (n=3). OB ARV conferring GSS below or equal to 2 in 10 patients, included: DRV/r (n=12), SQV/r (n=2), MVC (n=3) associated with NRTIs. Among them, 5 patients received in addition foscarnet induction treatment (4 of whom with ZDV). At M3 and M6 pVL was undetectable in 6/10 and 4/8 patients respectively, and median CD4 cells count was 165 (76-165) and 167 (118-159). DTG C12h was 4457ng/mL (2453-5790) in 9 patients. One patient died from progressive multifocal leukoencephalopathy at M4. No other serious clinical or biological events led to DTG discontinuation.

Conclusions: These preliminary results demonstrated that DTG containing regimens provide a substantial efficacy rate for salvage therapy in heavily ARV experienced HIV-2 infected patients with virus harboring resistance to first-generation INSTI. Larger patients numbers and longer follow up are needed to confirm these findings.

573 Long Term Outcomes of ART in HIV-2 Infection in Senegal, West Africa

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Background: Long-term outcomes of antiretroviral therapy (ART) for HIV-2 infection have not been reported. Emerging data suggest that ART for HIV-2 infection may be complicated by high rates of clinical and virologic failure, poor immune reconstitution and multi-class ARV-resistance.

Methodology: A cohort study of ART for HIV-2 infection in Dakar was initiated in 2005 and in Ziguinchor, Senegal in 2010. ART was provided by the Initiative Sénégalaise d'Accès aux Antirétroviraux. Patients were treated with 2 NRTIs and a protease inhibitor (PI), and Aluvia (lopinavir/ritonavir)-based ART became available in 2009. Patients were monitored every four months for clinical and immuno-virologic outcomes as well as adverse events. Time to virologic failure, genotypic ARV-resistance, CD4 count changes, adverse events, all cause mortality and loss to follow-up were analyzed.

Results: 165 patients were enrolled (females 68.5%; median age 49 years) between 2005-2013 with a median time of follow-up of 1.53 years (IQR: 0.52-3.76). All cause mortality was 10.8% with a median time to death of 1.00 years (IQR: 0.20-2.64). Lost to follow-up (LTFU; no contact > 1 year) was 22.4% with a median time to LTFU of 1.09 years (IQR: 0.46-2.42). 57.4%, 47.5%, and 34.9% of subjects had undetectable HIV-2 plasma viral loads at 1, 3 and 5 years respectively. Median CD4 counts increased from baseline (190 cells/mm3) to 277, 293, and 385 cells/mm3 at 1, 3 and 5 years, respectively. Fifteen new WHO stage 3 or 4 AIDS-associated clinical events were reported within the first year after initiation of ART, and 34 new events were reported during subsequent follow-up. Tuberculosis (n=19) and chronic diarrhea (n=23) were common. Of the 44 ARV-treated patients for whom

genotypic resistance data were available, 34% showed evidence of multi-class (NRTI and PI) drug resistance and an additional 34% showed evidence of NRTI resistance.

Conclusions: Long term outcomes of HIV-2-infected patients on ART in Senegal, West Africa are suboptimal with high rates of death, loss to follow up, AIDS-associated clinical events, immuno-virologic failure and ARV-resistance. Further studies comparing PI-based and integrase inhibitor-based regimens are needed, preferably in the setting of randomized clinical trials.

574 Raltegravir-Associated Mutations in HIV-2 Confer Cross-Resistance To Dolutegravir In Vitro

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Background: Dolutegravir (S/GSK1349572) recently became the third integrase strand transfer inhibitor (INSTI) approved for antiretroviral therapy of HIV 1. Although dolutegravir and other INSTI might also be useful for treating HIV-2 infection, the clinical efficacy of dolutegravir has not been evaluated in HIV-2 patients, and data assessing the activity of the drug against HIV-2 in culture are scarce.

Methodology: HIV 2 isolates from antiretroviral-naive individuals were tested for susceptibility to dolutegravir using a single-cycle indicator cell assay. Amino acid changes associated with INSTI resistance were engineered into a molecular clone of HIV-2 via site-directed mutagenesis, and the dolutegravir sensitivities of the resulting variants were determined in single-cycle and multi-cycle assays.

Results: Dolutegravir inhibited group A and B strains of HIV-2 with mean EC50 values comparable to that observed for wild-type HIV-1 isolates (2.0 ± 0.7, 2.8 ± 0.3, and 1.1 ± 0.2 nM, for HIV-2/A, HIV-2/B, and HIV-1, respectively). HIV-2 integrase substitutions E92Q, Y143C, Q148K and Q148R conferred 2-9-fold resistance to dolutegravir, and the combinations E92Q+Y143C, E92Q+N155H, T97A+N155H, G140S+Q148R and T97A+Y143C resulted in 6- to >5000-fold resistance to the drug. Altogether, 9 of the 13 HIV-2 mutants tested were resistant to dolutegravir in culture.

Conclusions: Unlike HIV 1, mutations in all three of the principal pathways involved in raltegravir and elvitegravir resistance confer cross-resistance to dolutegravir in HIV-2. Thus, three mutational pathways in HIV-2 lead to class-wide integrase inhibitor resistance. These findings suggest that dolutegravir-containing regimens may not be effective in HIV-2 patients that have developed resistance to other INSTI.

575 Predicting the Extinction of HIV-2 in Guinea-Bissau

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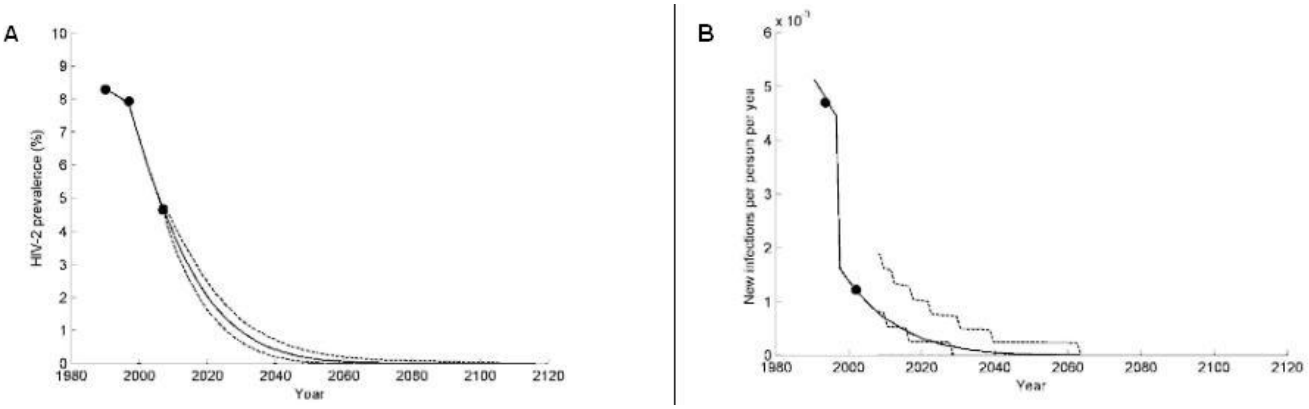
Background: HIV-2 is less virulent than HIV-1 but can cause AIDS indistinguishable from AIDS caused by HIV-1. Guinea-Bissau is believed to be the nucleus of the HIV-2 epidemic and the prevalence was >20% in the 1980s in elderly in Caio, a rural area. In 1990-2007, HIV-2 prevalence halved and in 2007 infection amongst young adults in the region was very low (<1% in 15-34 year olds). However, HIV-2 prevalence was still 12% amongst individuals aged ≥45, due in part to increased susceptibility of women to HIV-2 with increasing age. This suggests that HIV-2 may persist as an infection of the elderly. Through a model we aimed to answer the following questions: will HIV-2 in Caio go extinct and if so, when would this happen, or will it persist as an infection among elderly?

Methodology: A deterministic transmission model was developed and fit to the age-stratified incidence and prevalence data from the HIV-2 epidemic in Caio, as measured in 3 serosurveys in 1990, 1997 and 2007. In the model the population is segregated into 3 states: Susceptible, Infected and Removed (SIR model). A stochastic version of the model was also formulated by allowing death and infection to be governed by probabilistic methods and this version was used with 1000 simulations to make future predictions of HIV-2 prevalence and incidence.



Results: Our model predicts that HIV-2 infections (including dual HIV-1/2 infections) will continue to decline in prevalence and become extinct in Caió this century. HIV-2 prevalence is expected to fall below 0.1% by 2053 (95% CI: 2043-2074) (Figure 1A). New infections are predicted to cease around 2047 (2029-2083) (Figure 1B) but complete extinction is expected to take longer. Mortality rates are relatively low for HIV-2, as compared to HIV-1, meaning that the last few individuals to acquire infection may survive for decades. Extinction is expected to occur around 2071 (2054-2106).

Conclusions: Based on our model, it is predicted that HIV-2 infection will continue to decline rapidly in Caió such that new infections will cease and prevalence will reach low levels. HIV-2 will go extinct in Caió during the second half of this century. HIV-2 epidemics in other parts of the world have behaved in a very similar way thus far, making global extinction of HIV-2 a possibility. As low plasma viral loads play a key role in the restricted transmission and therefore decline of HIV-2, we highlight the relevance of our results to the potential control of the HIV-1 epidemic via universal treatment.

576 HIV-2 X4 Tropism Is Associated With Lower CD4 Cell Count in Treatment-Experienced Patients

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Background: Genotypic tools for HIV-2 tropism determination have been recently established. In vitro studies have demonstrated that maraviroc has efficacy against HIV-2. Currently, maraviroc use is only considered in highly pre-treated HIV-2 patients. However, R5/X4 tropism distribution is still unknown during HIV-2 infection. The aim of this study was to describe HIV-2 tropism distribution in treatment-experienced patients and to compare CD4 cell count and number of drug resistances mutations in R5 and X4 viruses.

Methodology: All samples received for HIV-2 tropism in routine testing between April 2009 and June 2013 issued from ART treated patients experiencing virological failure were included. At time of tropism determination, CD4 cell count, HIV-2 viral load and genotypic resistance testing (protease, RT, integrase) results were collected. Genotypic resistance tests were interpreted according to the new European resistance algorithm (http://www.geno2pheno.org/). Associations between tropism and variables were tested by Mann-Whitney or Fisher exact tests.

Results: 83 patients were included (47 Group A, 33 Group B, 3 not available). Among them, CD4 cell counts, HIV-2 viral load, and genotypic resistance results were available in 67 samples (81%), 75 (90%) and 77 (93%), respectively. 35 (42%) viruses were predicted as R5 and 48 (58%) as X4; with no significant difference between groups A and B (p = 0.65). Median CD4 cells counts were 220 (IQR = 155-395) and 88 cells/mm3 (IQR = 52-171) in R5 and X4 groups, respectively (p<0.0001). Tropism distribution among CD4 cell counts strata is depicted in the table below.

Among R5 and X4 groups, median HIV-2 viral load was 1,417 (IQR = 417-11,910) and 2,187 copies/mL (IQR = 526-4,730), respectively (p = 0.38). Patients with X4 viruses exhibited a significant higher number of drug resistance mutations in protease, RT, and integrase regions than patients with R5 viruses (median = 3 [IQR = 1-5] versus 1 [IQR = 0-4]; p = 0.01).

Conclusions: A high proportion of X4 viruses was observed (58%), particularly in patients with CD4 cell count below 100/mm3. Patients with X4 viruses had lower CD4 cell counts and a higher number of drug resistance mutations, suggesting a longer treatment history. Thus, as in HIV-1, maraviroc use in HIV-2 salvage therapy may be compromised by a high proportion of X4 viruses. These results suggest that maraviroc use must be evaluated earlier in the infection in order to optimize the HIV-2 limited therapeutic arsenal.

Distribution of R5/X4 HIV-2 tropism, stratified by CD4 cell count

CD4 cell count (/mm3)	0-50	51-100	101-200	201-350	>350
% R5 (n)	17 (2)	7 (1)	41 (7)	75 (9)	64 (7)
% X4 (n)	83 (10)	93 (14)	59 (10)	25 (3)	36 (4)

Session P-L1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Primary HIV Drug Resistance

577 Current First-Line Regimens Are Effective in Patients With Single Transmitted TAM

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Background: Currently the most prevalent transmitted resistance-associated mutations in Western European countries are Thymidine Analogue Mutations (TAMs). We hypothesize that in contrast to previously published data these mutations do not affect the efficacy of currently recommended first line combination antiretroviral therapy (cART) regimens with a low barrier to resistance development (GBR) (two NRTI and one NNRTI). This study analyzes the effect of transmitted single TAMs on efficacy of these regimens.

Methodology: Treatment-naive Men who have Sex with Men (MSM) diagnosed with HIV between 2002 and 2012 were selected from the ATHENA national observational HIV cohort in the Netherlands. Patients were classified into three groups: (1) a single resistance-associated mutation on a TAM position ('TAM group'), (2) a single resistance mutation on a non-TAM position or ≥2 resistance mutations ('RAM group'), and (3) no resistance or only non-wildtype mutations ('WT/non-WT'). Virological failure (VF) was defined as the first of <1 log10 decrease in HIV RNA 4-8 weeks after start of cART, 200 copies/mL

after 16 weeks. Time to VF was analyzed using proportional hazards models. Patients were censored at the date of treatment interruption, the date of the last available RNA measurement, or 64 weeks after starting cART, whichever was earliest. Active regimen was defined as a Genetic Susceptibility Score (GSS) ≥3.

Results: Of the 2314 diagnosed MSM, 104 (4%) were in the TAM group (97 full active regimen), 126 in the RAM group (75 fully active regimen). In total, 249 (11%) patients experienced VF. Compared to patients in the WT/non-WT group, time to VF was not different for the TAM group (relative hazard [RH] 1.04 (95% CI 0.58-1.86, p=0.9) or for RAM with a fully active regimen (RH 0.60, 0.25-1.47), but was shorter in RAM with a non-fully active cART regimen (GSS <3) (RH 2.19, 1.19-4.03). In 1537 (66%) patients starting on 1 NNRTI + 2 NRTI, RH for VF was 1.26 (95% CI 0.59-2.70, p=0.5) in the TAM group, 0.61 (0.15-2.47; p=0.5) in the RAM group with fully active cART, and 2.82 (1.32-6.08; p=0.008) in the RAM group with non-fully active cART compared to WT/non-WT. No differences were observed for patients starting high GBR regimens. Pretreatment viral load <100000 cps/mL was associated with lower hazard of VF compared to ≥100000 cps/mL (RH 0.52, 95% CI 0.40-0.69, p=<0.001).

Conclusions: The presence of a transmitted single TAM does not affect the efficacy of currently used first-line cART regimens.

578 Drug Resistance Mutations in Treatment-Naïve HIV-Infected Patients 2000-2013

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Background: HIV integrase (IN) has become an important target for HIV antiretroviral (ARV) therapy with the introduction of IN strand transfer inhibitors (INSTIs), such as raltegravir (RAL), elvitegravir (EVG), and dolutegravir (DTG). Presence of pre-existing mutations in IN may affect the efficacy of this class of ARVs. Here we report the results of a retrospective genotypic analysis of a large dataset of ARV-naïve subjects from Phase 3 clinical samples over a 13 years period.

Methodology: Plasma samples from 4 Phase 3 studies in ARV-naïve HIV-1 infected patients were collected at screening before any drug treatment. The plasma HIV-1 was population sequenced at IN, RT and PR and compared to the HIV-1 reference sequence NL4-3. The number of amino acid changes from reference was tabulated and compared across the studies, and statistical analyses performed. Characteristics such as presence of resistance-associated-mutations (RAMs), subtype, and enrollment year were analyzed.

Results: Sequences from clinical studies GS-99-903 (RT, n=598; IN, n=100), GS-01-934 (RT, n=501; IN, n=100), and GS-US-292-0104/0111 (RT/IN, n=1417), enrolled in 2000, 2003, and 2013, respectively, were included in the dataset (RT, n=2516; IN, n=1617). The clinical studies were enrolled mostly in the U.S. and Western Europe with predominantly subtype B HIV-1 (n=2317). From 2000/2003 to 2013, the presence of NNRTI hallmark transmitted drug resistance (TDR) mutations (K103N/S, Y181C/I/V, and/or G190S/A in RT) increased from 1.9% to 7.8%. NRTI TDR remained low, with TAMs decreasing slightly from 2.7% to 2.2% and the mutations K65R and M184V/I remaining below 0.1% through 2013. The frequency of primary INSTI RAMs (T66A/I/K, E92G/Q, G140S, Y143C/H/R, S147G, Q148H/K/R, N155H/S) remained extremely rare with only one instance of T66T/I mixture with wild-type observed in the 2013 dataset (0.07%). Additionally, the polymorphic T97A IN substitution, which has been associated with minor INSTI resistance, was present at low levels (1.2%) but not found along with other INSTI RAMs. Interestingly, during the same time period, the overall number of IN substitutions vs. reference among the subtype B sequences increased from an average of 11.4 to 12.9 substitutions per patient (p <0.0001) suggesting possible evolution within IN over time.

Conclusions: This analysis showed that through 2013, primary HIV-1 integrase resistance mutations were very rare (1/1617 samples) in treatment-naïve patients. Resistance to NRTIs also remained low, while primary NNRTI resistance was observed in >8% of treatment-naïve patients. These results suggest that transmitted drug resistance is unlikely to affect treatment with most INSTI-containing regimens.

579 Transmitted HIV-1 Drug Resistance Among Men Who Have Sex With Men, 11 US Jurisdictions, 2008–2011

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Background: Men who have sex with men (MSM) bear the heaviest burden of HIV in the United States. Effective antiretroviral therapy (ART) is crucial for viral suppression and reduced transmission. We used National HIV Surveillance System data to assess the prevalence of transmitted drug resistance among MSM.

Methodology: We analyzed HIV-1 *pol* sequences among persons newly diagnosed with HIV during 2008-2011 in 11 U.S. jurisdictions and who had no evidence of ART use. We used the CDC HIV-1 surveillance mutation list to identify transmitted drug resistance-associated mutations (TDRM) for non-nucleoside reverse transcriptase inhibitors (NNRTI), nucleoside reverse transcriptase inhibitors (nRTI), and protease inhibitors (PI). For MSM, we compared TDRM prevalence by age, race/ethnicity, large city of residence (Chicago, Dallas, Denver, Detroit, Los Angeles, Miami, New Orleans, New York City, Seattle), and duration of infection, determined using BED HIV-1 Capture EIA results. Absent a BED result, infections with a negative HIV test ≤6 months before HIV diagnosis were classified as recent. Infections with AIDS ≤6 months after HIV diagnosis were classified as long-standing (LS). To compare TDRM prevalence between groups, we calculated prevalence ratios (PR) and 95% confidence intervals (CI).

Results: Of all 16,985 diagnosed infections, 2,836 (16.7%) had any TDRM, compared to 1,894 (17.4%) of 10,894 infections among MSM. TDRM prevalence among MSM was 9.0% for NNRTI, 6.6% for nRTI, and 4.6% for PI. The most prevalent TDRM for NNRTI, nRTI, and PI were K103N (70.3%), M41L (24.8%), and L90M (29.6%), respectively. MSM aged 13–29 had the highest TDRM prevalence (18.6%) and had more TDRM than MSM aged 40–49 (15.9%) (PR=1.17; CI=1.05–1.32). TDRM prevalence did not differ significantly by race/ethnicity: black (17.7%), Hispanic/Latino (17.5%), white

(16.9%). The cities with the highest TDRM prevalence varied by drug class—any TDRM: Seattle (22.0%); NNRTI: Seattle (14.6%); nRTI: Miami (9.9%); PI: Dallas (7.5%). By duration of infection, 28.3% of MSM had recent infections, of which 18.8% had any TDRM, and 71.7% had LS infections, of which 16.8% had any TDRM (PR=1.12; CI=1.02–1.22). TDRM prevalence for NNRTI was higher in recent (10.9%) than LS (8.3%) infections (PR=1.31; CI=1.16–1.49).

Conclusions: Compared to all diagnosed infections, infections among MSM had a higher prevalence of any TDRM, most frequently NNRTI-associated mutations. Among MSM, TDRM prevalence was highest in the youngest age group and those recently infected, and prevalence of class-specific TDRM varied by city. These findings underscore the importance of timely resistance testing among MSM to identify drug resistance early in infection and ensure optimal ART provision, viral suppression, and reduced transmission.

580 Primary Resistance To Integrase Strand-Transfer Inhibitors in Europe

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Background: Primary HIV-1 resistance can compromise the efficacy of antiretroviral therapy (ART). The prevalence of primary resistance to integrase strand-transfer inhibitors (INSTI) in recently HIV-1-infected subjects remains unknown.

Methodology: This was a multicenter cross-sectional study within the European SPREAD surveillance programme which continuously collects data from a representative set of newly diagnosed patients. A representative set of 300 samples from 1950 patients diagnosed in 2006/2007 was selected from the main cohort. The prevalence of INSTI resistance was evaluated using quality controlled baseline population sequencing of integrase (IN). A subset of 20% were further evaluated using 454 IN sequencing. For both analyses, we assessed major mutations based on the IAS-USA mutation table. All integrase substitutions were classified according to their Stanford HIVdb score ≥10 for at least one INSTI. Minority variants (MV) were defined as substitutions present in 1-20% of viruses in the 454 analysis. Subtypes were determined from population sequencing data using the Rega Subtyping Tool vs 2 based on pol.

Results: For the population sequencing analysis, 279 samples were retrieved and successfully analysed. 67% of isolates were subtype B. No signature resistance mutations to INSTIs (N155H, Q148H/R/K Y143R/H/C) were detected. In 11 (4%) patients the following mutations on resistance associated positions were detected with HIVdb score≥10: L74M (n=2; 1%), T97A (n=2; 1%), E138A, A153F, E157Q (n=2; 1%), G163KT, R263K, V151I + G163EKR. In 31 (11%) patients mutations with HIVdb score <10 were found: L68I, L68V, L74I (n=13; 4.6%), L74V, T97S, A128T (n=2, 1%), E138D (n=2; 1%), E138G, G140W, V151I (n=6; 2%), 68V + L74V, 143DN + Q146E (n=1; 0.4%). Subsequently 56 samples were analysed with 454 sequencing. Median overall coverage was 4294 reads/substitution. Again, no signature mutations were detected. IN substitutions with HIVdb score≥10 were found in 7 (12.5%) subjects: E157Q in 5 (8.9%) subjects, 1 as MV; H51Y and G163R in 1 (1.7%) subject each, both as MVs; and G163K in 1 (1.7%) individual. IN mutations with HIVdb score <10 were: V151I in 6 (10.7%), 3 as MVs; L74I in 3 (5.3%), 1 as MV; and A128T, N155D, H51Q and T97I in 1 (1.7%) subject each, all as MVs.

Conclusions: As expected, no signature INSTI-resistant variants were circulating in Europe before the introduction of INSTIs, either as high- or low-frequency variants. However, polymorphisms contributing to INSTI resistance were not rare. As INSTI use becomes more widespread, continuous surveillance of primary INSTI resistance is warranted. These data provide a baseline for that purpose and will be key to model the kinetics of INSTI resistance transmission in Europe in the coming years.

581 Antiretroviral Drug Resistance Among HIV-Infected Black Men Who Have Sex With Men in the US

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Background: In the United States (US), Black men who have sex with men (MSM) are disproportionately affected by HIV. Understanding the current prevalence and patterns of antiretroviral (ARV) drug resistance in this population is important since ARV drug resistance can lead to treatment failure and limit treatment options. We analyzed ARV drug resistance among Black MSM from the HIV Prevention Trials Network (HPTN) 061 study. The HPTN 061 study enrolled 348 HIV-infected Black MSM (classified as newly or previously diagnosed) and 1,167 HIV-uninfected Black MSM from six major cities in the US.

Methodology: The ViroSeq HIV-1 Genotyping System was used to analyze ARV drug resistance in men who had a viral load >400 copies/mL at enrollment (N=171) or seroconversion (N=22). Eighty-three of the 171 men were classified as newly diagnosed (including 3 with acute infection and 11 identified as recently infected using a multi-assay algorithm); 88 were classified as previously diagnosed (including 31 who reported that they were in care). Samples were also tested for the presence of ARV drugs.

Results: Genotyping results were obtained for 168 (98.2%) of the 171 men who were HIV infected at enrollment and for all 22 seroconverters. ARV drug resistance was detected in 48 (28.6%) of the 168 men, including four (36.4%) of 11 men with recent HIV infection; none of the three men with acute infection had resistance. Nineteen (11.3%) of the 168 men had multi-class drug resistance (MCR), including two with resistance to all three major classes

of ARV drugs. Five (22.7%) of the 22 seroconverters also had drug-resistant HIV. The prevalence of drug resistance significantly differed by city: Boston, 7/14=50%; San Francisco, 5/10=50%; Los Angeles, 17/41=41.5%; New York City, 10/50=20%; Atlanta, 5/29=17.2%; Washington DC, 4/24=16.7% (P=0.01). ARV drug testing revealed that some men with ARV drug resistance were on failing ARV treatment regimens. Both ARV drug resistance and MCR were more common among men >30 years of age (P=0.02 and P=0.002, respectively). MCR was more common among men classified as previously diagnosed than among men classified as newly diagnosed (P=0.003) or seroconverters (P=0.02).

Conclusions: ARV drug resistance, including multi-class and transmitted drug resistance, is common among Black MSM in the US. In three of the six cities studied, >40% of the men had resistance. Overall, 11.3% of the men had MCR. Furthermore, 25% of the newly-infected men (acute infection, recent infection, seroconverters) had resistance, which most likely reflects transmission of resistant HIV strains. These findings underscore the public health importance and urgency of scaling up culturally appropriate and acceptable programs to engage Black MSM in care and promote adherence to ARV treatment.

582 Impact of Transmitted Drug Resistance On Susceptibility To First-Line HAART in France (2010-2012)

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Background: As recommended by the ANRS program for HIV-1 resistance surveillance, we estimated prevalence of transmitted drug resistance mutations (RAMs) and the evolution of the viral molecular epidemiology in primary HIV-1-infected patients in France.

Methodology: 796 primary HIV-1-infected patients were included in 2010-2012 (404 from the AC11 ANRS Group, 302 from the PRIMO Cohort and 90 from the OPTIPRIM trial). Genotypic resistance studies were performed on protease, reverse transcriptase and integrase genes. Reverse transcriptase (RT) and protease mutations were identified from the list for genotypic surveillance of transmitted HIV-1 drug resistance (Bennett et al, 2009). Concerning etravirine (ETR), rilpivirine (RPV) and integrase inhibitors (INI), we used the list of mutations identified from the ANRS resistance algorithm and the latest IAS-USA resistance mutations list. HIV-1 subtype was determined after phylogenetic analysis of the RT sequences.

Results: At inclusion, median viral load and median CD4 cell count were 5.5 log10 copies/ml [range: 1-8.14] and 490 cells/ml [range: 6-1600] respectively. Prevalence of viruses with reverse transcriptase or protease RAMs was 10.7% (85/796). Prevalence of NRTIs, NNRTIs and PIs RAMs was 5.2%, 7.3% and 2.0%, respectively. RPV and/or ETR RAMs were observed in 3.3%. Resistance to 2 or 3 classes of ARV was observed in 2.4% of patients. Integrase RAMs were observed in 1.5% (5/332, E157Q). Frequency of RAMs was higher in patients infected with B subtype compared to non-B (13.4% (72/535) vs 6.9% (18/261), P=0.006). MSM tended to be more frequently infected with resistant virus than heterosexual patients (12.1% (73/602) vs 8.1% (12/148), P=0.17. We observed an increase in frequency of virus with NNRTIs RAMs in 2010/12 compared to 2005/06 study (7.3% vs 4.6%) because of the recent survey of etravirine and rilpivirine RAMS.

Although subtype B still predominates in France (67%), the frequency of non-B viruses increased significantly in patients with PHI between 2010-2012 (33%) and 1996-1998 (10%). CRF02_AG was the most predominant non-B subtype (53.6%), because of the close links between France and West-African countries. However, we also described 121 strains belonging to 6 other subtypes and 12 other CRFs, and 1 group N virus (found in a patient originated from Togo), reflecting the exceptional viral diversity of the French epidemic.

Conclusions: In France in 2010-2012, the global prevalence of transmitted drug-resistant variants was 10.7% stable since 1996, and higher in B subtype infected patients. However, more than 95% of viruses are sensitive to French and WHO first line recommended HAART.

583 Persistence of Transmitted HIV-1 Drug Resistance Mutations Associated With Fitness Costs

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Background: Transmitted HIV-1 drug resistance mutations (TDR) can impair antiretroviral treatment (ART) but the persistence of many TDRs is poorly understood. We determined persistence times for TDR in treatment-naïve patients from longitudinal genotypic resistance tests (GRT) from the Swiss HIV Cohort Study Drug Resistance Database, and compared persistence times with fitness cost of TDRs.

Methodology: TDR were defined according to the WHO surveillance list. Sequential plasma samples from treatment-naïve individuals carrying TDR within the protease (PR) or reverse transcriptase regions (RT) were retrospectively sequenced. All GRT from treatment-naïve individuals with ≥ 2 GRT and TDR at baseline were included. We performed a Kaplan-Meier survival analysis for each single TDR carried by ≥ 5 individuals at baseline. We used Poisson regression to infer reversion rates (RR) for each TDR and thus were able to quantify persistence times. We estimated fitness costs of TDR in the genetic background in which they occurred. To this end we used a previously published and validated machine learning algorithm based on 70000 in-vitro replicative capacity measurements from Monogram Biosciences. Since negative fitness costs of resistance mutations are not reliable predictors, we focused the analysis on mutations with positive median fitness costs. Hazard Ratios (HR) were calculated with Cox-proportional-hazard models.

Results: Retrospective PR/RT sequence analysis was conducted on 918 samples from 210 treatment-naïve patients.Fulfilling all criteria, we included 633 sequential GRT from 155 treatment-naïve patients for our analysis. Twenty-one TDR were analyzed: NRTI=12, PI=6, and NNRTI=3. Persistence times varied considerably. Among all, the shortest persistence was the NRTI mutation T215Y with a reversion rate (RR) per 100 person-years (95% CI) of 72.71

(37.83, 139.75); whereas the longest was the NRTI mutation K219Q (RR=1.95 [0.27, 13.81]). RR was strongly associated with the fitness of individual mutations. This was particularly the case when comparing the same mutation occurring in different patients (and therefore in the context of different genetic backgrounds): The RR for mutations among the highest fitness-cost tercile was increased by a HR [95% CI] of 2.5 [1.4,4.4] (p=0.006) compared to mutations of the lowest tercile.

Conclusions: Our results show large variations in RR across different TDRs. Furthermore, even the same mutation may revert more rapidly or slowly depending on whether the overall genetic background exacerbates or compensates the mutation's fitness cost.

Session P-L2 Poster Session
Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Acquired HIV Drug Resistance

584 High HIV Resistance and Mutation Accrual at Low Viral Loads Upon 2nd-Line Failure in Western Kenya

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Background: World Health Organization (WHO) defines antiretroviral treatment (ART) failure as HIV viral load (VL) >1000 copies/mL in resource limited settings (RLS). 2nd-line ART failure with drug resistance can limit subsequent regimens, more in settings with limited VL and resistance testing and delayed failure diagnosis. Resistance data upon 2nd-line failure in RLS are limited, particularly below the WHO VL threshold.

Methodology: We examined 2nd-line failure, drug resistance and their correlates in western Kenya, in patients on ≥6 months lopinavir/ritonavir-based 2nd-line, after ≥6 months prior 1st-line ART. Patients with detectable VL had *pol* genotyping and follow-up peripheral blood mononuclear cells (PBMC) and plasma re-genotyping.

Results: 401 patients were enrolled, mean age 42 years, 60% female, median CD4 278 cells/μL, mean detectable VL 52,480 copies/mL, median 1.9 years on 2nd-line, median 2.8 years on prior 1st-line ART. 49% had detectable VL>40; 24% >1000 copies/mL. Lower CD4 count (Odds Ratio (OR) 0.70 per 100 cells, p<0.001), longer duration of ART interruption on 1st-line (OR 1.18 per month, p=0.03), shorter time on 2nd line (OR 0.83 per year longer, p=0.008), tuberculosis treatment on 2nd-line (OR 2.67, p=0.01), and ≥1 pregnancy (OR 2.35, p=0.01) were associated with VL>1000. 182 genotypes were available (109 plasma; 73 PBMC), 57% subtype A, 24% D and 19% other. Any plasma resistance was seen in 78%; 67% to nucleoside reverse transcriptase inhibitors (NRTIs), 73% non-NRTIs (NNRTIs) and 8% protease inhibitors (PIs); 63% had 2 or 3-class resistance. Archived resistance was seen in 78%. Of 37/109 patients with detectable VL<1000 and available sequences, 78% had any, and 71% 2 or 3-class resistance. Archived resistance was seen in 84% of available sequences from patients with detectable VL<1000. Patients with VL<1000 had more resistance mutations than those with VL≥1000 (rate ratio 1.47, p=0.02), mostly due to NRTI mutations (rate ratio1.89 p=0.002). Of 48/109 patients with follow up sequences after median 1.8 months on similar 2nd-line, 42% accumulated mutations, responsible for a predicted increase to intermediate or high-level resistance in 70% of patients. Of those, 8/20 (40%) patients had VL<1,000. Factors associated with resistance accumulation included higher CD4 (OR=1.55 per 100 cells higher, p=0.03), male gender (OR=3.92, p=0.04), older age (OR=1.07 per year older, p=0.04), and WHO stage 1 (OR=7.0, p=0.03).

Conclusions: We report high rates of 2nd line ART failure, circulating and archived drug resistance and resistance accumulation in a large HIV treatment program in western Kenya, including at VL levels below the WHO threshold for ART failure. These findings mandate careful strategic planning for ART and for VL and resistance monitoring in RLS.

585 Drug Resistance After 2nd-Line Failure Can Be Managed Using WHO-Recommended Regimens in Nigeria

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Background: In sub-Saharan Africa only a limited number of antiretroviral drugs is available. Virological failure, and subsequent drug resistance, during second-line treatment can therefore have substantial clinical ramifications as it can result in complete loss of therapeutic options. The Institute for Human Virology-Nigeria (IHVN), a US PEPFAR implementing partner, provides antiretroviral therapy (ART) to over 150,000 public and private sector patients through the AIDS Care and Treatment in Nigeria (ACTIONPlusUp) Program. We determined the extent to which virological failure during second line treatment with LPV/r, ATVr results in the loss of treatment options to WHO recommended treatment regimens at two IHVN PEPFAR supported sites in Abuja.

Methodology: Plasma samples from patients who failed LPV/r and ATV/r- based second-line regimens from January to August 2013 were assayed for HIV-1 RNA viral load (VL). Plasma virus from samples with VL >1000 cp/mL at time of failures were sequenced in the pol gene. The genotypes were interpreted using the Stanford HIV db interpretation program (version 6.3.1). We assigned the following genotypic susceptibility scores (GSS) to the 5 levels of resistance included in the Stanford HIV db program: 0, 0.25, 0.50, 0.75, and 1 for respectively the high-level resistance, intermediate resistance, low-level resistance, potential low-level resistance, and susceptible. We then calculated the GSS to the first-, second-, and third-line regimens recommended by WHO as the arithmetic sum of the individual GSS. We defined loss of drug options as a GSS of zero to any WHO recommended regimen. Exhaustion of drug options was defined as a GSS<2.

Results: Of the 936 HIV-infected patients receiving second-line ART, 56 (6.0%) were adults with confirmed virological failure. The mean (SD) HIV RNA and age were 5.1log10 (0.79) cp/mL, and 34.8 (15.6) years, respectively. A total of 9 sequences contained no drug resistance mutations. The five most frequently observed mutations were K103N (22.4%), M184V (20.4%), M41L (20.4%), M46I (19.4%) and I54V (15.3%). Complete loss of treatment options was only found in one patient (2%), with virus still susceptible to a second generation NNRTI. Exhaustion of drug options to first- and second line regimens was found in 16 patients (32%). If second generation NNRTIs and newer boosted protease inhibitors become available, then exhaustion of drug options will be reduced to 22%.

Conclusions: Complete loss of treatment options is very rare after failure to second-line treatment in Nigeria. Exhaustive loss of treatment options occurs in less than one out of three patients and can be partially avoided by providing third-line regimens. In most patients an active treatment regimen can be given after failure with second-line treatment.

586 Sociodemographic Determinants of HIV Drug Resistance in British Columbia, Canada

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Background: Baseline clinical factors and adherence to HAART are associated with resistance development after therapy. However, the interplay between sociodemographic and clinical factors influencing resistance development has not been well examined at a population level.

Methodology: A cohort of HIV-positive persons accessing treatment from the BC-CfE Drug Treatment Program (DTP) from 1996-2012 was followed longitudinally. Census-level sociodemographic (SD) predictors of uptake of HIV drug resistance testing were determined using multivariable GEE logistic regression. The determinants of the emergence and detection of drug resistance in the subset of ARV-naïve persons initiating HAART in the BC-CfE DTP was assessed with Weibull survival analysis. In brief, patients were grouped by Census Tract (CT) of residence at time of enrollment. Census level SD variables (population density, % single family housing, % immigrants, median income, education and unemployment levels) were assigned by CT. Models were adjusted for individual level clinical variables including baseline plasma viral load, CD4, gender, age, risk factors, physician experience and adherence. All available HIV protease-RT sequences (N~33,000) were used.

Results: A total of 11,083 DTP patients, including a subset of 5381 ARV-naïve at HAART initiation, were followed longitudinally. Of the 9310 (84%) patients with at least one post-therapy plasma sample eligible for testing (pVL>250 c/mL) only 4751 (51%) had a physician-ordered resistance test; however the proportion of samples tested markedly increased with calendar year ($p<0.001$). In univariate models, all SD variables investigated were significantly associated with uptake of testing and/or development of HIV resistance. After adjustment for individual-level clinical variables and adherence, an increased hazard for first resistance event was observed for persons living in CTs with higher unemployment levels (HR 1.08; $p=0.004$ per 10% increment) driven largely by the emergence of 3TC/FTC resistance (HR 1.12; $p<0.001$). However, persons living in CTs with higher proportions of single family residences (HR 0.65; $p=0.01$) and post-secondary education (HR 0.92; $p=0.009$ per 10% increment) were at decreased risk of NNRTI resistance. No SD factors were associated with resistance to other NRTIs or PIs.

Conclusions: HIV drug resistance was observed across all sociodemographic strata regardless of adherence levels. Unemployment rate within a census tract, a surrogate for lower socioeconomic status, was associated with an increased risk of resistance. However, the complex relationship between census-level SD variables makes it difficult to identify specific social groups or geographic locations at higher risk of developing resistance in BC.

587 Week 144 Resistance Analyses of the Phase 3 EVG/COBI/FTC/TDF Studies

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Background: Two phase 3, randomized, blinded, studies of elvitegravir/cobicistat/emtricitabine/tenofovir DF (EVG/COBI/FTC/TDF) in treatment-naïve subjects are ongoing (Studies 102 and 103). The week (W) 144 responses (Missing = Failure) were durable and similar for EVG/COBI/FTC/TDF vs. efavirenz ([EFV]/FTC/TDF) (82% vs 78%) and EVG/COBI/FTC/TDF vs. ritonavir-boosted atazanavir (ATV+RTV)+FTC/TDF (81% vs 79%). Resistance analyses through W144 are presented.

Methodology: HIV-1 genotypes (PR and RT) were analyzed at screening (GeneSeq, Monogram Biosciences); subjects with resistance to FTC, TDF, EFV, or ATV were excluded based on study. Retrospective integrase (IN) genotyping was conducted on 363 EVG/COBI/FTC/TDF baseline samples. Virologic failures had genotypic/phenotypic analyses at confirmed failure and baseline for PR, RT, and IN, or at first failure (EVG/COBI/FTC/TDF only) (Monogram and Labcorp).

Results: EVG/COBI/FTC/TDF subjects with baseline PI (N=18) or NNRTI mutations (N=95) including K103N in RT (N=27, Study 103) had high virologic response through W144 (82% for K103N). Baseline primary IN strand transfer inhibitor (INSTI) mutations were rare (N=4/337); all EVG/COBI/FTC/TDF subjects with T97A [N=3] and Y143H [N=1] rapidly suppressed and had W144 HIV-1 RNA <50 c/ml. In the EVG/COBI/FTC/TDF groups through W144, 18 subjects (2.6%; 18/701) developed primary INSTI (N=15) and/or NRTI resistance mutations (N=17) (Any resistance: 13 through W48, 3 between W48-W96, and 2 between W96-W144). Emergent INSTI mutations were E92Q (N=9), N155H (N=5), Q148R (N=3), T66I (N=2) and T97A (N=1) and emergent NRTI mutations were M184V/I (N=17) and K65R (N=5). In the EFV/FTC/TDF group, 14 subjects (4.0%; 14/352) developed drug resistance (8 through W48, 2 between W48-W96, and 4 between W96-W144) and was most commonly K103N (N=13) with M184V/I (N=4) plus K65R (N=3) in RT. In the ATV+RTV+FTC/TDF group, 2 subjects had M184I emerge post-W96. The first failure samples from 16 STB patients with emergent resistance were

retrospectively analyzed and failed to detect the known resistance in >50% of these patients due to either assay failures or successful genotypes in which no resistance was detected (N=5/16).

Conclusions: Treatment with EVG/COBI/FTC/TDF achieved durable high rates of virologic suppression in HIV-1 treatment-naïve subjects, including subjects with pre-existing NNRTI or PI resistance. Resistance development was infrequent (2.6% of STB-treated subjects). The most common patterns of resistance mutations to EVG/COBI/FTC/TDF were E92Q, Q148R, or N155H in IN with M184V/I in RT which were more readily detected at the confirmed virologic failure timepoint.

588 Emergent and Detectable Proviral DNA Drug Resistance in a Community Treatment Program

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Background: Drug resistance mutations (DRM) may circulate in HIV RNA and persist in CD4 cell DNA despite antiretroviral therapy (ART). To determine risks for transmission and community reservoirs of DRM, DNA genotype was assessed from PBMC DNA of viremic and suppressed ART recipients in a community clinic population.

Methodology: HIV-1 sequences from consecutive consenting patients on ART were enrolled and followed 6 monthly for 2 years. Viremic subjects (>50 copies/ml of RNA) had genotypes from plasma RNA and PBMC DNA, and those suppressed (< 50 copies/ml of RNA) from PBMC DNA only. Phylogenetic relationships were inferred using the Neighbor Joining method, with 2 Kimura parameters and 1000 bootstrap replicates. Statistical comparisons of median values were performed by non-parametric Rank-sum tests.

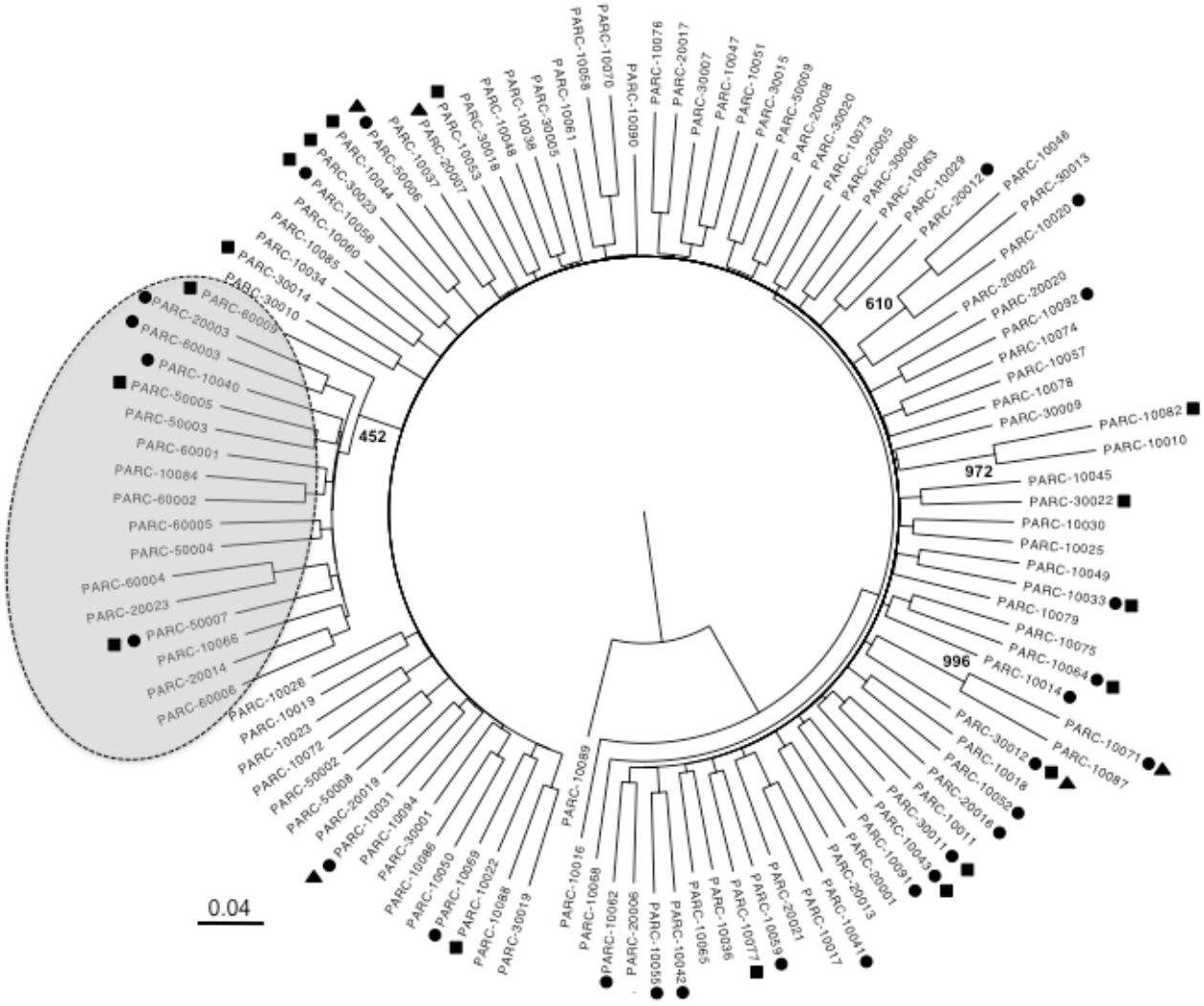

Figure 1: Neighbor Joining of pol sequences from proviral DNA, with 1000 bootstrap replicates. ● = NRTI resistance (25) ■ = NNRTI resistance (17) and ▲ = PI (5) resistance. Shaded sequences the cluster of 17 AA.

Results: Of the 124 individuals (27 female, 96 male and 1 transgender) 35 were African-American (AA), 30 Hispanic, 12 Asian and 47 White. The 38 viremic subjects had a median viral load and CD4 cell count of 5,865 copies/ml and 298 cells/mm3; 24/38 (63%) were wild-type (WT) and 12 (27%) had the same DRM in both RNA and DNA (concordance of 89%). Two had M184V in DNA but not in RNA and 2 in RNA but not DNA. Among the 12 with DRM, the median CD4 was significantly lower compared to those who were WT, 276 vs 381 cells/mm3 ($p<0.01$).

Among 86 suppressed individuals, 37/86 (43%) had one or more archival DRM; 9 had 2 classes and 1 had 3 classes of DRM. CD4 cells counts were similar between 35 with and 51 without DNA DRM (413 vs 427 cells/mm3).

Eleven of 86 (13%) of those suppressed at entry developed virologic failure by 48 weeks. DRM developed in plasma RNA of 6/11 (55%), 3 who were DNA WT and 3 with DNA DRM at entry.

Phylogenetic analysis (Fig 1) showed related sequences included 2 pairs of men with bootstrap values of 97 and 99 % and one trio (2 men and 1 woman) 61%. Seventeen older AA injection drug users (IDU) clustered with a low bootstrap value (45%).

Conclusions: Analysis of DNA genotype may guide treatment and identify transmission networks. DRM in archival DNA may pose a risk of transmission and re-emergence of resistance at failure and may limit future treatment options. The weak bootstrap linkage among a cluster of 17 older AA men and women who were former IDU, suggests a distant founder effect in this population.

589 Acquired Drug-Resistance Mutations and Mortality Among HIV Patients On First-Line ART

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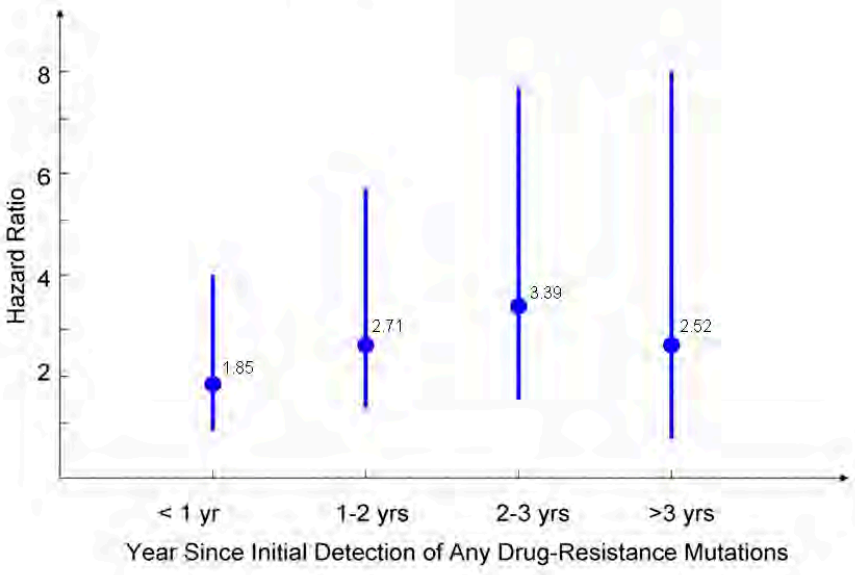
Background: The potential long-term clinical risks of staying on failing nucleoside reverse-transcriptase inhibitor/non-nucleoside reverse-transcriptase inhibitor (NRTI/NNRTI)-based first-line antiretroviral treatment (ART) regimens and acquired drug-resistance mutations (DRMs) have not been well elucidated.

Methodology: The study population included adult HIV patients who were initially ART-naive and who started first-line regimens between 2003-2005 at two sentinel sites in China. ART regimens were either AZT/DDI/NVP or D4T/DDI/NVP, primarily. Given the national treatment program policy at that time, patients had no access to protease-inhibitor-based second-line regimens and remained on first-line despite virologic failure for prolonged periods. HIV RNA and CD4 testing were performed at pre-ART baseline and every 6 months (including after virologic failure). Patients with HIV RNA>1,000 copies/ml on ART had longitudinal genotyping to test for drug resistance. We estimated the effects of acquired DRMs on mortality, using marginal structural models to account for time-varying confounding.

Results: Five hundred seventeen patients were included. After median 58 months follow-up, 404 (78%) patients had HIV RNA>1,000 copies/ml at least once, and 291 (56%) of the 517 had DRMs. At initial detection of DRMs, all patients but one had >1 NNRTI-class mutation and 63% had both NRTI- and NNRTI-mutations. Seventy six (15%) patients died. Patients were more likely to develop DRMs if they had HIV RNA > 10,000 copies/ml at baseline (HR=1.42) or at the previous visit (HR=1.39), CD4 count < 350 cells/mm3 at the previous visit (HR=1.92), no education beyond elementary school (HR=1.35), used alcohol (HR=1.43), were farmers (HR=1.49), initiated ART in 2003 (HR=2.77) or 2004 (HR=1.79). The mortality hazards ratio for acquired DRMs was 2.49 (95% confidence interval: 1.38-4.51) after adjusting via inverse-probability-weights (IPW) for baseline (including age, gender, occupation, site, education level, marital status, alcohol use, calendar time of treatment initiation, level of initial adherence, baseline CD4 count and viral load) and time-varying confounders (modification of first-line ART regimens, CD4 count and HIV RNA at the previous visit). The hazard ratio increased over time since first detection of DRMs (see Figure 1).

Conclusions: We identified an elevated risk of mortality associated with acquired DRMs. The excess risk increased with time since first detection of DRMs.

Figure 1. IPW hazard ratios for mortality with the development of any DRM versus no mutation, over time



590LB PrEP Exposure and the Risk of Low-Frequency Drug Resistance

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Background: Pre-exposure prophylaxis (PrEP) reduces HIV acquisition. However, for those who acquire HIV while receiving PrEP there is the potential for drug resistance to arise as a result of partial HIV suppression through PrEP medication exposure before HIV seroconversion is detected. The level of resistance selected by PrEP may not be detectable with standard sequencing methods, which only detect resistance present at frequencies above 20% of the viral population. Studies of antiretroviral treatment failure have suggested that resistance as low as 1% may be clinically significant during subsequent antiretroviral use. 454 ultra-deep sequencing can detect resistance at frequencies below 1%.

Methodology: In the Partners PrEP Study, a randomized trial of daily oral tenofovir disproxil fumarate (TDF) or tenofovir plus emtricitabine (FTC), plasma samples from the time of HIV seroconversion were tested for predefined mutations that could be selected by TDF (K65R and K70E) and FTC (K65R and M184IV) using 454 ultra-deep sequencing. Samples were considered resistant if the proportion of mutant sequences was significantly above that observed in wild-type genotype-matched controls using Fisher's exact test with correction for a 5% false-discovery rate. Plasma levels of tenofovir were measured among seroconverters in the active PrEP arms at the time of seroconversion. Fisher's exact test was used to determine associations with resistance.

Results: A total of 121 seroconverters were tested: 38 had received TDF, 25 FTC-TDF, and 58 placebo. PrEP-related resistance mutations (K65R, K70E and/or M184IV) were detected in 9 (7.4%) at levels >1%, 2 of which had previously been detected by standard sequencing. In the TDF arm, 2 of 38 (5.3%, p=0.65 vs placebo) had resistance >1%: 1 had K65R/K70E and 1 had M184IV. In the FTC-TDF arm, resistance was detected in 5 of 25 (20%, p=0.024 vs placebo): 4 had M184IV alone and 1 had M184IV/K65R. Two of the 58 (3.5%) placebo participants had M184IV resistance. Resistance was detected in 3 individuals retrospectively determined to be HIV infected (seronegative but RNA positive) when PrEP was initiated, and in 6 individuals infected after PrEP start. In seroconverters in the active PrEP arms, PrEP use was associated with higher risk of resistance: 6 of 23 (26%) with measurable drug levels versus only 1 of 39 (2.6%) without evidence of PrEP use had resistance >1% (p=0.009).

Conclusions: High-sensitivity resistance testing detected more resistance than standard sequencing in persons acquiring HIV who were exposed to PrEP, although resistance still occurred in a minority of subjects. More resistance was selected by FTC than TDF, as evidenced by the prevalence of M184IV compared to K65R.

591 Rilpivirine-Associated Resistance in HIV-1 DNA in Suppressed Patients Pretreated by NNRTIs

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Background: First generation NNRTI (efavirenz and nevirapine) failure is associated with a rapid selection of resistance-associated mutations (RAMs) which may impact on etravirine or rilpivirine susceptibility. Unfortunately in well suppressed patients historical resistance genotypes from plasma do not provide information regarding rilpivirine and etravirine-resistance. Our objective was to determine the presence of RAMs to rilpivirine, etravirine and the combination of tenofovir/emtricitabine/rilpivirine on HIV-1 DNA from patients enrolled in the ANRS Easier Trial.

Methodology: All 169 patients enrolled in the ANRS 138-EASIER trial were treatment-experienced, have received three antiretroviral drug classes (NRTI, NNRTI and PI) and had plasma HIV-1 RNA <400 cp/ml at baseline. Patients were treated for a median of 13.6 years and were controlled for at least 2 years. Treatment regimens at baseline were NRTIs (95%), PIs (99%), and NNRTIs (8%). Reverse transcriptase gene (RT) sequencing was performed on extracted HIV-1 DNA from whole bloodat the time of inclusion. We analysed the pattern and the prevalence of RAMs to rilpivirine, etravirine, tenofovir and emtricitabine according to the 2012 ANRS v22 algorithm.

Results: RT gene amplification was successful in 128/169 (76%) patients and 95% of HIV-1 as subtype B. Rilpivirine RAMs were detected in 40/128 (31%) of patients, with highest frequency for the mutations Y181C/I/V (23/40, 18%), K101E/P (9/40, 7%) and E138A/G/K/Q/R/S (8/40, 6%). Etravirine RAMs were detected in 5/128 (4%) of patients. Resistance to emtricitabine and tenofovir were detected in 72/128 (56%) and 12/128 (9%), respectively. Resistance to at least one drug included in the combination of tenofovir/emtricitabine and rilpivirine was observed for 88/128 (69%) patients.

Conclusions: In patients with suppressed viremia under ART, but who had previously failed efavirenz and/or a nevirapine-based regimen, the prevalence of resistance in HIV-1 DNA was high for rilpivirine (31%) and for the combination of tenofovir/emtricitabine/rilpivirine (69%). Conversely, resistance to etravirine was rare (4%). This result confirms that the switch to rilpivirine-based regimen should not be recommended in patients that previously failed to efavirenz and/or nevirapine-containing treatment.

592 Etravirine/Rilpivirine-Specific Mutations Selected by EFV and NVP in Kenyan Patients Failing ART

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Background: Antiretroviral drugs may produce different mutation patterns in different HIV-1 subtypes. We report here on the appearance of drug resistance mutations unique to etravirine and rilpilvirine exposure occurring in Kenyan patients with non-B subtypes failing first line therapy with neviripine or efavirenz.

Methodology: RV288 is a multi-center PEPFAR Basic Program Evaluation that is being conducted in Kenya, Tanzania, Uganda and Nigeria. This cross-sectional study will estimate the rate of virologic suppression of patients on first-line HAART in PEPFAR clinics and identify predictors of virologic suppression and immunologic recovery. Patients on HAART for at least 6 months were randomly selected from 7 different hospitals for a one-time study visit. Labs performed included a viral load, clinical chemistries and hematology, absolute CD4+ lymphocyte count and CD4+ cell percentage. Subjects with a viral load > 1000 cps/ml were referred for adherence counseling while a sample was submitted for genotypic resistance testing. Viral load (HIV RNA) was quantified from plasma by PCR using Roche Amplicor Version 1.5 with lower detection limit of 400 copies/ml.

Results: We found 617 out of 975 subjects (63%) had viral load <400cps/ml. Of 215 samples submitted for resistance testing, 115 (53%) had one or more resistance mutations. Interestingly, 14 of these subjects (13.8%) had an amino acid substitution at reverse transcriptase position 138 (A, G, K or Q; Table 1). These mutations are selected by etravirine and rilpivirine in subtype B viruses, reducing viral susceptibility to these drugs. Yet no subject had ever been exposed to either of these drugs. All subjects were failing either on efavirenz or nevirapine, which are not reported to produce mutations at this position, at least for subtype B viruses. All subjects had subtype A1 or D virus.

Conclusions: The potential for patients to acquire E138 mutations from efavirenz or nevirapine has not previously been reported. This increases the chances of patients failing these drugs to have cross resistance with etravirine and rilpivirine, which can occur by other mutations as well (e.g. Y181C,I; M230L) and emphasizes the importance of resistance testing in resource-constrained settings.

593 Detection of NNRTI Resistance Mutations After Interrupting NNRTI-Based Regimens

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Background: There is evidence that NNRTI mutants emerge after ART interruption (ATI) of suppressive NNRTI-based ART, due to the long half-life of NNRTIs. This has implications for both loss of treatment options for people undergoing ATI (e.g. due to poor adherence or stock-outs) and potential transmission of drug resistance. The aim of this study is to quantify the extent to which NNRTI mutations can be detected in the rebound viremia following ATI of suppressive NNRTI-based ART.

Methodology: The study population comprised patients in the UK HIV Drug Resistance Database who interrupted a suppressive NNRTI-based regimen, defined as viral load (VL) consistently <200 copies/ml after at least 6 months on ART and who had no evidence of NNRTI-mutations on previous resistance tests. NNRTI mutations in IAS December 2008 list were considered. Crude and adjusted relative risks (RR) of having NNRTI resistance detected in the rebound viremia after interruption were calculated using a modified Poisson regression approach. Covariates considered included demographic variables, antiretroviral drugs experienced, length of virologic suppression, time from ATI to resistance test, CD4 count nadir, CD4 count at ATI and at resistance test, VL at ATI, maximum VL ever measured and subtype.

Results: Of 1,636 eligible patients, 208 (13%; 95% CI: 11-14) had a resistance test performed after stopping suppressive NNRTI-based ART. They were either on EFV (39%) or NVP (61%) most commonly in combination with 3TC (85%) and/or AZT (63%). ART interruptions occurred after a median of 12 months since starting ART (IQR: 5-32 months). Among these, 25 (12%, 95% CI: 8-17) had ≥1 NNRTI resistance mutation detected at the first resistance test following ATI, a median of 12 months after ATI (IQR: 3-20 months). Similar rates of resistance were observed in patients with simultaneous (n=188) and staggered interruptions (n=20). The most common mutation found was K103N (64%), followed by G190A (12%), while K101E, V108I, Y181C, L100I, V106A, Y188L and P225H were found in 8% (n=2) or less. In multivariate analysis (including as covariates CD4 at ATI, CD4 nadir and being on NVP at ATI), the only independent predictor of NNRTI resistant mutations was a lower CD4 count nadir (RR per 100 cells higher = 0.67; 95% CI: 0.53-0.85).

Conclusions: To our knowledge this is the largest study to evaluate the detection of NNRTI resistance in the rebound viremia that follows interruption of a suppressive NNRTI-based regimen. It confirms that resistance is a relatively common phenomenon, occurring in 12% of patients tested. These estimates support the concept that interruption of EFV or NVP based ART carries a significant risk to the patient and inform models that incorporate HIV drug resistance emergence.

594 HIV-1 Resistance Outcomes in Seroconverters From MTN 003 (VOICE)

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Background: The emergence of drug resistance is a major concern when using antiretroviral agents for HIV prevention. Of six HIV prevention trials that included tenofovir (TFV)-based study products, only 3 cases of resistance have been reported in 155 participants who acquired HIV after enrollment and seroconverted on product. We evaluated seroconverters in MTN 003 (VOICE) for TFV, emtricitabine (FTC) and transmitted resistance.

Methodology: 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 as soon as HIV infection was confirmed, a median of 13 days (IQR 16 days) after seroconversion was detected by a positive rapid test and the participant had been withdrawn from study product. Population sequencing of the protease and reverse transcriptase (RT) genes (ViroSeq, Abbott) was performed on seroconverters with plasma HIV-1 RNA levels ≥ 200 copies/ml using kit-provided or alternate primers. Resistance mutations were identified using the Stanford Genotypic Resistance Interpretation Algorithm.

Results: HIV-1 genotypes were obtained for 355/368 (96%) participants, including 21/22 infected at enrollment, 301/312 HIV-1 seroconverters on study product, and 33/34 who seroconverted between product cessation and study termination. Of the 212 participants in TFV gel, TDF or TDF/FTC arms, no participant had resistance to tenofovir (K65R or K70E). Only 1/55 (1.8%) seroconverter randomized to TDF-FTC who acquired HIV-1 after enrollment developed M184M/V after 309 days on product. Of 9 participants on the TDF-FTC arm already infected at enrollment, 2 (22%) developed M184M/I/V after 26 and 29 days of reported product use. 8/355 (2.3%) participants from all arms had transmitted resistance to nevirapine or efavirenz (K103N/V106M and/or Y181C) while 34 (9.6%) participants had additional RT mutations from the 2009 World Health Organization transmitted drug resistance list, including A62V, D67N, T69N, K70R, V90I, A98G, K101E, V106I, E138A/K, V179 E/D/T, T215A and H221Y.

Conclusions: Acquired resistance to antiretroviral products used for HIV prevention was rare (1 of 212 participants receiving active product), with no cases of TFV resistance and one case of FTC resistance. Transmitted RT inhibitor resistance (12%) was more likely than acquired resistance to product (<1%). Low product use in the VOICE trial could explain the low frequency of acquired resistance. Better point-of-care tests are needed to exclude acutely infected individuals from prevention trials.

Session P-L3 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Mechanisms of HIV Drug Resistance

595 Impact of Raltegravir/Elvitegravir Selected Mutations On Dolutegravir Cross-Resistance

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Background: Mutations at position 148 of HIV integrase (IN) represent a major mutational pathway leading to raltegravir (RAL) and elvitegravir (EVG) resistance. Viruses containing certain Q148 mutation profiles are associated with poor dolutegravir (DTG) treatment responses. In this study, we investigated the effect of Q148H/K/R mutations and other RAL/EVG resistance associated IN mutations on DTG susceptibility using panels of patient-derived viruses and site-directed mutants (SDMs).

Methodology: Patient-derived viruses (N=210) containing Q148H/K/R mutations were identified by conventional nucleic acid sequencing. SDMs containing Q148H/K/R mutations alone and in combination with one or more additional IN mutations (L74I/M, E92Q, T97A, E138A/D/K/T, G140A/C/S) were constructed. DTG susceptibility was determined using a pseudovirus luciferase reporter assay (PhenoSense HIV Integrase).

Results: Patient viruses containing Q148H/K/R mutations displayed reduced DTG susceptibility with a median fold change in IC_{50} (FC)=4.6 (range 1.7 to 96.0). Q148K viruses that emerge less frequently than Q148H/R variants exhibited larger reductions in DTG susceptibility compared to Q148H/R viruses. All patient viruses contained one or more additional IN mutations with G140 substitutions occurring most frequently followed by E138 substitutions. Based on the analysis of a panel of SDMs, a single mutation at position 148 did not reduce DTG susceptibility (DTG FC=0.5 to 0.7). However, the addition of a second mutation at position 140 conferred measurable reductions in DTG susceptibility (FC=2.2 to 58). The further introduction of additional mutations at positions 74, 92, 97 and 138 conferred incremental reductions in DTG susceptibility. Q148K SDMs containing additional mutations displayed larger reductions in DTG susceptibility than corresponding Q148H/R SDMs, consistent with measurements in patient viruses.

Conclusions: In **this** study, we evaluated a large panel of patient viruses and site-directed mutants to fully characterize the degree of DTG cross resistance that is conferred by Q148K/H/R mutations in combination with additional RAL/EVG resistance associated mutations.

596 N348I in HIV-1 RT Confers Resistance To Etravirine and Rilpivirine But Restricts the Advent of E138K

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Background: E138K and M184I are mutations associated with clinical resistance to Rilpivirine (RPV) that compensate each other in regard to fitness deficits conferred by each mutation alone (the M184I is a mutation that confers resistance to FTC, a NRTI often used in association with RPV). This was never demonstrated to happen spontaneously for E138K and M184V/I as a result of treatment failure involving 3TC. In order to understand the reasons behind this different behavior of the virus we concentrated our attention on N348I. N348I is a mutation in the connection domain of RT that commonly emerges in treatment experienced patients and that is strongly associated with M184V. N348I compensates for the deficit in enzyme processivity associated with the latter mutation.

We wished to analyze this mutation alone and in association with M184V to assess if N348I can prevent or delay the emergence of E138K under Etravirine and RPV pressure and what the impact is of this mutation on viruses that present E138K.

In order to have a deeper understanding of this process, ultrasensitive techniques (such as AS-PCR) could be useful to assess the presence of minority variants of E138K under 3TC or FTC pressure alone.

Methodology: Site directed mutagenesis was used to construct the plasmids harboring the desired mutations. Selection studies under drug pressure were done in CBMCs and the measurement of HIV replication kinetics was assessed on the basis of p24 levels. To verify the replicative capacity of the recombinant clones containing the mutations a competitive assay was done using TZM-bl cells. These cells were used also for the analysis of phenotypic drug susceptibility. Reverse transcriptase expression and purification were assessed and the susceptibility of RT inhibitors was tested by DNA dependent DNA polymerase activity using recombinant RT enzymes. The processivity of recombinant RT proteins was analyzed using heteropolymeric RNA template.

Results: The results of this study show that the mutation N348I alone or in association with M184V can prevent or delay the emergence of E138K. In addition, N348I can enhance the resistance that E138K confers against ETR and RPV and decrease the replication capacity of E138K virus.

Conclusions: These findings help to explain why the combination of these two mutations (N348I/E138K) confers low replication capacity to HIV and why N348I prevents the emergence of E138K.

597 Analyses of Accessory Mutations in HIV-1 Protease Reveal Interdependent Mechanisms of Resistance

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Background: The HIV-1 protease is crucial to the maturation of budding virions. Low adherence to protease inhibitors due to toxicity cause both primary active site mutations, which result in a loss of enzymatic fitness, and accessory mutations, which restore fitness and stability of the enzyme, to arise. The contribution of accessory mutations in conferring drug resistance has been studied in great detail but remains elusive. Discerning the synergy of both types of mutations to sustain resistance to highly potent inhibitors while perpetuating viral longevity is the basis of this study. Kinetic and structural analyses of four accessory mutations have revealed possible interdependent mechanisms of mutations beyond the active site and their role in drug resistance.

Methodology: In this study, four HIV-1 protease mutants, L76V, L90M, V32I, and V32I+L33F, were characterized for their impact on Darunavir inhibition. Each of the mutants was first tested for DRV susceptibility using a FRET based kinetics assay that measures the fluorescence intensity readout of a hydrolyzed Matrix-Capsid substrate mimic. Each of the four mutants were then co-crystallized with DRV and characterized for changes in static Cα distances, hydrogen bonding, and van der Waals contacts. Using the trajectories from 10ns molecular dynamics simulations the root mean square deviations and fluctuations for each mutant complex was assessed. The trajectories from the simulations were also used to calculate distances for inter and intra- monomeric active site residue pairs to determine the bearing of accessory mutations on active site residues.

Results: Although the four mutations observed in this study do not directly lie within the active site or bind to DRV they each impact various aspects of DRV inhibition including a 22.5 fold change in KI exhibited by the V32I+L33F double mutant. Analyses of the co-crystal structures reveal that while no major changes can be observed in both overall structure and static Cα distances, there are significant changes in van der Waals contacts upon the introduction of L33F. Results from molecular dynamics simulations suggest that each mutation affects DRV binding via a network of intra-monomeric main chain polar contacts to reduce protease susceptibility to DRV by altering the conformations of residues within the active site.

Conclusions: The interdependent mechanisms of resistance employed by the accessory mutations in this study account for loss of susceptibility to one of the most potent HIV-1 protease inhibitors. Detailed structural analyses employing similar methodologies described above could potentially lead to further discernment of the synergy of accessory mutations and aid in proactively meliorating the current HIV-1 protease inhibitor armamentarium.

598LB Two Distinct Mechanisms of Resistance To Allosteric HIV-1 Integrase Inhibitors

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Background:

Allosteric HIV-1 integrase (IN) inhibitors (ALLINIs) are an important new class of HIV-1 inhibitors. ALLINIs bind at the IN catalytic core domain (CCD) dimer interface in the LEDGF/p75 binding pocket. Consequently, they inhibit HIV-1 IN interaction with its cellular cofactor LEDGF/p75 as well as promote aberrant

IN multimerization. Selection of viral strains emerging under ALLINI pressure has revealed mutations at the IN dimer interface near the inhibitor binding site. Here we have investigated A124D and H171T IN substitutions that confer resistance to potent ALLINI BI-D.

Methodology: We used biochemical, x-ray crystallography and virology methods to understand the mechanisms for IN H171T and A124D resistance to ALLINI BI-D. Specifically, we utilized size exclusion chromatography (SEC) and dynamic light scattering (DLS) to monitor BI-D induced aberrant multimerization of IN. Homogeneous-time resolved fluorescence (HTRF)-based assays were used to determine the potency of BI-D for inhibiting IN-LEDGF/p75 interactions. Furthermore, we have solved the x-ray crystal structure of BI-D bound to HIV-1 IN CCD containing the H171T substitution. Additionally, binding free energy calculations were performed on complexes of BI-D and IN(WT and H171T).

Results: Viruses containing the A124D or H171T mutations in IN are significantly resistant to BI-D treatment in infected cells. SEC and DLS analysis of BI-D interactions with purified mutant INs revealed differing mechanisms of resistance with respect to aberrant multimerization. BI-D treatment promoted higher order oligomerization of WT and H171T IN, whereas the compound did not significantly affect A124D IN. However, H171T IN exhibited significantly reduced binding affinity with LEDGF/p75, whereas WT and the A124D IN bound LEDGF/p75 with similar affinities. Furthermore, x-ray crystallography and binding free energy calculations have revealed the importance of the doubly protonated form and the Nd-protonated tautomer states of H171 for binding BI-D and LEDGF/p75.

Conclusions: ALLINI BI-D resistance IN mutations H171T and A124D underscore the inhibitors bimodal mechanism of action. A124D IN overcomes BI-D inhibition by avoiding BI-D induced aberrant multimerization, while the H171T substitution adversely affects BI-D binding to HIV-1 IN and concomitantly affects IN-LEDGF/p75 binding.

599 Impact of CD4 Mimetics-Resistant Mutations On Susceptibilities To Anti-Env nMAbs

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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. In this study, we induced the CD4MCs resistant variants using primary isolate to elucidate the interactions between gp120 and CD4MCs, and also investigated the phenotypic change in the CD4MCs resistant isolates against other entry inhibitor and anti-Env neutralizing monoclonal antibodies (nMAbs).

Methodology: To induce resistant variants against five CD4MCs (NBD-556, YYA-021, HAR1-71, JRC-II-191 and HAR4-31) in vitro, we exposed PM1 cells to the bulked and cloned primary KP-5P virus (subtype B, R5). We constructed infectious clones with CD4MC-resistant mutation following in vitro selection. The susceptibility of mutated Env/NL4-3 infectious clones to a CCR5 inhibitor (maraviroc, MVC), 3D6 (anti-CD4bs) and 4E9C (anti-CD4i epitope) were evaluated using single-round assay in TZM-bl cells.

Results: V255M was most frequent mutation in six of ten CD4MC resistant viruses, while T375I mutation was most frequent in three of ten CD4MC resistant viruses. M426I was observed as a major clone in only YYA-021 resistant virus using the bulked virus. To investigate a relationship between the resistant mutations in gp120 and sensitivity to CD4MCs, we constructed Env-mutant clones carrying a single mutation within the KP-5P gp160 backbone, and determined the sensitivity of each clone to CD4MCs. The three mutations, V255, T375 and M426 were associated with high level of resistance to all CD4MCs tested. Furthermore, we examined susceptibilities of the mutated clones to CCR5 inhibitor MVC, CD4bs nMAb 3D6 and CD4i nMAb 4E9C. In this assay in TZM-bl cells, there was no substantial difference between the wild type and CD4MCs resistant clones in sensitivity of MVC. The clones containing V255M or M426I substitutions became relatively resistant to 4E9C compared to the wild type clone, whereas the clone with T375I showed low sensitivity to both 3D6 and 4E9C nMAbs. This finding suggests that the T375I mutation can negatively affect the neutralizing activity of CD4bs and CD4i nMAbs for inducing the conformational change in the Env more than V255I and M426I mutations.

Conclusions: V255M, T375I and M426I, which are located inside of the Phe43-cavity are key mutations for acquiring highly resistant ability to CD4MCs. In these mutations, T375I may contribute to the closing of neutralizing antibody epitopes for CD4i and CD4bs nMAbs.

600 M184I and M230I Minority Variants in ART-Naïve Patients Are Linked To APOBEC3G/F Activity

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Background: In a recent multicohort European case-control study in ART-naïve patients, presence of at least 1 IAS-2013 RT minority variant (MV) was associated to an increased risk of first-line NNRTI-containing treatment failure. Most prevalent MVs detected were V90I(4%), V106I(3%) ,V108I(3%), M184I(3%), M230I(2%) and all corresponding to G-to-A mutations. We evaluated whether these mutations could result from APOBEC3G/F activity on the viral genome.

Methodology: ART-naïve HIV-1 infected subjects with no NNRTI resistance by bulk genotyping subsequently undergoing NNRTI containing antiretroviral treatment were selected from 6 European Cohorts. Sequencing of RT was performed using 3 amplicons from the 454 Life Sciences/Roche HIV-1 drug resistance prototype assay plus an additional amplicon for robustness. AVA software (v2.7) was used to obtain error-corrected sequences from which all polymorphisms relative to HXB2 were identified. Then, consensus references were obtained for each sample and sequence data were re-aligned against such consensus using MosaikAligner. These alignments were used to screen for G-to-A nucleotide mutations. GRD-to-ARD sequence contexts were used as APOBEC target sites, while G(YNIRC)-to-A(YNIRC) served as control sites. A Fisher test was run for each sequence to define APOBEC3G/F edition status. All sequences were then pooled and co-occurrence of each of the polymorphisms and APOBEC3G/F edition was tested for significance (Fisher Test, $p<0.05$).

Results: 353 subjects were included in the study. 326 (93%) samples provided sequence data suitable for analysis for 1 or more amplicon. Of these, 245(75%) and 71(22%) were subtype B and non-B, respectively, while 10(3%) were of unknown subtype. APOBEC3G/F signals were detected in 32 patients. In 8 of them, APOBEC3G/F edited sequences accounted for more of 1% of each sample sequence. M184I and M230I corresponded to APOBEC3G/F mutation patterns while V108I, V90I and V106I did not. Global analysis at the sequence level, separately for each amplicon, showed significant ($p<0.05$) co-occurrence of APOBEC3G/F edited sequences with M184I, M230I, but not with V90I, V108I and V106I mutations. Stop codons were found in many, but not all, of APOBEC3G/F edited sequences.

Conclusions: M184I and M230I mutations were predominantly found in APOBEC3G/F edited sequences in ART-naïve patients. This suggests that APOBEC3G/F are modulators of viral diversity in vivo to a larger extent than previously expected.

601 Characterising the Complex Mutational Pathways Associated With Maraviroc-Resistant HIV-1

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Background: The drug maraviroc differs from other HIV-1 drugs as it binds the host cell coreceptor CCR5 as opposed to a virus protein. Lack of sensitivity to such entry-inhibitor drugs occurs primarily through emergence of pre-existing viruses that use the CXCR4 coreceptor, while genuine CCR5-antagonist resistance occurs through virus use of the drug-bound CCR5 coreceptor. The aim of this project is to understand the R5 resistance pathway in a comprehensive way based on envelope sequence data.

Methodology: We use population genetic, coevolutionary, recombination, positive selection and structural analysis to analyse the envelope protein sequences from 20 patients from the clinical trials MOTIVATE 1 and 2. All these patients have exclusively CCR5-using (R5) virus. All patients have two groups of sequences that have been sequenced before and after treatment with maraviroc/placebo-arm. Three patients under placebo-arm treatment are used as control.

Results: We find the resistant viral population to be phylogenetically distinct from those susceptible to the drug and associated with a clear genetic bottleneck in each patient, consistent with de novo emergence of resistance. We find limited overlap in the envelope sites or point mutations involved. Particularly, we find: (1) complex coevolutionary networks (indicating epistatic interactions in the context of protein structure) in both the sensitive and resistant populations. (2) A subset of coevolving sites are under positive selection indicating their importance for drug resistance. (3) CD4 binding sites formed a unique coevolutionary network that is independent of the V3 loop. (4) The coevolutionary network formed between the V3 loop and other regions of gp120 and gp41 intersects with sites involved in the N-linked glycosylation motif. (5) Key residues in the signal peptide involved in Env function and expression level coevolve with the potential N-linked glycosylation sequence motifs (NXS/TX). (6) Finally, there is no statistically significant change of the V3 loop structural disorder between sensitive and resistant R5 virus. This indicates changes in other protein regions are required for achieving the binding specificity required for resistant R5 virus, which is consistent with the results of the above coevolutionary analysis.

Conclusions: Coevolution between V3 loop, N-linked glycosylation motifs and the signal peptide are key to V3/gp120/gp41 folding into particular conformations that can utilize drug-bound CCR5 for cell entry. Collectively our results demonstrate that although each viral population's resistance pathway is context dependent, the evolutionary trajectories of the viruses are significantly constrained accounting for the low levels of resistant R5 virus.

Session P-L4 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

HIV Drug Resistance Variants

602 Impact of Minority Drug-Resistant and X4 Variants in Naïve Patients Starting ART With <100 CD4+/mm^3

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Background: HIV-1-infected subjects initiating first-line antiretroviral therapy (ART) with CD4+ counts <100 c/mm3 are at increased risk for developing virological failure (VF), opportunistic diseases and death. The impact of drug-resistant minority variants (DRMV) and HIV-1 tropism on the efficacy of first-line ART in this very advanced population is unknown.

Methodology: This was a post hoc analysis from 2 open-label, prospective, randomized clinical trials comparing the efficacy of first-line ART with efavirenz (EFV) vs. indinavir/ritonavir (IDV/r) + Combivir® (ADVANZ study), and EFV vs. atazanavir/ritonavir (ATV/r) vs. lopinavir/ritonavir (LPV/r) + Truvada® (ADVANZ-3 study). Subjects were ART-naïve, had CD4+ counts <100 c/mm3 and wildtype HIV-1 by bulk sequencing at study entry. Stored pre-ART samples were reanalysed for the presence of DRMVs and X4 HIV-1 using 454 sequencing. The detection threshold for DRMVs was 1%; X4 HIV-1 was defined as ≥2% variants with a Geno2Pheno FPR ≤3.5%. VF was defined as 2 consecutive VL≥200 c/mL or one VL≥1000 c/mL at or after month 6 of ART. The different study arms were combined in 2 groups: those starting EFV (EFV group) and those starting a PI/r regimen (PI/r group). DRMVs were defined according to the IAS-USA 2013 list. Only DRMVs conferring resistance to ARV classes included in the regimen started (Tx-DRMVs), i.e. NRTI and NNRTI for the EFV group and NRTI and PI for the PI/r group were considered for the VF analyses. 2-tailed Fisher exact tests and Kaplan-Meier analyses were used to evaluate associations between pre-existing Tx-DRMV or X4 HIV-1 with VF.

Results: The combined dataset included 145 evaluable subjects; 59 received EFV and 86 PI/r therapy (29 ATV/r, 28 IDV/r and 29 LPV/r). Median (IQR) pre-ART CD4+ counts and VL were 39 (20; 60) cells/mm3 and 257,424 (69,192; 500,001) c/mL, respectively. 52 (36%) subjects had X4 HIV-1; 60 (41%) had DRMVs detected. Presence of Tx-DRMV was associated with an increased risk of VF when considering all subjects [Hazard Ratio (HR)=2.0 (95CI: 1.0-4.3), p=0.049] and those starting EFV [HR=4.8 (95CI:1.0-24.6), p=0.031], but not in those initiating PI/r [HR=1.15 (95CI:0.4-3.9), p=0.795]. Similar associations were observed in the Kaplan-Meier analyses. HIV-1 tropism was not associated with VF in any analysis.

Conclusions: Detection of pre-existing DRMVs is helpful to select optimal first-line ART in subjects with <100 CD4+/mm3. X4 tropism was not associated with an increased risk of VF in this study.

603 Antiretroviral-Naïve and -Treated Patients Can Harbor Viruses in CSF More Resistant Than in Plasma

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Background: The neurological disorders in HIV-1 infected patients remained prevalent. The issue of whether HIV-1 in cerebrospinal fluid (CSF) originates from viral replication sources in central nervous system or from peripheral blood and the consequences on antiretroviral (ARV) resistance is still a subject of debate. In this study, the resistance of HIV-1 in plasma and CSF was compared in a multicenter study supported by the "Agence Nationale de Recherche sur le Sida et les Hépatites Virales" (ANRS).

Methodology: Blood and CSF samples were collected at time of neurological disorders for 244 patients in 22 centers in France and 1 center in Switzerland. Demographic data and ARV treatment were collected. The viral loads (VL) were > 50 copies/mL in both compartments. Bulk genotypic resistance tests were realized on both plasma and CSF. The genotypic susceptibility score (GSS) of current treatment was calculated according to the 2013 ANRS AC-11 genotype interpretation algorithm: 0 (resistant), 0.5 (intermediate) or 1 (susceptible) to the drugs. Comparisons between groups were performed by using non-parametric tests.

Results: On 244 patients, 89 and 155 were ARV-naïve and ARV-treated, respectively. The variables were in median: age 42.79 and 44.61 years; CSF VL 4.64 and 4.09 log10 copies/mL; plasma VL 5.10 and 3.70 log10 copies/mL; nadir CD4 119 and 59 cells/mm3; CD4 131 and 230 cells/mm3 for ARV-naïve and ARV-treated respectively.

In ARV-naïve patients, detection of mutations in CSF and not in plasma viruses were reported for the reverse transcriptase (RT) gene in 3 of 89 patients (3.4%) (K101E, F116Y, Y181C/I, M184I, Y188L, T215F/Y) and for the protease gene in 9 of 89 patients (10.1%) (L10V, V11I, L33F/V, M36I, I62V, L63P, V77I, V82A).

In ARV-treated patients, 23 of 155 (14.8%) patients had HIV-1 mutations only in the CSF for the RT gene and 30 of 155 (19.4%) patients for the protease gene. Two mutations appeared statistically more prevalent in the CSF in comparison with the plasma: M41L (p= 0.0455) and T215Y (p=0.0143). Furthermore, 88.5% of ARV-treated patients had viruses with a similar GSS of current treatment in the two compartments, 7.4% with a GSS in CSF < GSS in plasma, and 4.0% with a GSS CSF > GSS in plasma.

Conclusions: For ARV-naïve and ARV-treated patients, in most of cases, resistance mutations were present in both studied compartments. However, in some cases, the virus was more resistant in CSF than in plasma reducing the number of future therapeutic options. Then, in case of neurological troubles with a positive HIV-1 VL in CSF, the genotype should be recommended both in plasma and CSF to adjust the ARV handling.

604 Retention and Decay of HIV-1 Drug Resistance Mutations in Proviral DNA

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Background: The persistence of HIV-1 drug resistant mutations (DRM) in the reservoir of integrated, latent provirus and their fixation and decay rate over time may impact future treatment options. The retention of K103N and other DRM in subjects who failed an Efavirenz (EFV)-based regimen were assessed after suppression to <50 copies/ml for 2-11 years on a protease inhibitor (PI)-based regimen. PBMC proviral DNA was genotyped to determine the kinetics of retention and decay of K103N and other DRM.

Methodology: Proviral DNA was isolated from peripheral blood mononuclear cells (PBMC) of 28 subjects from ACTG 364 and ACTG 5095 with documented K103N in plasma viral RNA at time of EFV failure. HIV-1 *pol* was amplified and subjected to population sequencing. For most samples, genotypes were obtained at three time points (first suppression (t_1), most recent suppression (t_3), and between first and most recent suppression (t_2)). Repeated measures logistic regression (generalized estimating equations) was used to identify factors associated with detectable K103N in proviral DNA.

Results: At t_1, t_2, and t_3, 50% (14/28), 62% (13/21) and 48% (11/23) of subjects had detectable proviral K103N with median 0.6 (Q1-Q3: 0.6-0.7), 2.6 (1.8-4.0) and 4.2 (2.5-7.1) years of suppression. Years since suppression was not associated with the likelihood of detectable proviral K103N (P=0.53). In adjusted model with years since suppression, $\log_{10}$ plasma HIV RNA level at EFV failure was associated with increased likelihood of observing proviral K103N (P=0.04); odds of detectable proviral K103N was 2.6 (95% CI: 1.0-6.4) times higher per $\log_{10}$ higher HIV RNA at EFV failure. Other covariates (protocol study, age, CD4 count and HIV RNA at baseline) were not associated with detectable proviral K103N. Frequency of NRTI mutations was 75% (21/28) in RNA at EFV failure, 54% (15/28) in DNA at t_1, 48% (10/21) at t_2, and 39% (9/23) at t_3. Detection of nucleoside reverse transcriptase inhibitor (NRTI) mutations in DNA decreased with time on suppression (P<0.01).

Conclusions: K103N in plasma was subsequently identified in the proviral DNA of ~50% of subjects for up to 11 years during PI-based suppression. These results imply seeding of the HIV reservoir during viral failure and confirm the stability of drug resistance in HIV reservoirs during long-term suppressive ART among at least 50%. In those with undetected proviral resistance by population sequencing, persistent drug resistance can exist at lower levels and be clinically relevant.

605 Prevalence of Minority Resistant Variants To ETR, DRV, and RAL at Baseline in the ANRS 139 TRIO Trial

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Background: ANRS 139 TRIO trial was a 96-week phase II non-comparative trial that evaluated the raltegravir (RAL), etravirine (ETR) and darunavir/r (DRV) combination in highly-experienced patients harboring multi-resistant viruses. 87% of the patients of the trial also received a NRTI- and/or ENF-containing OBT regimen. A high level of virological suppression was observed with 93% of patients with viral load (VL) <50 c/mL at W48, and 88% at W96. The aim of this sub-study was to assess the prevalence of minority resistant variants (MRV) at baseline (BL) in ANRS 139 TRIO trial.

Methodology: Bulk sequencing at baseline of reverse transcriptase (RT), protease (PR), and integrase (IN) regions was performed and sequences were interpreted according to the ANRS procedures described at www.hivfrenchresistance.org. MRV were assessed using both MiSeq and 454 technologies, with an arbitrarily assigned limit of detection of 1%.

Results: Among the 103 patients included, BL median VL was 4.2 log10 c/mL (IQR = 3.6-4.6). BL bulk sequencing showed a median number of major PI, NNRTI and NRTI resistance-associated mutations (RAM) of 4, 1, and 6, respectively. However, all patients exhibited viruses susceptible to all 3 drugs of the regimen. Deep sequencing was available in 73, 46 and 87 samples for RT, PR and IN regions, respectively. MRV exhibiting at least 1 ETR RAM were detected in 27 patients (37%). Median proportion of ETR MRV was 4.4% (IQR = 2.0%-7.9%). MRV exhibiting at least 1 DRV RAM were detected in 12 patients (26%) with the median proportion of 6.2% (IQR = 2.9%-10.4%). Considering the presence of MRV, 23 (32%) and 18 (39%) patients exhibited plasma virus resistant to ETR and DRV, respectively. Regarding IN region, MRV exhibiting at least 1 RAL RAM were detected in 6 patients (7%). Among them, 5 exhibited Q148K-mutated MRV with a proportion between 1 and 2%. No patients exhibited MRV to all 3 drugs of interest. During trial follow-up (W96), 19 patients exhibited virological failure (VF). Prevalence of baseline ETR/DRV/RAL MRV according to the virological outcome is depicted in the table below.

Conclusions: In these highly pre-treated patients, but naïve to IN inhibitors, MRV to ETR, DRV, and RAL were detected in 37%, 26% and 7% of patients. The frequency of patients with baseline MRV was not higher in patients experiencing VF when compared to those in success. Further analysis of this dataset should help determine what role, if any, the level of detection of MRV can play in resistance assessments.

Prevalence of MRV at baseline						
	RT (n=73)		PR (n=46)		IN (n=87)	
	Virological Failure (n=13)	Virological Success (n=60)	Virological Failure (n=9)	Virological Success (n=37)	Virological Failure (n=16)	Virological Success (n=71)
MRV +	5 (38%)	22 (37%)	1 (11%)	11 (30%)	0(0%)	6 (8%)
MRV -	8 (62%)	38 (63%)	8 (89%)	26 (70%)	16 (100%)	65 (92%)

Session P-L5 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Laboratory Detection of Drug Resistance and Tropism

606 Pan Degenerate Amplification and Adaptation for Highly Sensitive Detection of ARV Drug Resistance

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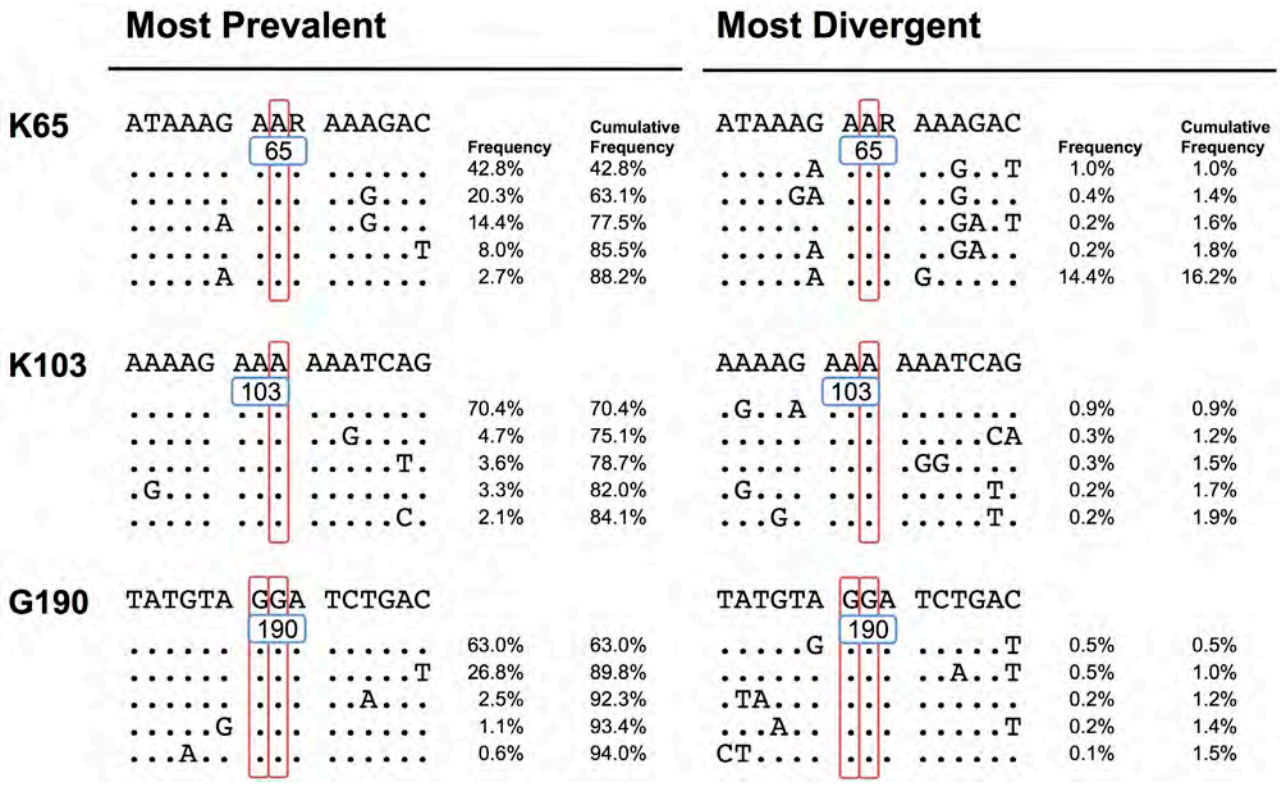
Background: Current drug resistance detection assays are unable to rapidly detect low-level, clinically relevant variants. Molecular probes, such as TaqMan-MGB, can distinguish a single nucleotide polymorphism (SNP) of interest but with the caveat that probes are sensitive to secondary polymorphisms (i.e. non-drug resistance) in the probe-binding region. The highly polymorphic nature of HIV results in the accumulation of secondary polymorphisms that abrogate probe hybridization resulting in a failure to detect drug resistance.

Methodology: Pan Degenerate Amplification and Adaptation (PANDAA) allows fluorescent probes to detect multiple drug resistance mutations by quantitative PCR. Probes to differentiate the K65R, K103N, and G190S/A wild-type and drug resistance SNPs were designed to match the majority consensus from >5,000 HIV-1 Group M sequences. Synthetic constructs of the most prevalent and most divergent probe-binding regions for K65R, K103N, and G190S/A were used to determine assay sensitivity (Figure 1). PANDAA was compared to in-house population genotyping of 30 HIV-1 subtype C-infected patients from Botswana with detectable viral load 6 months after initiating TDF/FTC/EFZ, and 77 ARV-naïve patients from Tanzania infected with either subtype A, C, D, or a CRF.

Results: PANDAA was sensitive to 10 copies/reaction using templates containing multiple secondary polymorphisms, and was able to successfully differentiate between wild-type and drug resistance polymorphisms in genetically diverse populations. Drug resistance could be detected in ~1% of a mixed virus population at 1,000 copies total viral RNA, with increasing sensitivity at higher viral loads. PANDAA quantitatively confirmed patient genotyping results obtained using population sequencing, with results obtained in an average of two hours after viral RNA purification.

Conclusions: By removing secondary polymorphisms, PANDAA successfully detected drug resistance in the most genetically divergent samples. We have developed a fast and inexpensive method that is easily adapted to allow accurate quantitation of numerous drug resistance polymorphisms, even when present at very low levels.



607 Genotypic Tropism Testing of Proviral DNA To Guide Maraviroc Initiation in Aviremic Subjects

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Background: Maraviroc (MVC) is a suitable drug for aviremic subjects on antiretroviral treatment (ART) developing toxicity, but its prescription requires prior tropism testing. It is unknown if proviral DNA genotypic tropism testing is reliable to guide MVC initiation in aviremic subjects.

Methodology: This was a Phase 4, prospective, single-arm study (ID: NCT01378910) in 24 HIV care centers in Spain. Participants were MVC-naïve HIV-1-infected adults with HIV-1 RNA (VL) <50 c/mL on stable ART during the previous 6 months, requiring an ART change due to toxicity, with no antiretroviral resistance to the ART started and R5 HIV by proviral DNA genotypic tropism testing (defined as a Geno2Pheno FPR>10% in a singleton). Subjects fulfilling the inclusion criteria initiated MVC with 2 NRTIs, and were followed for 48 weeks. Virological failure was defined as 2 consecutive VL>50 c/mL. Here, we present a pre-specified interim virological safety analysis performed when at least 2/3 subjects reached week 24 of follow-up. Recent adherence was calculated as: (# pills taken/# pills prescribed during the previous week)*100.

Results: Out of 142 subjects screened, tropism results were available from 134: 46 (34%) were X4 and 88 (66%) R5. 74/88 (85%) subjects were included and switched to MVC +2 NRTIs, and 61/74 (82%) had reached week 24 when this analysis was performed. Of these, 20% were women, 31% MSM, 36% had CDC category C, 36% were HCV+ and 10% HBV+. Previous ART included PIs in 33 (55%) subjects, NNRTIs in 26 (43%) and INIs in 1 (2%). Reasons for treatment change were dyslipidemia in 21 (34%) subjects, gastrointestinal symptoms in 11 (18%), psychiatric symptoms in 3 (5%) and "other" in 26 (43%). Median CD4+ counts were 616 cells/mm3 at screening and median nadir CD4+ counts were 143 cells/mm3. MVC was given alongside TDF/FTC in 32 (52%) subjects, ABC/3TC in 26 (43%), AZT/3TC in 2 (3%) and ABC/TDF in 1 (2%). 51 (84%) subjects maintained VL<50 c/mL through week 24, whereas 10 (16%) discontinued treatment: 2 (3%) withdrew informed consent, 1 (2%) was lost to follow-up, 1 (2%) developed an ART-related adverse event (rash), 2 (3%) died due to non-study-related causes (1 myocardial infarction at week 0 and 1 lung cancer at week 36), and 4 (6%) developed virological failure (Table).

Conclusions: In this interim 24-week virological safety analysis, initiation of MVC plus 2 NRTIs in aviremic subjects based on genotypic tropism testing of proviral HIV-1 DNA was associated with low rates of virological failure up to week 24.

Characteristics of subjects developing virological failure (VF)								
Subject	ART	Week of VF	HIV-1 RNA at VF (c/mL)	Tropism at VF (Geno2Pheno FPR, %)	Recent adherence at VF (%)	Resistance mutations at VF (IAS-USA 2013)	Salvage ART	Regained VL <50c/mL with salvage ART
1	MVC+TDF/FTC	4	300	X4 (0.1)	100	NA	DRV/r+ETR	Yes
2	MVC+TDF/FTC	12	14,102	X4 (1.3)	100	RT: 41L, 67N, 184V, 215Y PR: 36I, 63P	TDF/FTC+ETR	Yes
3	MVC+ABC/3TC	24	416	R5 (52.1)	100	RT: 90I, 184I PR: 64V	TDF+DRV/r+EFV	Yes
4	MVC+TDF/FTC	12	59	NA	100	NA	MVC+TDF/FTC	Yes

608 Characterization of NNRTI Mutations in HIV-1 RT Using Single Molecule, Real-Time SMRT® Sequencing

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Background: Genotypic testing of chronic viral infections is an important part of patient therapy and requires assays capable of detecting the entire spectrum of viral mutations. Single Molecule, Real-Time (SMRT) sequencing offers several advantages to other sequencing technologies, including superior resolution of mixed populations and long read lengths capable of spanning entire viral protein coding regions. We examined detection sensitivity of SMRT sequencing using a mixture of HIV-1 RT gene coding regions containing single NNRTI mutations.

Methodology: SMRTbell templates were prepared from PCR products generated from a prospective reference material being developed by BC Center of Excellence for HIV/AIDS, and contained a mixture of fifteen infectious viruses containing single NNRTI resistance mutations (*viz* V90I, K101E, K103N, V108I, E138A/G/K/Q, V179D, Y181C, Y188C, G190A/S, M230L and P236L) built upon the HIV-1LAI molecular clone. Templates were sequenced on the PacBio *RS* II to obtain single molecule long reads using P4/C2 chemistry, using 180 minute movie collection without stage start. The relative abundances of the mutant viruses were then estimated using codon-aware analysis methods.

Results: Sequencing of these templates produced average readlengths of 5.0 KB, comprising 40,000-fold coverage across the entire amplicon per SMRT cell. All the expected mutations in the mixture of mutant viruses were accurately identified. Frequencies of NNRTI variants estimated ranged from 0.5% to 12.5%.

Conclusions: Codon analysis revealed a number of variants across the amplicon with highly consistent results across SMRT cells. From a single SMRT cell, variants were accurately and reliably detected down to 0.5% with simple analyses. Long polymerase reads and high accuracy reads make it possible to call variants from just a few molecules. SMRT sequencing can identify species comprising a mixed viral population, with granularity and low cost of consumables allowing for smaller multiplexing of samples and first-in-first-out processing.

609 Celera RUO Integrase Resistance Assay Performs Well Across Several Subtypes

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Background: Sequence variation is a major obstacle to developing molecular based assays for multiple subtypes. This study sought to independently assess performance characteristics of the ViroSeq™ HIV-1 Integrase RUO Genotyping Kit (Celera, US) for samples of multiple different subtypes.

Methodology: 157 samples were used in the validation, 105 from integrase inhibitor naïve patients' plasma samples sent for routine HIV-1 drug resistance testing after failing a 1st- or 2nd-line regimen, and 52 from an external virology quality assurance program (VQA). 15 identical VQA samples were tested in two different laboratories to assess assay reproducibility. Viral RNA was extracted using the ViroSeq extraction module and reverse transcribed and amplified in a one-step reaction. Four sequencing primers were used to span codons 1-288 of integrase. The Rega subtyping tool was used for subtype assignment. Integrase polymorphisms and mutations were determined as differences from the HXB2 sequence and the Stanford database, respectively. Sequences obtained from the two laboratories were aligned and sequence homology determined.

Results: HIV-1 RNA in the 157 samples ranged from 3.15 to 6.74logcopies/ml. Successful amplification was obtained for 95% of samples (n=149). The 8 samples that failed to amplify were subtype D (n=3), subtype C (n=1), CRF02_AE (n=1), subtype A (n=2), and unassigned subtype (n=1). Of the 149 successfully amplified samples, 126 (79%) were successfully sequenced with bidirectional coverage. Of the 23 unsuccessful samples, 12 (8%) failed sequencing and 11 (7%) did not have full bidirectional sequence, a result of failure of sequencing primers Primer A (n=1); Primer B (n=4); Primer C (n=2) and Primer D (n=6). For the 15 VQA samples that were sequenced in the two different laboratories, homology of the sequences obtained ranged from 99.01% to 100%. However, Lab 2 detected 23 mixtures; whereas Lab 1 only detected 9 mixtures in the 11219 nucleotide analysed, possibly due to differences between the labs in the methods of sequence analysis. Mutations associated with integrase resistance were observed in seven of the 137 (5%) samples [Q148K; E138K; G140A (n=1)], T97A (n=2), L74I (n=4). Of the four samples with L74I, 3 were subtype G.

Conclusions: Of the 157 samples tested, 79% (n=126) were successfully amplified and a bi-directional sequence obtained. Sequencing results were similar between two testing laboratories with the exception of mixture detection. Mutations associated with integrase inhibitor resistance were observed in only 5% of integrase inhibitor naive samples, and some of these mutations are likely to be due to subtype specific polymorphisms rather than selection by an integrase inhibitor.

610 Feasibility and Clinical Utility of HIV-1 Genotype Testing in the Setting of Low-Level Viremia

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Background: We evaluated reliability and clinical usefulness of genotypic resistance testing (GRT), in patients failing combination antiretroviral therapy (cART) with viremia levels 50-1000 copies/mL, for whom GRT is generally not recommended by current guidelines.

Methodology: Genotyping success rate (GSR) was evaluated in 12828 HIV-1 plasma samples with viremia >50 copies/mL, tested using the commercial ViroSeq HIV-1 Genotyping System or a homemade system. Samples were stratified in 6 groups according to different viremia levels (50-200; 201-500; 501-1000; 1001-10000; 10001-100000; >100000 copies/mL). Phylogenetic analysis was performed to test the reliability and reproducibility of the GRT at low viremia levels.

Drug-resistance was evaluated in 3895 samples from 2200 treatment failing patients (viremia >50 copies/mL). Multivariable logistic regression analysis was used to evaluate the impact of viremia-levels at genotyping on the prevalence of drug-resistance. Resistance mutations panelled in the IAS list 2013 have been considered.

Results: Samples analysed were mainly from patients carrying a subtype B virus (80%), but also from patients carrying non-B subtype viruses (20%, prevalence of the most prevalent ones: CRF02_AG=4.7%; C=4.3%; F=3.3%). Overall, GSR was 96.4% and was independent from subtype. Viremia levels of 50-200 and 201-500 copies/mL afforded GSR of 67.2% and 88.1%, respectively, reaching 93.2% at 501-1000 copies/mL and ≥97.3% above 1000 copies/mL. Phylogenetic analysis revealed a high homology among sequences belonging to the same subject for 96.4% of patients analysed.

The overall drug-resistance prevalence was 74%. Substantial levels of resistance were found also at low viremia levels for all drug classes, with high rates for NRTI and NNRTI. In particular, detection of any drug-resistance was: 50-200 copies/mL=52.8%; 201-500=70%; 501-1000=74%; 1001-10000=86.1%; 10001-100000=76.7%; >100000=63% (P<0.001). Multivariable logistic regression confirmed that the risk of having drug-resistance was associated with viremia levels at GRT (P<0.001). The distribution of drug-resistance stratified for viral load was confirmed also considering samples only from patients failing their first-line regimen, though at a lower prevalence was observed (53% vs. 74%). This prevalence was not correlated with pre-therapy viremia (P=0.441).

Conclusions: In patients failing cART with viremia levels 50-1000 copies/mL, HIV-1 genotyping provides reliable and reproducible results, that are informative about emerging drug-resistance also at low viremia levels. Results may be helpful for the therapy optimization in patients under virological failure, to decrease the risk of virological failures with drug-resistance accumulation.

611 Tropism Testing by MiSeq Is Comparable To 454-Based Methods But Exhibits Contamination Issues

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Background: Bench-top next-generation sequencing (NGS) has become increasingly popular for HIV applications within the past five years. While "454"-based methods have dominated HIV research, the Illumina MiSeq is gaining popularity based on cost, ease of use, read depth and accuracy through homopolymer regions.

Methodology: A total of 514 plasma samples were run on two NGS platforms, and sequencing data from the HIV V3 region were analyzed. Stored first-round PCR products were obtained from the samples which were originally sequenced on a Roche/454 GS-FLX.

The samples underwent further amplification with adaptors appropriate for the Illumina MiSeq. Barcoded samples were sequenced in multiplexed runs of 96 samples on both instruments. Samples were excluded if they had <750 reads by GS-FLX or <10,000 by MiSeq. CXCR4-using tropism was assigned if ≥2% of sequences had a geno2pheno false-positive rate <3.5 - parameters which were previously optimized for the 454, though not the MiSeq.

Results: Both platforms were well correlated in terms of the proportion of X4 reads per sample (slope= 0.91, R^2=0.90). Median read depth was ~89,000 by MiSeq and ~2500 by GS-FLX. For tropism classifications, the platforms were 89% concordant (459 of 514 samples, Kappa=0.78).

Of the 55 samples with discordant classifications, 62% were X4 by MiSeq but R5 by 454, indicating potential over-sensitivity for minor variants by MiSeq. The median difference in %X4 reads between platforms was 0.2% higher by MiSeq (interquartile range [IQR]: -1.1%-1.3%). Where discordant, samples differed by an absolute value of 2.5% X4 (IQR: 1.3%-8.3%).

We also noted systematic low-level carry-forward contamination on the MiSeq platform: on average, a minimum of 0.04% of the total number of recovered reads (standard deviation 0.02%) were obvious contaminants (non-V3 sequences carried over from previous runs). Contaminant sequences persist in subsequent runs, appearing as many as 7 runs after they were originally processed.

Conclusions: The MiSeq and GS-FLX systems were well correlated with each other and gave similar tropism classifications in 89% of samples. Where discordant, MiSeq tended to call more samples as X4. Laboratories using MiSeq platforms should account for carry-over contamination where possible in their data processing.

612 A Proposed HIV Reference Sample Characterized by Three Next-Generation Sequencing Platforms

Alejandro Gonzalez-Serna[1], Chanson J. Brumme[1], Winnie Dong[1], Eric Cai[1], Art F. Y. Poon[1], Kelly D. Huber[2], Nicolas Sluis-Cremer[3], Ellen E. Paxinos[4], Luke C. Swenson[1], Paul Richard Harrigan[1, 5]

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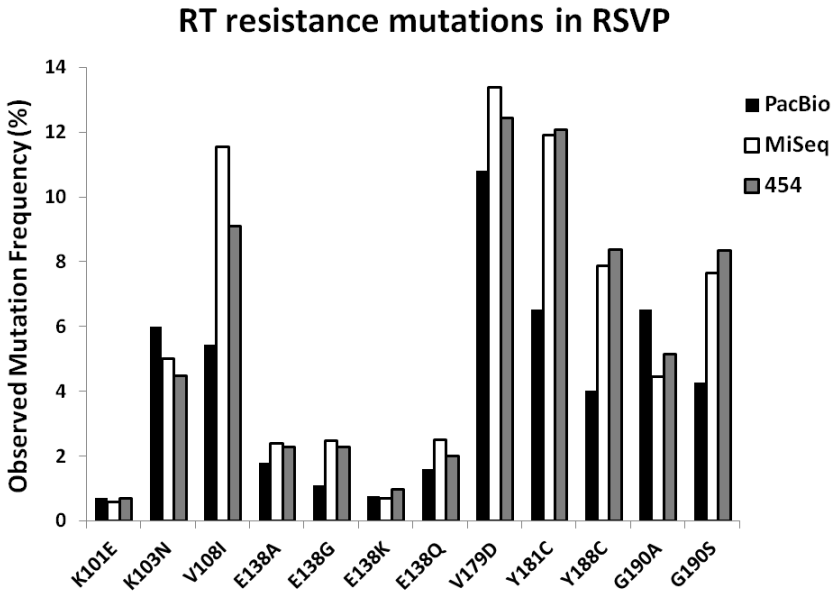
Background: "Deep" sequencing allows detection of low frequency minority variants, but establishing the analytical characteristics of such assays, including the error rate and limit of detection, will require repeated sequencing of known reference samples. We present sequencing results from three next-generation platforms for one such potential sample.

Methodology: Fifteen infectious viral clones, each containing a single NNRTI resistance mutation (V90I, K101E, K103N, V108I, E138A/G/K/Q, V179D, Y181C, Y188C, G190A/S, M230L and P236L) were created by site directed mutagenesis of HIV-1LAI. Mutants and wild-type viruses were pooled at equal infectivity into a single sample, "RSVP" (reference sample for validating platforms), which was extracted and subjected to RT-PCR. Two second round PCR amplicons were generated: a 1.8 kb region of pol (HXB2 2469-4295) sequenced on the PacBio® RS (v1), and 339 bp region of RT (HXB2 2813-3151) was sequenced on the Illumina MiSeq (v2 2x250 paired end) and 454 Life Sciences GS-Jr. Cross-platform variation was evaluated including amino acid (aa) frequency of the expected NNRTI mutants and error rates in the region covered by all three platforms (RT codons 96-194). A logistic regression model was used to model the error rates. In addition, serial dilutions of the 1st round PCR product were sequenced by MiSeq.

Results: Approximately 50,000, 185,000, and 3100 sequence reads were obtained for PacBio, MiSeq and 454 respectively. The frequency of minor NNRTI resistance variants detected by the three platforms was similar (see figure). When raw sequences were analyzed (no quality score filtering) marginally higher error rates were observed for PacBio compared to MiSeq and 454. For MiSeq, discarding bases with quality below a specific cutoff (q-score 10, 15, 20, 25) resulted in improved error rates, with q20 balancing a tradeoff between read retention and sequencing accuracy (q20 error rate 1.2%). Sequencing errors in homopolymer-rich regions were frequently observed in 454 sequences, occasionally in PacBio, but rarely in MiSeq. Additionally, MiSeq results were robust to dilution of the 1st round PCR product up to 200,000-fold.



Conclusions: We have characterized the performance of three next-generation sequencing platforms using a proposed HIV reference sample; RSVP is a mixture of protease-RT from 16 HIV-1 variants that we are making available to interested groups to use when validating the detection of minority NNRTI resistant variants.

Session P-L6 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Cost Effectiveness Studies of ART and Drug Resistance Testing

613 Antiretroviral Switch Strategies for Lowering Costs of Therapy: 48-Week Cost-Efficacy Analysis

Josep M Llibre[1], Gloria Cardona[2], Jose R Santos[3], Angels Andreu[2], Xavier Bonafont[2], Bonaventura Clotet[1]

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Background: The economic recession has led to a generalized shortage of investment in public health and the antiretroviral treatment (ART) budget in some European countries. Some ART were proactively switched in selected individuals to generate cost savings. We undertook a complete 48 week cost-efficacy analysis to evaluate this strategy.

Methodology: We defined cost-reduction measures (CRM) as all those switches that aimed to reduce the cost of treatment in patients with virological suppression (HIV-1 RNA <50 c/mL). We registered all treatment changes and a 48 week snapshot analysis (HIV-1 RNA <50 c/mL) was performed. All direct costs were considered: cost of therapy calculated from manufacturer sales price plus 4% VAT, all resource consumption used in the management of toxicity, any treatment change, and therapeutic failure, for which we used the official rates to apply by the hospital.

Results: During the study period, 673 switches were made, of which 378 (56.2%) were CRM (16% of all patients treated), leading to overall savings of €87,410/month. Switching TDF/FTC for ABC/3TC was the most common CRM (129, 31.3%), followed by simplification to PI/r monotherapy (102, 26%). The CRMs that generated the greatest savings were switching to PI/r monotherapy (38%), substitution of raltegravir (24%), switching TDF/FTC for ABC/3TC (13%), and switching to nevirapine (5%). After 48 weeks, 318/378 (84.1%) patients remained on the same treatment, while 60 (15.9%) had changed it. Only in 30 patients (7.9%) the change was related with the prior switch: side effects (22, 5.8%) and virological failure (8, 2.1%). The most common side effect was low-grade gastrointestinal toxicity (diarrhea and abdominal discomfort) by abacavir (2.4%), lopinavir (1.3%), and darunavir (0.5%), followed by rash by nevirapine (1,1%), and central nervous system toxicity by efavirenz (0.5%). Changes unrelated to the switch included adverse events (20, 5.3%), pharmacokinetic interactions (7, 1.9%), treatment withdrawal (2, 0.5%) and simplification (1, 0.26%). All toxicities were grade 1-2. Among 8 virological failures, 4 had been switched to PI/r monotherapy, 3 to triple PI/r, and 1 unboosted ATV. The switch was related to the virological failure in only 1 subject. 375/378 patients had plasma HIV-1 RNA <50c/mL at 48 weeks. During 48 weeks, treatment changes cost €40,124, extra visits 2,553 €, and supplemental tests 2,971 €, there fore generating a final net saving of €922,855.

Conclusions: Proactively switching the ART in properly selected patients with sustained virological suppression generated significant cost savings at 48 weeks and proved to be a cost-effective strategy. These findings might have implications for decision makers in designing safe strategies that maintain HIV-1 suppression at lower costs.

614 The Cost-Effectiveness of Genotype Testing for Primary Resistance in Brazil

Paula M. Luz[1], Bethany L. Morris[2], Beatriz Grinsztejn[1], Kenneth A. Freedberg[2, 3], Valdilea G. Veloso[1], Rochelle P. Walensky[2, 4], Yoriko M. Nakamura[2], Paul E. Sax[5, 6], Claudio J. Struchiner[1], A. David Paltiel[7]

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Background: A recent surveillance study in 20 centers from 13 populous cities in Brazil reported a primary NNRTI resistance prevalence of 4.4%. Yet, a policy of universal genotype-resistance testing (GRT) prior to first-line ART initiation is not recommended by the Brazilian National AIDS Program guidelines. We sought to evaluate the cost-effectiveness of such a policy.

Methodology: We used a previously published microsimulation model of HIV disease (CEPAC-International), populated with data from Brazil. We compared the clinical impact, costs, and cost-effectiveness of no initial genotype test to GRT, simulating both patients who did and did not have primary NNRTI resistance, and weighing the results based on primary resistance prevalence. Model parameters were derived from the HIV Clinical Cohort at the Evandro Chagas Clinical Research Institute of the Oswaldo Cruz Foundation and from published official Brazilian Governmental data: 69% were male, mean age 36 years (SD 10 years), mean CD4 348/µL (SD 300/µL), and a genotype cost of 2012 US$233. We assumed annual costs of US$2,200 for 2nd-line ART and US$12,750 to US$23,280 for 3rd- through 5th-line ART; these were varied broadly in sensitivity analyses. Costs were discounted at 3%/year. A strategy was defined as "very cost-effective" (or "cost-effective") if its incremental cost-effectiveness ratio was less than 1x (or 3x), the 2012 Brazilian per capita GDP of US$12,340.

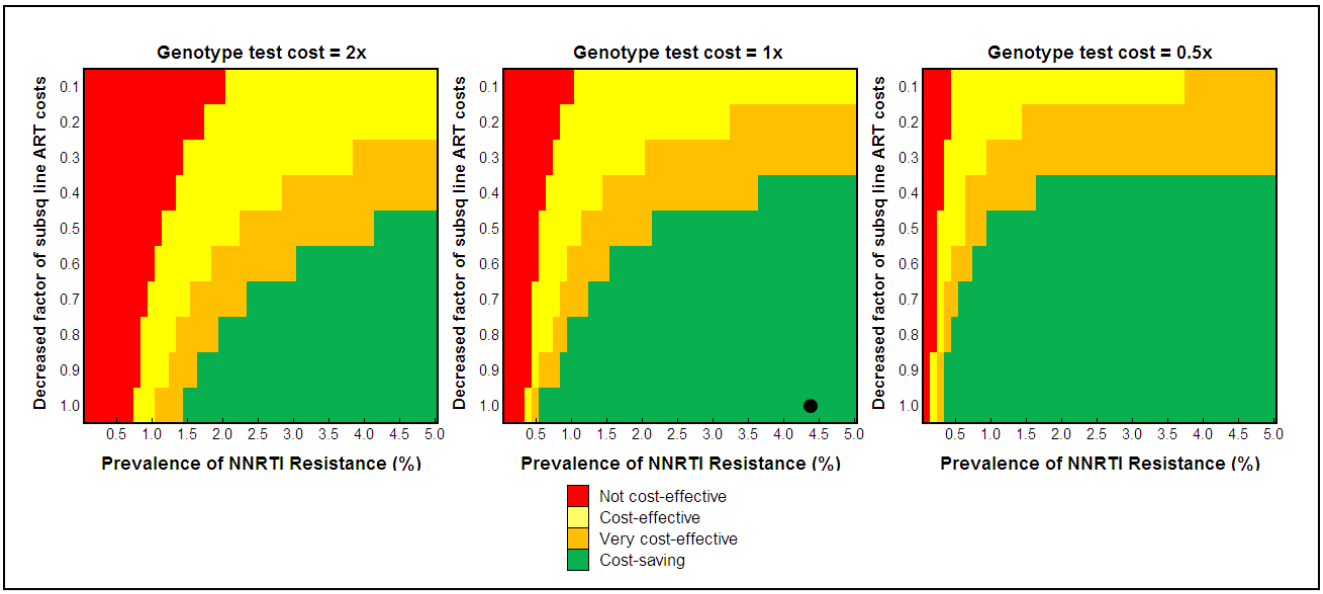

Figure 1. Multivariate sensitivity analysis varying genotype test cost, subsequent-line ART costs, and primary NNRTI resistance prevalence. The black dot indicates the base case result.

Results: Compared to no initial genotype test, GRT increased discounted life-expectancy from 18.52 to 18.55 years and reduced discounted lifetime cost from US$98,100 to $97,000; thus, in the base case, GRT was cost-saving. GRT was cost-effective at primary resistance prevalences as low as 0.4% and remained cost-effective even when subsequent-line ART costs were assumed to be equal to second-line ART costs (ICER of US$14,290). Cost-inefficient results were observed only when simultaneously holding multiple parameters to extremes of their plausible ranges (Figure 1).

Conclusions: This study is the first to demonstrate the attractiveness of GRT in a middle-income country with free-of-charge access to antiretroviral therapy. The cost of baseline genotype-resistance testing in ART-naïve individuals in Brazil has the potential to improve survival and save money over the lifetime of the patient, as it reduces the need for more costly subsequent-line therapies. Initial genotype-resistance testing should be recommended by the Brazilian National Health System.

Session P-M1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

HIV Early Detection: Application of New Assays

615 Application of the Geenius™ HIV1/2 Supplemental Assay for Detection of Recent HIV Infections

Sheila M. Keating[1,2], Gary Murphy[3], Alex Welte[4], Reshma Kassanjee[4], David Matten[4], Shelley N. Facente[1], Mila Lebedeva[1], Michael P. Busch[1,2], Christopher D. Pilcher[5], Consortium for Evaluation of Performance of HIV Incidence Assays (CEPHIA)

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Background: Assays that measure evolving biomarkers during HIV seroconversion are being used in cross sectional studies for HIV incidence estimation. The Bio-Rad Geenius™ HIV 1/2 Supplemental Assay has been developed for HIV-1 and HIV-2 antibody (Ab) confirmation and differentiation. It is a rapid (30 minute), immunochromatographic test that utilizes serum, plasma, finger stick or whole blood to detect HIV Ab. Single-use dual-path lateral flow cartridges include HIV-1 (p31, gp160, p24, p41)and HIV-2 (gp36, gp140) antigen bands and a protein A control band bound to the membrane solid phase, and protein A conjugated to colloidal gold dye particles for detection. Band intensities are captured by an automated reader enabling quantification of IgG Ab levels. Previous analysis by Bio-Rad of CEPHIA Developmental and Qualification Panels led to provisional criteria for interpretation of results for HIV incidence applications.

Methodology: Geenius™ assays were performed on the 2500-member CEPHIA Evaluation Panel. This panel consists of clade diverse specimens from 918 individuals from the United States, Brazil and Africa, predominantly ART-naïve, with estimable dates of infection (from 0-12 years), supplemented by "challenge" specimen sets from patients with factors predisposing to false recent results (elite controllers, suppressive ART, and AIDS). A Geenius™ recency index was calculated using HIV-specific band intensities for p31, gp41, and gp160 relative to the control band. Regression and frequency estimation were used to estimate mean duration of recent infection (MDRI: mean time, within 1-year post estimated exposure, that subjects return recent results) and false recent rate (FRR: proportion of recent test results among patients at least 1-year post infection).

Results: Using the manufacturer's cutoff for recent infection discrimination (index=1.5) the MDRI was calculated to be 157 (140.5-174.7) days. The FRR on eligible specimens was 8.9% [7.3-10.7%]. False recent misclassification was common in specimens from patients on suppressive ART (71.3% [65.7-76.5%]) and from elite controllers (38.7% [28.8-49.4%]), but was uncommon in specimens from patients with AIDS or low CD4 counts (4.8% [2.7-7.9% CI] and 3.9% [1.8-7.2% CI] respectively). Weighting clinical stages among untreated individuals had no impact.

Conclusions: This is the first evidence that the Geenius™ assay may be used as a method for identifying recent HIV infection. The MDRI and FRR presented here are similar to other currently used methods for recent HIV infection. The rapid test format allows for classification of recent infections at the same time that rapid HIV1/2 Ab confirmation and differentiation is performed.

616 Cost Effectiveness of Adding 4th-Generation Immunoassay Screening After a Negative Rapid HIV Test

Angela B. Hutchinson[1], Stephanie Cohen[2], Emily Westheimer[3], Cynthia Gay[4], Elliott Marseille[5], Laura Hall[6], Lisa Hightow-Weidman[4], Benjamin Tsoi[3], Mark Pandori[7], Philip J. Peters[1]

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Background: While point-of-care rapid HIV tests are essential to

HIV prevention services in high-risk communities, these assays may not detect early HIV infection. We evaluated the cost-effectiveness of using 4th generation lab-based immunoassay (4G IA) following a negative rapid HIV test to screen for early infection.

Methodology: A published mathematical model was used to estimate HIV transmissions averted and cost per quality-adjusted life years gained (QALYs) attributable to 4G IA screening following rapid testing. HIV transmissions averted due to serostatus awareness and viral load suppression were calculated for a one year period, conservatively assuming infected persons would be diagnosed one year later in the absence of 4G IA screening. Testing outcomes were derived from the STOP study, a multi-site, prospective evaluation of HIV testing methods. Participants from 12 HIV testing sites in sexually transmitted infection clinics and community-based HIV testing programs in New York City, San Francisco, and North Carolina were screened with a point-of-care rapid HIV test. Rapid negative specimens were then tested for early HIV infection with 4G IA (Architect HIV Ag/Ab Combo assay). Specimens with repeatedly reactive 4G IA results were confirmed with Multispot (HIV-1/HIV-2 Rapid Test) and discordant 4G IA/Multispot results were resolved with an HIV-1 nucleic acid amplification test. Key input values included: 80% receipt of test results, 75% uptake of antiretroviral therapy (ART), costs of $11.00 for HIV negative

tests and $58.34 for HIV positive tests and treatment costs per case averted of $402,000. Testing costs were derived from a CDC micro-costing study and other model inputs from the literature. Sensitivity analyses were conducted on key variables.

Results: From September 2011 to July 2013, rapid HIV testing detected infection in 963 (1.35%) of 71,616 participants. Screening of the remaining 70,653 rapid test-negative specimens with 4G IA identified an additional 127 (0.18%) infections, adding $785,700 in testing costs and $2,015,900 in total program costs (including costs for earlier ART initiation). The 4G IA testing resulted in 6.6 HIV transmissions averted, 29.2 QALYs saved, and overall cost-savings. In threshold analysis, the acute HIV positivity rate could drop to 0.13%, at which point the program is no longer cost-saving but would have a cost-effectiveness ratio of $1,900/QALY gained, and to 0.07%, and still remain below the $100,000/QALY threshold. At base case positivity rates, testing costs could increase approximately four-fold and remain below the $100,000/QALY threshold.

Conclusions: Using 4G IA to screen rapid-test negative specimens for early HIV infection can be a cost-effective strategy in populations at high risk for HIV.

617 Performance of HIV Rapid Tests To Identify Seroconverters in MTN 003 (VOICE)

Urvi M. Parikh[1], **Edward Livant[2]**, Cliff Kelly[3], Rashika Maharaj[4], Marshall W. Munjoma[5], Patrick Karugaba[6], Natasha Samsunder[7], Rosetta Lindiwe Nhlangulela[8], Jeanne Marrazzo[9], Zvavahera M. Chirenje[5], on behalf of the VOICE Study Team

[1]University of Pittsburgh School of Medicine, Division of Infectious Diseases, Pittsburgh, PA, United States, [2]Magee-Womens Research Institute & Foundation, University of Pittsburgh Medical Center, Pittsburgh, PA, United States, [3]Fred Hutchinson Cancer Research Center/SCHARP, Seattle, WA, United States, [4]Medical Research Council of South Africa HIV Prevention Research Unit, Durban, South Africa, [5]UZ-UCSF Collaborative Research Programme in Women's Health, Harare, Zimbabwe, [6]Core Laboratory, MU-JHU Research Collaboration, Kampala, Uganda, [7]Centre for the AIDS Programme of Research in South Africa (CAPRISA), Durban, South Africa, [8]Laboratory, Aurum Institute, Klerksdorp, South Africa, [9]University of Washington Division of Allergy & Infectious Diseases, Seattle, WA, United States

Background: Accurate and efficient identification of seroconverters in antiretroviral-based HIV prevention trials is critical for minimizing emergence of resistance. The use of second-generation (IgG) HIV-1 rapid tests followed by confirmation by Western blot and/or HIV-1 RNA is the most common strategy to identify seroconverters in HIV prevention studies. We evaluated 150,125 HIV rapid tests performed in MTN 003 (VOICE) to assess the performance of this detection algorithm.

Methodology: VOICE evaluated the safety and effectiveness of oral tenofovir disoproxil fumarate (TDF), oral TDF-emtricitabine and vaginal tenofovir 1% gel for the prevention of HIV infection in 5029 women from 15 clinical sites in South Africa, Uganda and Zimbabwe. Participants underwent monthly HIV testing with one or two concurrent rapid tests including Alere Determine™ HIV-1/2, Orasure Oraquick *Advance*® Rapid HIV-1/2 and/or Trinity Biotech™ Unigold Recombigen® HIV. Confirmation of infection following a positive rapid test was done using Western blot (WB) (Bio-Rad). HIV RNA PCR (Abbott M2000 or Roche TaqMan) was used to resolve negative or indeterminate WB following one or two positive rapids.

Results: Rapid testing correctly identified HIV infection status (positive or negative) at 77,795/77,915 (99.85%) follow-up visits in VOICE. Of the 161 rapid tests from 104 participants at 120 visits where rapid test results were discrepant with WB and/or RNA PCR test results, 51/161(32%) were due to a false positive rapid and 110/161 (68%) were due to a false negative rapid. Of note, 48 false-positive cases had rapid test results for subsequent visits; of these, 14 (29%) cases (from 7 participants) resolved by switching the falsely positive rapid kit to a different rapid kit. The resolution of HIV status after discrepant results took a median of 32 days (IQR 27-48 days). The overall sensitivity for Determine, Unigold and OraQuick was 88.78%, 85.86% and 61.54% respectively, and specificity was 99.96%, 99.97% and 99.99% respectively. The positive predictive values of the tests were 91.75%, 94.89% and 94.12% respectively.

Conclusions: In a diverse clinical trial setting, the combination of Determine, Unigold and Oraquick accurately (99.85%) characterized HIV infection status in VOICE, but had limited sensitivity (61-88%) for identifying acute seroconverters. Resolution of discrepant results prolongs the confirmation of seroconversions. The use of newer antigen/antibody rapid tests could improve current HIV testing algorithms by reducing the time from infection to detection.

618 Algorithms and Acute Infections: Innovations in Routine HIV Screening

Kara I. Geren[1], Eric O. Moore[2], Robert E. Fromm[3], Dan Hobohm[4], Joy Jenkins[5], Heather L. Jordan[5], Frank LoVecchio[1], Nancy Lowman[5], Robert McGuire[6], Cheri K. Tomlinson[2]

[1]Emergency Medicine, Maricopa Integrated Health System, Phoenix, AZ, United States, [2]Grants Administration, Maricopa Integrated Health System, Phoenix, AZ, United States, [3]Administration, Maricopa Integrated Health System, Phoenix, AZ, United States, [4]Clinical Laboratory, Maricopa Integrated Health System, Phoenix, AZ, United States, [5]Adult Emergency Department, Maricopa Integrated Health System, Phoenix, AZ, United States, [6]Information Technology, Maricopa Integrated Health System, Phoenix, AZ, United States

Background: CDC recommends routine, opt-out HIV screening in all healthcare settings if the undiagnosed prevalence is ≥0.01%. Acute/Stage 0 HIV infections are defined as a positive initial serologic test, negative or indeterminate supplemental antibody test, and positive HIV RNA test. Acute phase transmission rates are as much as 16 times higher than the overall sexual transmission rate. Early diagnosis of HIV infection results in better health outcomes. Testing for HIV antigens and antibodies using 4th generation technology allows earlier diagnosis of HIV, notably during the acute phase.

Methodology: The Adult Emergency Department (ED) of the Maricopa Integrated Health System (MIHS), a metropolitan safety-net hospital serving predominantly uninsured and minority populations, implemented routine, opt-out HIV screening using 4th generation testing technology. During triage, ED nurses inform patients that all blood draws include an HIV test at no additional cost. Patients are informed of their right to opt-out and ask questions. Consent is inferred unless the patient opts-out or is excluded per MIHS policy. Following a documented, pre-defined department protocol, nurses place an "HIV: If labs drawn" order for which an ED physician cosign is required. Notifications of preliminary positive results are completed by the physician and Care Management with transition to a Linkage to Care Specialist upon discharge.

Results: In our first 27 months, MIHS conducted 24,634 tests through the ED. Only 15% of patients actively opted-out of HIV screening. We have confirmed 69 previously undiagnosed cases of HIV infection (0.28% positivity rate). Of those cases, 17 (25%) are acute infections. Initial mean HIV viral load in acute cases is 4,813,837 cpy/ml compared to 403,288 cpy/ml in chronic cases. Latest mean viral load in acute cases is 12,038 cpy/ml with 53%

having achieved viral suppression. Latest mean viral load in chronic cases is 58,977 cpy/ml with 41% having achieved viral suppression. Initial mean CD4 count in acute infections is 554 compared to 280 in chronic cases. Latest mean CD4 count in acute cases is 743 compared to 414 in chronic cases. The mean between ED and first HIV medical appointment is 39 days in acute cases and 51 days in chronic.

Conclusions: Our experience confirms that individuals with acute HIV infection often seek medical care for their symptoms presenting opportunities to intervene. In the absence of 4th generation testing technology, one in four diagnosed cases at our ED may have been misclassified as HIV-negative. Because MIHS has routinized testing, notification, and linkage to care activities, we are able to identify previously undiagnosed cases earlier, get them into care sooner, and suppress their viral load faster than more chronic infections.

619 Evaluation of the Proposed US CDC Algorithm for Detection of Acute HIV Infection in Serial Samples

Leigh Anne Eller[1], Mark Manak[1], Ashley Shutt[1], Rapee Trichavaroj[2], Joseph Oundo[3], Cornelia Lueer[4], Fatim Jallow[5], Jerome Kim[6], Merlin Robb[1], Sheila Peel[6]

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Background: A new HIV diagnostic algorithm has been proposed by the US CDC to improve acute HIV infection (AHI) detection and type differentiation of anti-HIV-1 from HIV-2 antibodies. The algorithm employs a 4th generation HIV-1/2 ELISA (4th gen) followed by the Multispot HIV-1/HIV-2 Rapid Test and nucleic acid testing, if indicated. We evaluated algorithm performance on well-characterized panels of serial samples collected from AHI cases identified by the Early Capture HIV Cohort (ECHO) Study, RV217.

Methodology: Individuals at high risk of HIV infection from Tanzania, Uganda, Kenya and Thailand were screened twice-weekly by Aptima HIV-1 Qualitative RNA assay (Gen-Probe, Inc. San Diego, CA). Following a reactive (R) Aptima result, serial samples collected twice weekly from consenting participants were screened with GS Combo Ag/Ab EIA (4th Gen), GS HIV-1/2 Plus O EIA (3th Gen), HIV1/2 Multispot (Bio-Rad Laboratories, Redmond, Washington), HIV-1 p24 Antigen (Ag) Test (Bio-Rad, France) and Abbott m2000 real-time quantitative HIV RNA assay (Des Plaines, Illinois). In this algorithm, an individual is considered HIV uninfected if the 4th gen ELISA is non-reactive (NR), and HIV infected if a R 4th gen ELISA is confirmed by positive (POS) Multispot result. An individual is considered to be an AHI case, if the 4th gen ELISA is R, Multispot is negative, and HIV nucleic acids is detected.

Results: Of 29 Acute HIV infection cases, only 7 were R by 4th gen ELISA at the earliest timepoint (median 2 days past R Aptima) with a detectable viral load. HIV-1 viral loads in the very early NR GS Combo samples ranged from 2.16 to 5.95 log10 copies/ml and were on the early viral upslope before peak viremia. In the 22 4th gen NR cases, p24 concentrations were lower than the package insert sensitivity of 50pg/ml. Five of seven (5/7) cases demonstrated R GS Combo results with p24 levels less than 50pg/ml (range 25-49 pg/ml). GS Combo reactivity was detected at a median 7 days (range 2-15) after the first reactive RNA test, 6 days before peak viral load, and 8 days before 3rd gen ELISA reactivity. Multispot reactivity was detected on median day 20. No HIV-2 infections were observed. Using the simulated algorithm, GS Combo reflexing to Multispot, in samples collected within the first 14 days post HIV-1 RNA positivity, 29/29 acute infections with p24 levels above 50pg/ml.

Conclusions: The proposed US CDC algorithm identified 29/29 individuals with HIV-1 acute infection. Only 7/29 AHI cases were detected at the first visit when HIV-1 viremia and p24 concentration were low. This algorithm, with the addition of a 4th gen ELISA, enhances AHI detection sensitivity. Robust point of care HIV viral load detection would further reduce the diagnostic window, especially when screening most-at-risk cohorts.

Session P-M2 Poster Session
Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

HIV Diagnostics

620 Evaluation of the Hologic Aptima HIV-1 Quant Dx Assay With HIV-1 Subtypes

Mark M. Manak[1], Holly Hack[1], Tracy Trsic[2], Sangeetha Nair[2], Andrew Worlock[2], Sheila A. Peel[3], Jennifer Malia[3], Linda Jagodzinski[3]

[1]DLDM, US Military HIV Research Program, HJF, Silver Spring, MD, United States, [2]Hologic, San Diego, CA, United States, [3]DLDM, US Military HIV Research Program, WRAIR, Silver Spring, MD, United States

Background: An important consideration in selection of HIV-1 viral load assays is the ability to detect and accurately quantify the diversity of current HIV-1 subtypes. In this study, we evaluated the quantitation of HIV-1 subtypes by a new Hologic Aptima HIV-1 Quant Dx Assay, which is currently in development, on the fully automated PANTHER System and compared it to that of the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 v2.0 and the Abbott m2000 RealTime HIV-1 Assays.

Methodology: Assay performance to include precision, linear dynamic range, and lower limit of detection (LLOD) was evaluated using well-characterized panels of cultured virus spiked into HIV negative plasma. LLOD was determined by testing thirty replicates each of 2-fold serial dilutions of cultured subtype B virus at 100 to 1.5 copies/ml. Subtype sensitivity was evaluated on 62 previously subtyped plasma samples from Uganda, Kenya, Tanzania and Thailand and 171 HIV-1 isolates from 35 different countries. Samples diluted to ~1E5 copies/ml were tested using the Hologic Aptima, Roche TaqMan, and Abbott m2000 quantitative HIV-1 RNA assays.

Results: The Aptima assay demonstrated good linearity from 1E2 to 1E7 copies/ml, with R^2 values >0.992 for all subtypes. Assay accuracy was within 0.15 log of the target value of the secondary HIV-1 WHO standard. Probit analysis of serial dilutions of cultured HIV-1 established a LLOD of 3.1 copies/ml (50%) and 15 copies/ml (95%), with a precision of 10.4% at 100 copies/ml. Quantitation of HIV-1 subtypes by the Hologic assay agreed closely with those by the Roche and Abbott assays, and were within 0.5 logs in 94.8% and 84.9% of the samples, respectively; the remainder within 1 log of the Hologic measurement.

Conclusions: The Hologic Aptima HIV-1 Quant Dx Assay demonstrated excellent specificity, precision, sensitivity, and linear dynamic range. The assay was capable of accurate quantitation of all major HIV-1 subtypes including subtypes A, B, C, D, F, G, H, O, CRF01_AE, CRF02_AG and complex mixtures, with results comparable to that of the Roche TaqMan v2.0 and Abbott m2000 quantitative HIV-1 RNA assays. The fully automated assay is easy to perform, and results for at least 275 samples can be obtained within an 8 hour shift.

621 CAP/CTM V. 2.0 Using Dried Blood Spots Ineffective at Diagnosing Antiretroviral Treatment Failure

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Background: The 2013 WHO guidelines for antiretroviral treatment (ART) of HIV infections recommend viral load (VL) for routine monitoring and diagnosis of treatment failure (TF) defined as > 1,000 copies/ml. Due to operational simplicity, dried blood spots (DBS) are recommended as an alternative specimen type however at a higher TF diagnostic threshold of 3-5,000 copies/ml. DBS based VL testing has been extensively evaluated in comparison with plasma based testing however performance has varied. We assessed DBS against plasma based VL performance under field laboratory conditions using the Cobas Ampliprep/TaqMan Version 2.0 (CAP/CTM), a common platform for screening for suspected virological TF.

Methodology: EDTA whole blood (WB) specimens were obtained at three health facilities from 823 ART patients after ≥6 months on ART when blood was submitted for routine or targeted plasma VL tests at the Namibia national reference laboratory. DBS were prepared from these blood specimens within 6 hours after blood draws. DBS were dried overnight and packaged according to the WHO recommended method. DBS VL was determined using CAP/CTM HIV-1 version 2.0 test kits following the manufacturer's instructions. The assay has a lower detection limit of 2.60 $\log_{10}$ copies/ml. DBS VL data were analyzed using plasma VL as reference standard.

Results: Using DBS (n=823) the clinical sensitivity, specificity, positive (PPV) and negative predictive value (NPV) with 95% confidence intervals (CI) were 0.99 (0.96 - 0.99), 0.55 (0.52 - 0.59), 0.33 (0.29 - 0.38) and 0.99 (0.99 - 1.0), respectively, at a threshold of 5,000 copies/ml; and 0.99 (0.97 - 1.0), 0.26 (0.22 - 0.29), 0.29 (0.26 - 0.33) and 0.99 (0.90-1.0), respectively, at a threshold of 1,000 copies/ml. The prevalence (95% CI) of TF was 0.18 (0.16 - 0.21) and 0.23 (0.21 - 0.26) in plasma and 0.55 (0.51 - 0.58) and 0.80 (0.77 - 0.83) in DBS at the 5,000 and 1,000 copies/ml thresholds, respectively.

Conclusions: Low specificity and PPV of the CAP/CTM on DBS at both evaluated threshold levels indicate high rates of false positive results for virological TF may occur if this approach were used for routine ART patient monitoring and TF diagnosis. Even use of the more conservative DBS specific TF threshold of 3-5,000 copies/ml recommended by the 2013 WHO guidelines may result in uneccessary ART regimen changes for patients responding favorably to current treatment. These results add to the published literature highlighting suboptimal specificity and PPV of DBS based VL testing. As such, recommendations for use of DBS for routine VL monitoring may require further evaluation. Additional research is needed to better understand the effectiveness of these approaches in routine programmatic settings, including the performance of other assay versions and types.

622 Reliable and Accurate CD4 T Cell Count and Percent of the New Portable Flow Cytometer CyFlow MiniPOC

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Background: An accurate, reliable, and affordable CD4 T cells count is essential in several parts of the world. Flow cytometry is the "gold standard" for CD4 T cell count, but this technique is expensive and requires sophisticated equipment and trained personnel. In addition, the lack of ready access to technical support and quality assurance programs limits the use of flow cytometry techniques in resource-constrained countries. Instruments are now available that can solve these problems. We have tested the new portable flow cytometer for CD4+ T cell count percentage, named CyFlow MiniPOC (Partec), and analysed its sensitivity, carry-over contamination and repeatability. Its accuracy has been compared analysing the same blood samples with 2 other systems based upon CyFlow Counter (Partec) or Cytomic FC 500 (Beckman Coulter).

Methodology: Venous blood from 59 adult HIV-1+ patients (age: 25-58 years; sex: 43 males; CD4 count: 34-1,115 cells/ul; CD4%: 3.1-48.0) was collected in EDTA blood, stained with the Partec MiniPOC CD4% count kit - dry kit, and analysed within a maximum of 2 hours. CD4 T cell count and percentage were determined by the CyFlow MiniPOC instrument, equipped with a 30 mW, 532 nm laser and three optical parameters for detection of side scatter (SSC), orange and red fluorescence. CD4 T cell count and percentages were measured in parallel by CyFlow Counter and by a dual platform system based upon Cytomic FC 500 (Cytostat tetrachrome kit for mAbs) and Coulter HMX (for absolute cell count). All measures were performed in triplicate.

Results: The accuracy of CyFlow MiniPOC against Cytomic FC 500 showed a correlation coefficient of 0.98 and 0.97 for CD4 T cell count and percentage, respectively (linear regression analysis). The accuracy of CyFlow MiniPOC against CyFlow Counter showed a correlation coefficient of 0.99 and 0.99 for CD4 T cell count and percentage, respectively. CyFlow MiniPoc showed an excellent repeatability: CD4 absolute number and percentage were analysed on two instruments, with an intra-assay precision below +/- 10% deviation. The sensitivity was linear in the range 0-5,000 CD4 T cells/ul. There was no effect of carry-over contamination for samples at all CD4 values, regardless of their position in the sequence of analysis.

Conclusions: The cost-effective and portable instrument MiniPOC produces reliable and accurate results that are fully comparable with highly expensive dual platform systems. Indeed, data perfectly correlate with those obtained with Cytomic FC 500/Coulter HMX. Finally, using CyFlow MiniPoc permits to perform in a fast and easy way a very high number of CD4 T cells counts per day.

623LB A Recombinant HIV-1 Gag Virus Panel for the Evaluation of p24-Antibodies and HIV Diagnostic Tests

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Background: Diagnostically, the HIV-1 p24 protein is currently only used in HIV-1/2 Ab + Ag combination screening tests (4th generation). However, there is growing interest in new test development to extend its use to diagnosing paediatric HIV infection and disease monitoring as inexpensive alternatives to PCR-based tests. Regarding the global HIV-1 diversity, such tests should detect all subtypes with similar sensitivity. Readily available, inexhaustible tools for subtype evaluation and test comparisons are a pre-requisite for efficient test development. To this end, we developed a panel of 44 recombinantly expressed virus-like-particles (VLPs), which contain the Gag-Protease region of HIV-1 subtypes A, B, C, D, F, G, H, circulating recombinant forms 01_AE, 02_AG, BF/BG, and group O. We characterised 10 mono- or polyclonal antibodies (mAb, pAb) for their subtype-binding profiles and initiated an evaluation of commercially available 4th generation screening tests.

Methodology: Patient-derived PCR-amplified Gag-PR regions were cloned into pCMVdr8.91, allowing expression of non-infectious VLPs in tissue culture. Concentrations were standardized based on the VLPs' reverse transcriptase activity. To assess p24 antibody binding, VLPs were lysed and coated on ELISA plates. For testing diagnostic kits, dilutions of VLPs corresponding to 2, 10 and 50 IU/mL (WHO p24 standard) were prepared in HIV-negative plasma.

Results: p24 amino acid divergence of our panel within a given subtype ranged from 4.5-8.9% and was similar to that of the Los Alamos subtype reference sequences (2.9-9.1%). Overall, weighted panel diversity was 6.8%, compared to 4.9% for the subtype-matched reference sequences. Binding profiles of p24 antibodies showed that only one mAb detected 43/44 panel members (97.7%), sensitivity for the other six mAbs ranged from 19/44 - 40/44 (43.2 - 90.9%). Subtype B and CRF01_AE were detected by the 7 mAbs most effectively (mean sensitivity 85.7%), but mean sensitivity to CRF02_AG was low (37.1%). The three pAb tested (one a pooled HIV-serum) showed a sensitivity of 100% for all subtypes except D, G and CRF02_AG (83.3%, 83.3% and 86.7%, respectively).

To date, we have tested two commercial combination screening tests and noted a large difference in performance. The ARCHITECT HIV Ag/Ab Combo assay detected all but one VLP, even at low concentration, whereas the Access HIV combo assay completely missed 16/44 subtypes.

Conclusions: Our HIV-1 Gag subtype panel has a broad diversity and served as a useful tool to assess the breadth of subtype detection. Moreover, initial results indicate that there is a need to carefully assess the capability of existing diagnostic kits for detecting the p24 of diverging subtypes.

624 Evaluation of Pima CD4 Point-Of-Care Device in Western Kenya for Potential Use in Field Settings

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Background: Pre-treatment loss to follow-up can be a barrier to effective antiretroviral treatment (ART) programs. CD4 point-of-care (POC) testing may reduce this by improving linkage to care. However, an implementation challenge is accuracy when operated by lay health workers (HIV testing counselors and community health workers) in field settings. We validated the accuracy of Pima's CD4 POC device (PCD4D) when performed by lay health workers (LHW) versus laboratory technicians (LT), with LT-performed FACSCalibur as the gold standard, using capillary and venous blood from HIV-1 infected patients.

Methodology: In Phase I, we compared PCD4D performed in the laboratory by LT against FACSCalibur for 280 venous specimens. In Phase II we compared PCD4D performed by LHW versus LT from 147 paired capillary and venous specimens, and compared these to LT-performed FACSCalibur (venous and capillary). Statistical analyses included agreement

		*Pima Lab tech (Venous)	Pima Lab tech (Venous)	Pima Lay HW (Venous)	Pima Lab tech (Capillary)	Pima Lay HW (Capillary)
FACSCalibur (Venous)	CCC	92 (91,94)	91 (89,94)	87 (84,91)		
	Absolute Mean bias	39 (26, 52)	66 (53, 78)	86 (72, 100)		
	Sensitivity	89 (78, 95)	100 (86,100)	94 (77, 99)		
	Specificity	89 (84,93)	98 (93, 100)	95 (89, 98)		
FACSCalibur (Capillary)	CCC				94 (93,96)	93 (91,95)
	Absolute Mean Bias				36 (25,48)	44 (32, 57)
	Sensitivity				79 (62, 90)	86 (67, 93)
	Specificity				98 (93,100)	99 (94, 100)

* Phase I results on 280 venous specimens; other cells indicate Phase II results on 147 paired capillary and venous specimens

Table 1: Correlation Concordance Coefficient (CCC), absolute mean bias, sensitivity and specificity of Pima CD4 POC compared to FACSCalibur for both capillary and venous blood, operated by lay healthworkers (LHW) and laboratory technicians (LT). [Statistic, (95% CI)]

(Bland-Altman tests), correlation concordance coefficient (CCC), and sensitivity plus specificity for classification as above/below FACSCalibur-defined CD4 count of 350 cells/mm^3 (Kenya's current threshold for ART initiation).

Results: Phasel: PCD4D compared favorably with FACSCalibur on venous specimens; venous sensitivity and specificity at 350 cells/mm^3 were both 88.9% (Table 1). Phase II: Good performance was observed for venous PCD4D results from both LHW (CCC=87, bias-86cells/µl) and LT CCC=91,bias-66cells/µl). Capillary PCD4D also compared favorably: LHW (CCC=93,bias-44cells/µl), LT (CCC=94,bias-36cells/µl). Venous sensitivity and specificity were 100 and 98% respectively for LT, and 94 and 95% for LHW. Using capillary blood, the sensitivity and specificity were 79 and 98% (LT) and 86 and 99% (LHW).

Conclusions: POC CD4 results were comparable to FACSCalibur for both venous and capillary specimens, when operated by both lay health workers and lab technicians. POC CD4 testing has potential to enhance HIV care and treatment programs without burdening laboratory technicians in resource limited settings.

625 Comparison of Central and Local HIV-1 RNA Quantification From Two International Clinical Trials

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Background: Central measurement of plasma HIV-RNA (pVL) is common in clinical trials. Despite the increased expense and complexity, central testing is believed to reduce variability. In the setting of two international randomised clinical trials we aim to compare trial outcomes on the basis of central and local laboratory assessed pVL.

Methodology: Data were available from ENCORE1 and SECOND-LINE study participants. Central pVL data were generated at a single laboratory from batch retrospective assay of cryo-preserved samples (Abbott m2000rt lower limit of detection (LLD) 40 copies/mL) and 33 local laboratories (LLD 20-50 copies/mL) performing a variety of real time assays under differing infra-structure constraints. The trials' endpoint, non-inferiority between arms (Δ -10 and -12% respectively) in proportion <200copies/mL at week 48, intention to treat missing=fail were calculated from central+ local (where central was missing) and local measure alone. The distribution of log10 pVL copies/mL at week 0 was summarised and described using a Bland-Altman plot (distribution of difference ±1.95 standard deviations (lower (LLA) and upper level (ULA) of agreement) and average of test results).

Results: Of the participants in follow up at week 48, 98% had local and central pVL measures (ENCORE1 603/615, 602/615; SECOND-LINE 510/519, 508/519 respectively). The point estimates (% difference [95%confidence interval]) determined by central+local measure were very similar to those by local measure alone in both studies (1.9 [-1.9, 2.1], 2.5 [-1.6, 6.6] ENCORE1; 1.8[-4.7, 8.3], 0.3[-6.4, 7.0] SECOND LINE respectively). Non-inferiority in both trials was established by both determinations.

At week 0 mean pVL was greater than 4.0 log10 copies/mL in both trials on both measures. Local measures were marginally lower than central measures (mean difference pVLlog10 -0.10 and -0.17 respectively) (Figure 1). The limits of agreement were narrower for ENCORE1 than SECOND-LINE (±0.66, ±1.14 log10¬ copies/mL respectively).

Conclusions: The comparison of primary endpoints revealed no difference in interpretation of trial outcomes based on the use of local or central pVL measures. These data indicate that in a clinical trial setting, where the outcome of interest is pVL within routine limits of detection, central laboratory testing is not warranted.

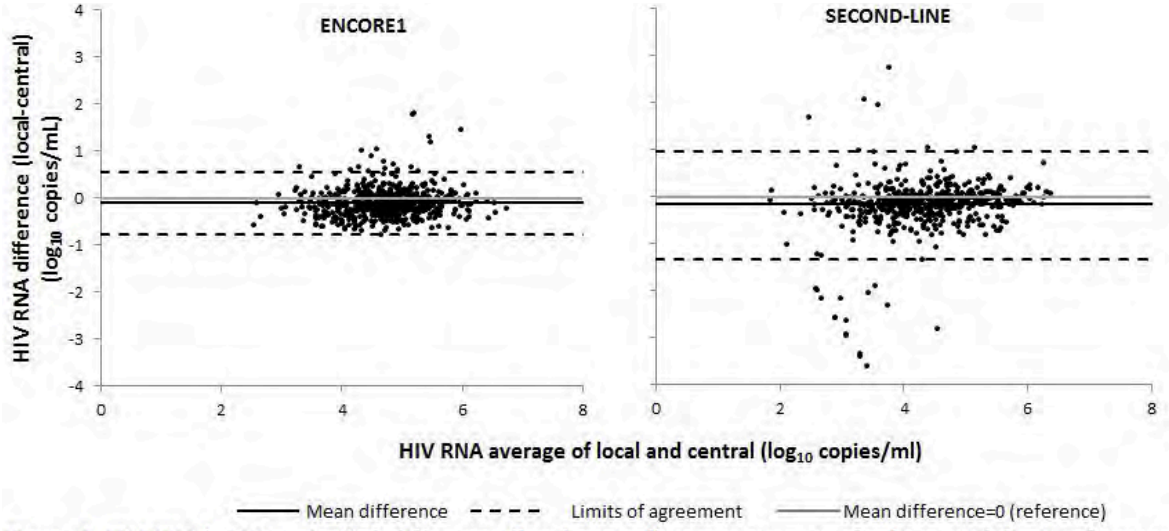

Figure 1. HIV RNA log10 copies/ml difference (local-central) versus average of values, with limits of agreement, by trial.

626 HIV-1 Can Be Confirmed by Bio-Rad Geenius™ HIV 1/2 Confirmatory Assay Using Dried Blood Spots

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Background: Confirmatory assays for HIV diagnosis are not well implemented in limited income settings, impeding an early HIV detection and, consequently, delaying the prescription of antiretroviral treatment in the infected population. Bio-Rad Geenius™ HIV 1/2 Confirmatory Assay is a single-use immunocromatographic test for the confirmation and differentiation of individual antibodies of HIV-1 and HIV-2 in venous whole blood, serum or plasma samples. Since plasma/serum is difficult to collect and/or process in remote settings from limited resource countries and in mobile populations, our objective was to validate for the first time the assay Geenius™ HIV 1/2 for diagnostic use utilising dried blood spots (DBS) specimens.

Methodology: Geenius™ HIV 1/2 test was performed to confirm the HIV infection in 70 women previously diagnosed as HIV-1 positive by one to three rapid tests using whole blood samples in the Hospital of Bata, Equatorial Guinea, from November 2012 to August 2013. DBS specimens were prepared by adding two drops of blood to fill each circle of 903 filter paper cards (GE Healthcare). Cards were dried overnight at room temperature and stored at –20°C until their shipping at room temperature to Madrid, Spain for testing. After their arrival, they were stored at –80°C until use. Blood from one DBS circle per patient was eluted in 150 µl elution buffer for 1 hour with gentle rotation. The test was performed according to the manufacturer indications, but using 40 µl of the eluted circle as specimen. The results obtained from Geenius™ HIV 1/2 were confirmed by western blot (New Lav Blot I, Bio-Rad) using the same elution volume.

Results: Geenius™ HIV 1/2 (Bio-Rad) successfully confirmed the HIV-1 infection using DBS in all 70 tested women from Equatorial Guinea with at least one positive rapid test and only using a low volume of eluted dried blood. No HIV-1/HIV-2 coinfections were found in the study cohort.The HIV-1 positivity was confirmed in all cases in DBS by western blot (Bio-Rad).

Conclusions: This is the first report that proves a good performance of Geenius™ HIV 1/2 assay (Bio-Rad) for the confirmation of the HIV-1 infection using only two drops of dried blood. Our results approve the utility of this rapid confirmatory assay using a low volume of dried blood when a lack of adequate infrastructure to collect, store or transport plasma or serum is found. DBS are a practical alternative to plasma for HIV serological diagnosis.

627 Standard Diagnostics Bioline HIV/Syphilis Duo Test: Multi-Site Laboratory Evaluation

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Background: The WHO and UNAIDS recommend an integrated strategy for the elimination of congenital syphilis and mother-to-child transmission of HIV. Laboratory-based syphilis diagnostics are complex and implementation can be hampered by logistical difficulties. Recently, test developers have created rapid tests that can detect multiple infections with the same specimen using a single device. The SD BIOLINE HIV/Syphilis Duo qualitative test uses a solid phase immunochromatographic assay to detects antibodies to all isotypes (IgG, IgM, IgA) specific to HIV-1 including subtype-O, HIV-2 and *Treponema (T.) pallidum* in human serum. This is a simple point-of-care test that can be used in all health care settings to allow immediate treatment. This study was a multisite laboratory-based evaluation of the performance of the SD Bioline HIV/Syphilis Duo test using well- characterized stored serum samples in four countries.

Methodology: A total of 4 laboratory sites participated in the evaluation: Ghana, Peru, Togo, Kenya, and Myanmar in 2012 and 2013. Each site used well-characterized serum specimens for detection of HIV antibodies and *T. pallidum* antibodies using the SD Bioline HIV/syphilis duo test, using a combination of *Treponema pallidum* particle agglutination assay (TPPA) or *T.pallidum* Hemaglutination Assay (TPHA) and rapid plasma reagin (RPR) for detection of *T. pallidum* and enzyme immunoassay (EIA), Western Blot, and rapid tests for the detection of HIV antibodies. We calculated the sensitivity and specificity of test performance from the pooled data using the exact binomial method.

Results: The test performance from each site is displayed in the table. The pooled sensitivity for the HIV antibody component was estimated to be 99.89% (95% CI: 99.39% to 100%) and the specificity was 99.86% (95% CI: 99.25% to 100%). For the *T. pallidum* component, the pooled sensitivity was estimated to be 99.80% (95% CI: 98.89% to 99.99%) and the combined specificity was estimated to be 99.71% (95% CI: 99.16% to 99.94%).

Conclusions: The sensitivity and specificity of the SD Bioline HIV/Syphilis Duo test using serum were very high at each site for HIV and *T. pallidum* antibodies when compared to the gold standard testing. This dual test could be a timely breakthrough for the UNAIDS and WHO strategy for the dual elimination of HIV and syphilis**.** The Bioline HIV/syphilis duo test should be considered for improved coverage of screening for HIV and syphilis infections.

Performance of SD Bioline HIV/Syphilis Duo Test in Well-characterized Serum Specimens									
HIV antibody	Country	Year	N	True Positives	False Positives	False Negatives	True Negatives	Sensitivity	Specificity
	Ghana	2012	400	250	0	0	150	100%	100%
	Togo	2013	310	203	0	0	107	100%	100%
	Myanmar	2013	245	114	1	0	130	100%	99.24%
	Kenya	2013	698	345	0	1	352	99.71%	100%
-	-	-	-	-	-	-	-	-	-

Treponema pallidum antibody	Country	Year	N	True Positives	False Positives	False Negatives	True Negatives	Sensitivity	Specificity
	Ghana	2012	400	250	1	0	149	100%	99.33%
	Togo	2013	241	88	1	0	152	100%	99.20%
	Myanmar	2013	200	74	1	1	124	98.67%	99.20%
	Kenya	2013	698	85	0	0	613	100%	100%
-	-	-	-	-	-	-	-	-	-

Session P-N1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

HCV Testing and Epidemiology

628 High Hepatitis C Infection Rate in Birth Cohort Testing of an Urban, Primary Care Clinic Population

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Background: CDC and USPSTF recommend all persons born within 1945-1965 (Birth Cohort) be tested for hepatitis C (HCV) at least once, given a 3.25% prevalence rate, five times higher than among adults born in other years. Additionally, though the reported rate of HCV in US population are three times higher than that of HIV, Washington DC has reported rates of 2% and 2.6% respectively. We hypothesize that HCV testing in a large, urban primary care clinic, regardless of ascertainment of risk factors, will reveal higher rates than those previously published in the US.

Methodology: Beginning December 2012, we established a HCV testing program in the Primary Care Clinic at MedStar Washington Hospital Center, with CDC grant funding (HepTLC), to sequentially test in this Birth Cohort, link directly to care, and create a sustainable testing program. Eligibility includes: born between 1945-1965, without predetermined risk factors, and not previously HCV tested or positive. HCV antibody positive patients are linked to care with Infectious Disease or Gastroenterology regardless of RNA status. Comparisons are performed between those HCV-infected and not infected, all using chi-square and Student's t-test.

Results: As of September 26, 2013, 9% of the 1,087 tested were found to be HCV infected. Those infected had a mean age of 58.7 +4.9 years; 94% were African American, 56% were men, 55% were past IV drug users (IDU), and 73% had public insurance. Those infected were more likely to be men (OR 2.7 [CI95 1.8-4.1]) and have public insurance (OR 2.1 [CI95 1.3-3.4]) than in those un-infected. Of the 3,929 eligible patients, 45% missed their appointments, 28% were tested; 27% were not tested, this latter group is considered as missed opportunities. Overall clinic appointment adherence was 55%; although 87% of those HCV infected were linked with an HCV expert and 69% were adherent with their first appointment.

Conclusions: This HCV prevalence rate of 9% in this Washington, DC urban clinic is significantly higher than both the previously reported rate of 3.25% in the Birth Cohort, and the reported rate of 2% in the District of Columbia. Furthermore, those who tested positive did not have previously identified risk factors, although 55% reported a prior history of IDU once queried. Rates of testing (28%) were equivalent to rates of missed opportunities for testing (27%); factors associated with the latter need to be identified and addressed. Given these very high prevalent rates in those without pre-identified risk factors, and along with an improved therapeutic cure on the horizon, testing initiatives need to become standard of care and maintained as sustainable models.

629 Prevalence and Risk Factors of Hepatitis C Virus Infection in China's National Methadone Program

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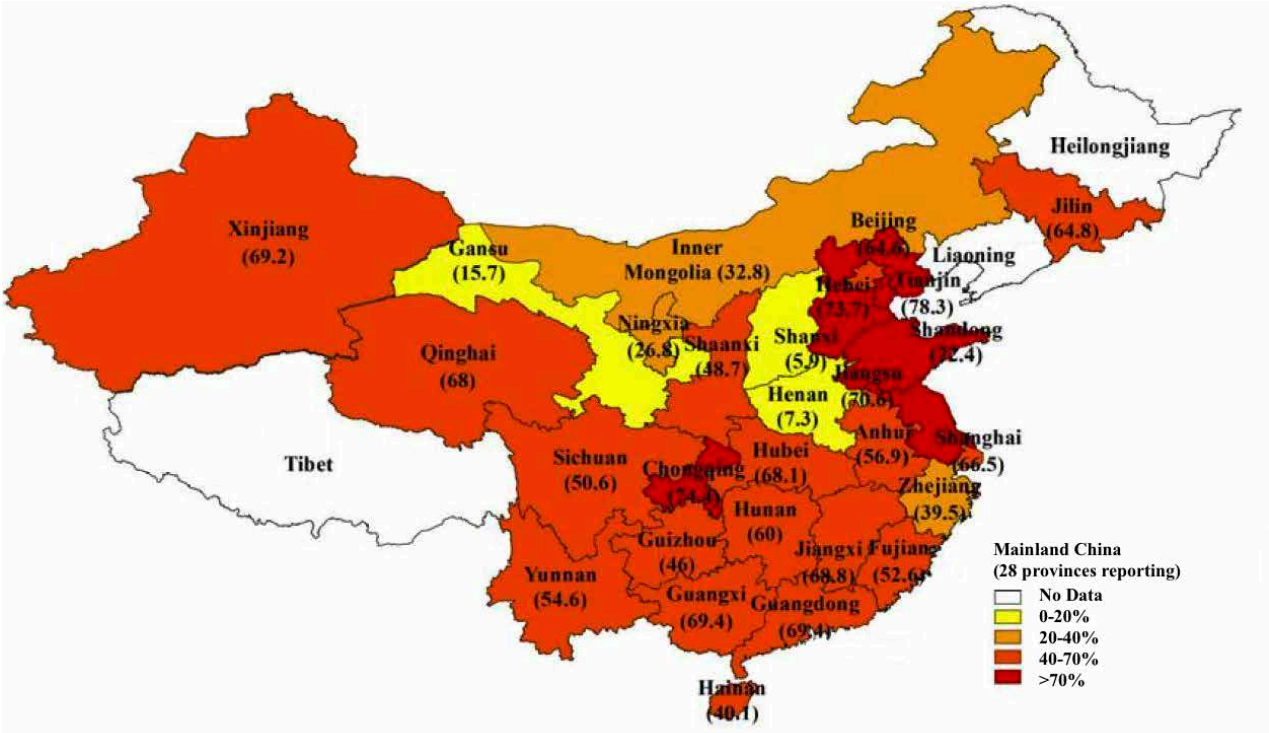
Background: Approximately 13 million people in China are infected with Hepatitis C virus (HCV), while China has over 3 million injection drug users (IDUs). Established in 2004, the Chinese National Methadone Maintenance Treatment (MMT) Program has expanded to become the world's largest drug treatment network. Despite the large HCV-infected population in China, HCV prevalence in the National MMT Program has not been reported. We sought to assess the prevalence and risk factors of HCV infection among clients in the National MMT Program in China.

Methodology: We conducted a cross-sectional HCV seroprevalence study of all adults at enrollment into the National MMT Program from March 2004 to December 2012. The National MMT Program has 756 sites in 28 provinces. Clients provided information on gender, age, ethnicity, marital status, occupation, drug use, and injecting and needle sharing behaviors using a standardized form. Clients were screened for HIV and HCV. Local providers uploaded daily records into a real-time, online central data system. We used univariate and multivariate logistic regression analyses to determine risk factors for HCV infection.

Results: Among 304,658 clients, 166,343 (54.7%) were HCV-infected, 17,670 (5.8%) were HIV-infected, and 14,014 (4.6%) were HIV-HCV co-infected. HCV prevalence among newly enrolled clients declined each year: 67.6% in 2005, 62.9% in 2006, 61.6% in 2007, 59.7% in 2008, 55.0% in 2009, 50.3% in 2010, 50.1% in 2011, and 46.6% in 2012. Figure 1 presents the widespread geographical variation of HCV prevalence; five provinces reported

HCV prevalence above 70% and 19 provinces reported HCV prevalence above 50%. The overall prevalence of IDU was 66.8%, and the distribution closely mirrored HCV infections (Figure 1). Univariate risk factors for HCV infection were female gender, age 30-45 years, Uyghur or Zhuang ethnicity, unmarried, unemployed, IDU, and drug use history >3 years. In multivariable analysis, the strongest correlates of HCV infection were IDU (AOR: 8.2) and drug use history >9 years (AOR: 2.0). Other risk factors for HCV infection were female gender (AOR: 1.4), age >30 years (AOR: 1.3), Uyghur or Zhuang ethnicity (AOR: 1.3), unmarried (AOR: 1.2), and unemployed (AOR: 1.1).

Conclusions: HCV prevalence remains high among clients receiving MMT in China, particularly among IDUs. These findings highlight the importance of HCV and HIV screening upon MMT enrollment in China, and suggest integration of services to prevent or reduce IDU practices.



630 The Burden of Hepatitis C Infection in Pennsylvania State Prisons and Implications for Treatment

Madeline Mahowald[1], Sarah Larney[1, 2], Nicholas Scharff[3], Curt Beckwith[1, 4], Lynn E. Taylor[1, 4], Nick Zaller[1, 4], Timothy Flanigan[1, 4]

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Background: An estimated one million persons with undiagnosed hepatitis C virus infection (HCV) come into contact with the U.S. correctional system each year. Nevertheless, there is limited published data about the HCV prevalence among American prisoners, particularly among women. Moreover, few studies have investigated the prevalence of the various genotypes among HCV-infected prisoners, which is important for guiding treatment and predicting response. The development of new HCV agents makes this a particularly relevant time to further characterize the disease among a population of patients who often come from groups with an increased prevalence of HCV, including persons with mental health conditions, with illicit substance use, and those living in poverty, as well as persons who may have relatively increased access to healthcare while incarcerated.

Methodology: The Pennsylvania Department of Corrections screens all incoming persons for anti-HCV antibody. We performed a secondary data analysis of the anti-HCV test results for all adults entering the Pennsylvania state prison system from 2004-2012, in total and stratified by sex, birth cohort, and year of incarceration. For those patients with a positive result who underwent further testing, we examined HCV RNA and genotype data. We describe these results and the implications of the findings for HCV testing policy within prison systems as well as the treatment of inmates in the era of direct-acting agents.

Results: Among 101,727 prisoners with 130,495 unique tests, overall anti-HCV prevalence from 2004-2012 was 18.1% (95% CI 17.9-18.4). It was higher among women (31.3%) than men (16.8%) (relative risk 1.87, 95% CI 1.81-1.93) and highest among persons born before 1965. The total prevalence among persons born from 1945-1965 was 35.3% (95% CI 34.6,36.0). For all persons outside that birth cohort, the prevalence was 13.5% (95%CI 13.2-13.7). The prevalence decreased in men from 21.7% in 2004 to 14.6% in 2012, a trend not observed among women. Of 101,727 prisoners, 7633 (7.5%) underwent HCV RNA testing at least once. Of these, two thirds had detectable HCV RNA. Of 101,727 prisoners, 3247 (3.2%) underwent genotype testing, with 76.6% having genotype 1, 0.9% having mixed genotypes that included type 1, 11.7% with genotype 3, and 9.3% with genotype 2.

Conclusions: Universal anti-HCV screening is feasible in a correctional setting. The burden of HCV among prisoners in Pennsylvania is high, particularly among women. The high concentration of HCV-infected people makes correctional settings a high-yield venue for expansion of routine HCV testing and treatment. The development of more effective therapies of short duration provides the opportunity to achieve viral eradication among incarcerated populations.

631 Impact of Rapid Hepatitis C Testing On Receipt of Hepatitis C Results in a Public STD Clinic

Oluwaseun Falade-Nwulia[1,2], Shruti Mehta[3], Mark Sulkowski[1], Jackline Lasola[1], Khalil Ghanem[1], Patrick Chaulk[2], David Thomas[1]

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Background: With rapid improvements in the efficacy and safety of hepatitis C treatments, the factors that will determine net treatment effectiveness are the rates of testing of high risk populations and linkage to care. Rapid hepatitis C tests have been demonstrated to be accurate in diagnosis of hepatitis C. Their impact on receipt of hepatitis C antibody results in public health settings such as sexually transmitted disease (STD) clinics is not known.

Methodology: Rapid hepatitis C antibody testing was implemented and routinely offered to all STD clinic attendees at the Baltimore City Health Department (BCHD) Druid STD clinic starting in June 2013. Prior to this, risk-based hepatitis C testing with a standard laboratory based ELISA, was offered at the BCHD STD clinics. We compared the rates of documented hepatitis C posttest counseling and linkage to care of those tested by the rapid method to those tested with the standard of care, ascertained by review of electronic medical records. Written documentation of provision of hepatitis C antibody results was available for patients who received rapid testing. For those who received the standard of care, failure to return to the STD clinic 6 months after laboratory hepatitis C antibody testing was considered lack of receipt of results.

Results: Prior to implementation of the rapid test, 767 individuals (65.5 male) received a standard hepatitis C ELISA, which requires 7 days for results to be available, between January 1, 2012 and December 30, 2012. From June 24, 2013 to September 30, 2013, 1,478 individuals were offered the rapid hepatitis C test with results available in 20 minutes, of whom 1163 (79%) accepted and received rapid hepatitis C testing. 59.5% of rapid tested patients were male. Patients receiving standard of care hepatitis C testing were on average older than rapid hepatitis C tested patients: median age (IQR); 34 (25-47) years and 28 (24-39) years respectively. Out of 137 individuals with positive hepatitis C antibody test results from the standard of care, 90 (67%) individuals received their hepatitis C antibody results. In contrast, 72 (100%) of 72 hepatitis C antibody positive individuals from the rapid tested patients received their hepatitis C antibody results, alcohol screening and posttest counseling on the day of rapid testing; p-value <0.001. Additionally for individuals found to be hepatitis C antibody positive on rapid testing, 69 (96%) of 72 had blood drawn for follow up hepatitis C RNA testing on the day of rapid hepatitis C testing.

Conclusions: Implementation of rapid hepatitis C tests has the potential to dramatically reduce loss to follow up and facilitate early linkages to hepatitis C care.

632 Hepatitis C Antigen Testing: A Reliable Alternative for Diagnosing Acute HCV Infection

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Background: In recent years there have been multiple epidemics of Hepatitis C (HCV) co-infection in HIV-infected populations. The early identification of acute HCV infection can have important implications for both treatment and partner notification to reduce onwards transmission. Acute HCV infection is diagnosed using HCV RNA testing methods which are more sensitive and specific then HCV antibody tests, particularly in immunosuppressed patients. Recently tests against the core antigen of HCV have become available. Our aim was to compare HCV core antigen and HCV RNA testing in the detection of early HCV infection.

Methodology: 100 HIV-infected individuals who presented with isolated alanine transaminase (ALT) values above the upper limit of normal at routine blood sampling (>41 IU) were tested for acute HCV infection using HCV core antigen testing (Abbott Archetect +/- Biorad), HCV RNA viral load (Abbott Real Time PCR (qRT-PCR) and standard in house HCV antibody testing. A cut off value for quantitative HCV antigen testing of 5.0 IU/mL was used in the analysis. Sequential samples were collected over a twelve month period between April 2012 and October 2013. Retrospective testing of previously stored serum samples determined which infections were acute; chronic HCV infections were excluded from the analysis. All HCV positive patients were genotyped and entered into a co-infection clinic for assessment and treatment in accordance with local guidelines.

Results: The mean age of patients was 41 years (27-73), 6 were female, 77% were MSM, 6% were of Black ethnicity and 4% reported IVDU. None had pre-existing liver disease and no alternative cause of raised ALT had been previously identified. Genotype 1aor 1b predominated (90%). Fifteen cases of acute HCV were identified during the 18 months of this study screening isolated ALT rises alone. All 15 were identified by the HCV RNA PCR. HCV antigen testing initially identified 13 positive and 2 'indeterminate' results; these became positive on retesting. On serology, five patients were HCV antibody negative and 4 showed only a weak positive signal at the time sampled.

Conclusions: With the increase in HCV infections amongst HIV-infected populations, a quick, easy and cost-effective method of testing for acute HCV is needed. HCV antigen testing may offer an alternative to HCV PCR as a screening tool in the clinical setting. Relying on HCV antibody tests as a screening tool is likely to miss some acute infections.

673 Hepatitis C Virus Incidence in the Amsterdam Cohort Study Among Men Who Have Sex With Men: 1984-2011

Joost W. Vanhommerig[1,2], Ineke G. Stolte[1], Femke A. E. Lambers[1], Ronald B. Geskus[1,3], Thijs J. W. van de Laar[4], Martien W. Borgdorff[1,3], Sylvia M. Bruisten[1], Janke Schinkel[2], Maria Prins[1,5]

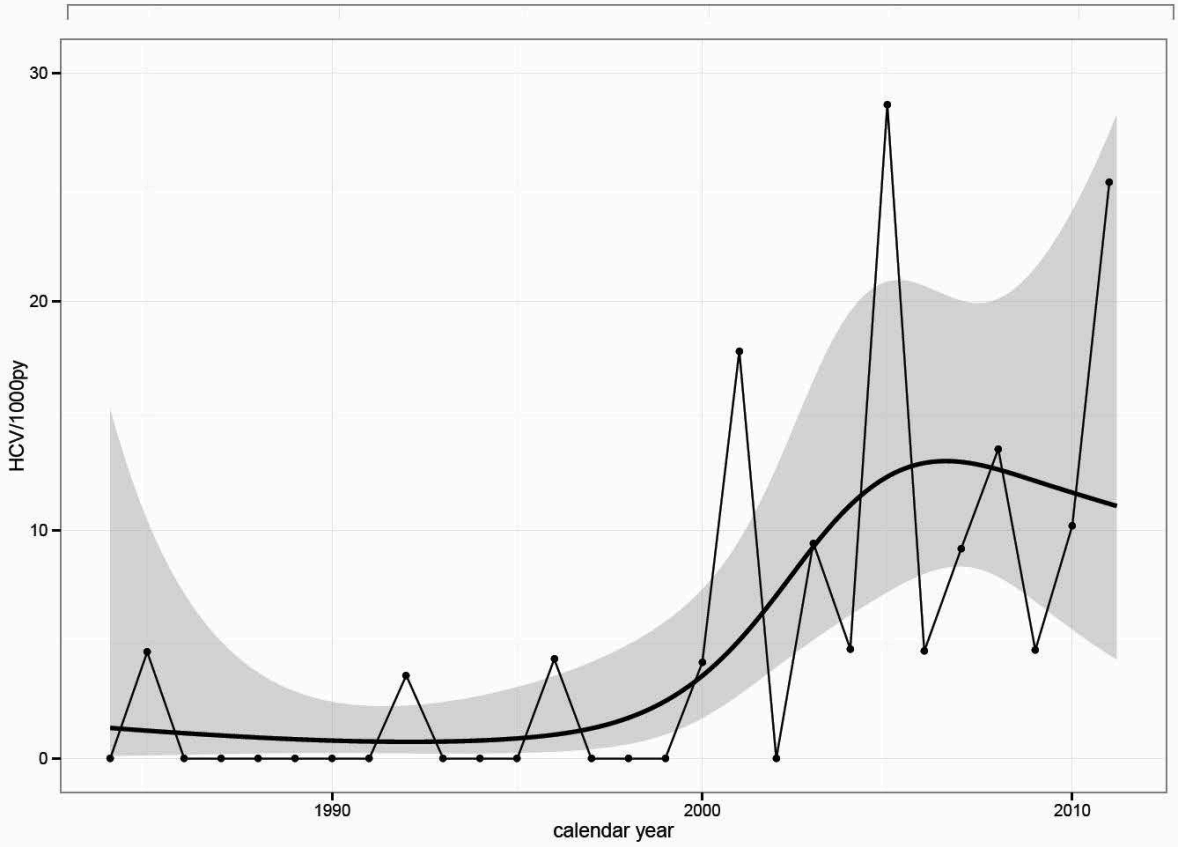
[1]Department of Infectious Diseases, Public Health Service, Amsterdam, Netherlands, [2]Department of Medical Microbiology, Academic Medical Center, Amsterdam, Netherlands, [3]Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, Amsterdam, Netherlands, [4]Department of Blood-borne Infections, Sanquin Blood Supply Foundation, Amsterdam, Netherlands, [5]Department of Internal Medicine, Center of Infectious diseases and Immunology Amsterdam (CINIMA), Academic Medical Center, Amsterdam, Netherlands

Background: Since 2000, an epidemic of hepatitis C virus (HCV) has emerged among HIV-infected men who have sex with men (MSM). Among HIV-infected MSM in the Amsterdam Cohort Study (ACS), an increase in HCV incidence was observed between 2000 and 2003. Data collected during bi-annual surveys at the Amsterdam STI clinic, suggest that the HCV epidemic among HIV-infected MSM in Amsterdam has levelled off in recent years. We updated our previous ACS analysis to examine recent changes.

Methodology: All MSM with ≥2 study visits in the ACS between 1984 and 2012 were included. HCV antibody tests were performed retrospectively for all participants until 2003. In order to update the HCV status for HIV-infected MSM, linkage with several clinical and laboratory databases took place. If no negative HCV test result was available after 2008, the last visit before 2012 was tested for HCV antibodies. HIV-uninfected MSM were tested at their first 6-monthly ACS visit after STI screening was introduced in 2009. On finding HCV seroconversion, samples from earlier visits were tested to identify the moment of seroconversion. Incidence rates were calculated and time trends were analyzed using Poisson regression. We allowed for smoothly varying trends via restricted cubic splines.

Results: Between October 1984 and January 2012, 2,080/2,457 MSM had ≥2 study visits, and they contributed a total follow-up of 17,310 person-years (PYs). Twenty-nine incident HCV infections were documented. All incident cases had been infected with HIV prior to HCV infection. The overall observed HCV incidence (per 1,000 PYs, 95% CI) was 4.5 (3.0-6.5) among HIV-infected MSM and 0.0 (0.0-0.3) among HIV-uninfected MSM. Among HIV-infected MSM, a significant increase in HCV incidence was observed after 2000 (2005 vs 2000: incidence rate ratio, IRR, 3.41, 95% CI 1.58-7.34). After 2005 however, a non-significant decrease in HCV incidence was observed (2010 vs 2005: IRR, 0.94, 95% CI 0.38-2.36). The observed and modeled HCV incidence rates over time are shown in the attached figure.

Conclusions: No incident HCV infections were found among HIV-uninfected MSM. Among HIV-infected MSM, HCV incidence rates increased significantly after 2000. However, HCV incidence seems to have levelled off in recent years, in line with recent findings from the Amsterdam STI clinic. The levelling off might be explained by an increase in testing for HCV, improved HCV treatment uptake, risk reduction, or a saturation-effect among MSM at highest risk for HCV infection.



Session P-N2 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

HCV Pre-Clinical Studies and Pharmacology

635 Longitudinal Analysis of RAVs by PrimerID 454-Sequencing in the Boceprevir P-05063 Study

Richard J. O. Barnard[1], Abha Chopra[2], Mark Watson[2], Don Cooper[2], Cassandra Jabara[3], Daria Hazuda[1], Stanley Lemon[3], Simon Mallal[2]

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Background: Although resistance associated amino acid variants (RAVs) declined to below detectable levels by Sanger sequencing methodology in the majority of patients enrolled in the long-term follow-up study P05063, ~30% of these patients had viruses with RAVs detected by population sequencing >2 years after cessation of boceprevir dosing. In order to further investigate the persistence of RAVs and to assess the limits of detection of the population sequencing technique employed in boceprevir clinical trials, RAVs were quantified using a sensitive clonal quantitative nucleotide sequencing method.

Paired samples from 20 patients at baseline (prior to boceprevir treatment) and >2 years after virologic failure with RAVs in a boceprevir clinical study were evaluated for RAVs using PrimerID/454-sequence analysis.

Methodology: Viral RNA was isolated from blood plasma and cDNA generated by reverse transcription using a PrimerID tag. Approximately 20,000 copies of viral RNA from each sample were present in the cDNA synthesis reaction. The gene was then amplified by nested PCR. Once amplified, 3 to 4 tagged samples were combined and sequenced on the 454 GS FLX+ Platform with XLR70 Titanium Chemistry as per manufacturer's instructions with ~300,000 beads loaded per region.

Results: The PrimerID 454 sequencing method identified RAVs at baseline in 6/20 patients whereas two of these patients had RAVs detected by population sequencing. The additional baseline RAVs identified by PrimerID were detected at ≤2.6% of the total circulating virus population. Of the 20 patients that experienced virologic failure with RAVs detected by population sequencing, 9/20 no longer had RAVs detected by 454 technology after 1-2 years of follow-up. Of the 11/20 patients with detectable RAVs, the RAVs had declined to ≤4.3% of the total circulating viral population in all but three patients. In these three patients with RAVs detected at high levels, the RAVs were also detected by population sequencing.

Conclusions: The 454-Primer ID technology employed in this study detected RAVs present at low levels (>10%) in the circulating population. The clinical implications of the additional low level RAVs detected by PrimerID sequencing at baseline and during long term follow-up, which in the majority of cases were detected at levels below 1% of the total circulating virus population, are not understood.

636 ABT-493, a Potent HCV NS3/4A Protease Inhibitor With Broad Genotype Coverage

Teresa Ng[1], Thomas Reisch[1], Tim Middleton[1], Keith McDaniel[1], Dale Kempf[1], Liangjun Lu[1], Guoqiang Wang[2], Lijuan Jiang[2], Yat Sun Or[2], Tami Pilot-Matias[1]
[1]AbbVie Inc., North Chicago, IL, United States, [2]Enanta Pharmaceuticals Inc., Watertown, MA, United States

Background: HCV NS3/4A protease inhibitors (PIs) are proven therapeutic agents used in treating chronic HCV infection. First generation PIs (boceprevir or telaprevir), when combined with pegylated interferon and ribavirin (P/R), improve the cure rate in patients harboring HCV genotype (GT) 1 infections. Their usage, however, is limited by the emergence of drug resistant variants during treatment, and their lower potency against several other HCV GTs. In addition, these agents must be combined with P/R, which leads to significant side effects in treated patients. We report here the preclinical virological characterization of ABT-493, a next generation PI identified as a lead compound by AbbVie and Enanta, with potent activity across HCV GTs, and activity against the major resistant variants selected by other PIs currently in clinical development.

Methodology: The antiviral potency of ABT-493 was evaluated in assays using subgenomic HCV replicons expressing wild-type or common drug-resistant variant proteases from a number of HCV GTs. In addition, the resistance profile of ABT-493 was determined by colony selection in replicons containing GT 1a, 1b, or 3a protease.

Results: ABT-493 inhibited replication of HCV stable subgenomic replicons containing NS3 genes from GT 1a, 1b, 2a, 3a, 4a, or 6a with EC_{50} values ranging from 0.85 to 2.8 nM. Of note, ABT-493 was potent against replicon containing GT3a protease, with an EC_{50} value of 1.6 nM. ABT-493 retained its activity against common GT1a and 1b variants at NS3 amino acid positions 155 and 168 that conferred resistance to other HCV PIs. Resistant colony selection studies in GT1a and 1b subgenomic replicon cells identified A156T in GT1a and A156V in GT1b as the most frequent variants, which conferred 1400- and 1800-fold reduced susceptibility to ABT-493, respectively. However, these variants had *in vitro* replication capacities of only 1.5% and 9.2% that of their corresponding wild-type replicons. In a replicon containing GT3a NS3 protease, ABT-493 selected very few colonies at concentrations ≥ 100-fold over its EC_{50} value. The colonies that survived the selection contained either A156G alone, or Q168R co-selected with Y56H, which conferred 1500- or 1100-fold loss in susceptibility to ABT-493, respectively.

Conclusions: Based on its preclinical profile, ABT-493 is anticipated to have broad genotype coverage and be active against most of the clinically important drug resistant variants selected by other PIs in GT1. It is, therefore, an excellent drug candidate to be included in the development of a direct-acting antiviral regimen for the treatment of chronic HCV infection.

637 Use of Dried Blood Spots for Measuring Intracellular Ribavirin-Triphosphate

Leah C. Jimmerson, Jia-Hua Zheng, Lane R. Bushman, Kyle P. Hammond, Peter L. Anderson, Jennifer J. Kiser
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Background: Ribavirin (RBV), a nucleoside analog, undergoes intracellular phosphorylation to a mono-(MP), di-(DP), and triphosphate (TP). RBV-TP accumulates in red blood cells (RBC) leading to ATP depletion, membrane oxidative damage, and ultimately hemolytic anemia. Therefore, measuring RBV-TP in RBC is of interest for pharmacokinetic/dynamic analyses. We describe the development and validation of a method to measure RBV-TP in RBC using dried blood spots (DBS) obtained from patients undergoing RBV-based treatment for chronic Hepatitis C virus (HCV) infection.

Methodology: Whole blood was obtained in EDTA Vacu-tainer tubes from HCV infected subjects receiving RBV treatment for 1 day-48 weeks. Blood was used for two sample types, DBS and RBC. For DBS, a 3 mm punch was sonicated in 500 µL 70:30 methanol:water and the lysate was extracted using a QMA cartridge to separate TP from MP and DP followed by de-phosphorylation and another solid phase extraction to further purify RBV. For RBC, blood was centrifuged and RBC were obtained from the pellet, counted, and lysed in 5 mL 70:30 methanol:water followed by an identical extraction to the DBS. Concentrations were measured using liquid chromatography-mass spectrometry. DBS results are reported as pmol/punch and RBC as pmol/10^6 cells. Precision was determined in n=6 replicates of 3 patient samples in 3 separate extractions. Storage stability (room temp., 4°C, -20°C, -80°C) was assessed up to 310 days.

Results: Samples were measured in an assay range of 0.5-200 pmol/sample. Precision was within 7.8% and 9.4% for inter- and intra-extraction, respectively. Samples kept at room temperature tested within ±10.5% of immediate extraction up to 21 days post spotting. Long term storage stability was determined in 9 subjects at various points in treatment up to 48 weeks. Stability at room temperature tested at -40.1% to -83.4% compared to -80°C when stored for 196-310 days. A negative trend in 4°C stability was shown up to -20.1% compared to -80°C. Both -20 and -80°C storage conditions were comparable within ±11.2%. Analysis of 10 paired DBS and RBC samples demonstrated an r^2 of 0.969 and an average of 10 million RBC/punch.

Conclusions: Measurement of RBV-TP in DBS was shown to be precise, stability indicating up to 21 days at room temperature and at least 310 days when frozen. DBS correlated well to intracellular RBC concentrations. DBS offers many advantages for RBV-TP quantification in clinical trials because cell processing is eliminated, it requires a small blood volume, there is minimal processing time, little cost and there are no biological specimen shipping requirements.

638 Ritonavir-Boosted Atazanavir, Lopinavir, & Darunavir Increase HCV NS5A Inhibitor MK-8742 Levels

Wendy Y. Yeh[1], William Marshall[1], Joanne Ma[1], Eric Mangin[1], Xiaobi Huang[1], Patricia Jumes[1], Stephen Youngberg[2], Joan Butterton[1]
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Background: MK-8742, a potent, once-daily inhibitor of the hepatitis C virus (HCV) NS5A, is being developed for the treatment of chronic HCV infection in mono- and HCV/human immunodeficiency virus (HIV)-coinfected patients. The aim of this study was to assess the potential two-way pharmacokinetic (PK) interaction and tolerability of MK-8742 when coadministered with ritonavir (RTV)-boosted HIV protease inhibitors (PI), such as atazanavir/ritonavir (ATZr), lopinavir/ritonavir (LPVr), and darunavir/ritonavir (DRVr). MK-8742 is a substrate of CYP3A4, P-glycoprotein (P-gp) and the organic anion-transporting polypeptide (OATP) in vitro. A ketoconazole DDI study demonstrated that MK-8742 is a CYP3A4 substrate in vivo. ATZr, LPVr, and DRVr are substrates and potent inhibitors of CYP3A4/P-gp in vivo and potentially inhibitors of transporters (e.g., BCRP and OATP).

Methodology: This was an open-label, 3-parallel panel, 3-period study in 10 healthy male and female subjects per panel, ages 19-55 years. In Period 1, subjects received 50 mg of MK-8742 once-daily (QD) for 7 days, followed by a 7 day washout. In Period 2, subjects received either 300 mg ATZ/100 mg RTV QD, 400 LPV/100 mg RTV twice-daily (BID), or 600 mg DRV/100 mg RTV BID for 14 days, immediately followed by Period 3. In Period 3, 50 mg MK-8742 was co-administered with ATZr, LPVr, or DRVr for 7 days.

Results: Coadministration of MK-8742 with ATZr, LPVr, and DRVr was safe and well-tolerated. MK-8742 did not significantly impact lopinavir or darunavir PK, with the lopinavir AUC_{0-12} geometric mean ratio (GMR, LPVr+MK-8742/LPVr) [90% confidence interval (CI)] of 1.02 [0.92, 1.13], darunavir AUC_{0-12} GMR (DRVr+MK-8742/DRVr) [90% CI] of 0.95 [0.86, 1.06], and atazanavir AUC_{0-24} GMR (ATZr+MK-8742/ATZr) [90% CI] of 1.07 [0.98, 1.17]. MK-8742 exposures were significantly increased when coadministered with the ritonavir-boosted HIV PIs, with the AUC_{0-24} GMR (MK-8742+HIV PI-RTV/MK-8742) [90% CI] of 4.76 [4.07, 5.56] with ATZr, 3.71 [3.05, 4.53] with LPVr, and 1.66 [1.35, 2.05] with DRVr.

Conclusions: Co-administration of MK-8742 with LPVr, ATZr and DRVr did not significantly affect lopinavir, atazanavir or darunavir exposures. There was a significant increase in MK-8742 exposures when MK-8742 was co-administered with LPVr, ATZr, and DRVr, which can be attributed to CYP3A4/P-gp inhibition by the HIV PIs/r and potentially inhibition of the transporter (e.g., OATP)-mediated disposition of MK-8742.

639 ABT-530, an HCV NS5A Inhibitor With Potent Pangenotypic Activity and High Barrier To Resistance

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Background: NS5A plays a critical role in HCV replication. Results from clinical studies with first generation NS5A inhibitors have validated NS5A as a drug target for direct-acting antiviral (DAA) therapy. We report here the virological characterization of a next generation HCV NS5A inhibitor, ABT-530, which has a more favorable preclinical profile than earlier generation NS5A inhibitors, including broad genotype (GT) coverage, high genetic barrier to resistance, and activity against common viral variants that are resistant to other NS5A inhibitors.

Methodology: The antiviral potency and resistance profile of ABT-530 were evaluated in assays using subgenomic HCV replicon cell lines expressing NS5A from different HCV GTs. Resistant variants selected by ABT-530, as well as those commonly reported to confer resistance to other NS5A inhibitors currently in clinical development, were evaluated using chimeric replicons in transient transfection assays. The genetic barriers to resistance in HCV replicons were measured in colony selection assays.

Results: ABT-530 is a potent HCV inhibitor exhibiting broad genotype coverage with EC_{50} values ranging between 1.4 and 4.3 pM against HCV replicons containing NS5A from GT 1a 1b, 2a, 2b, 3a, 4a, 5a, and 6a. ABT-530 maintains nearly wild-type levels of activity against GT1 to GT6 chimeric replicons containing NS5A variants at amino acid position 28, 30, 31, 32, 58 or 93, commonly found to confer resistance to other NS5A inhibitors. Resistant colony selection studies with ABT-530 at 10-fold over its EC_{50} value using a GT1a replicon cell line yielded only a very small number of resistant colonies, and even fewer colonies survived selection at 100-fold over its EC_{50} value. No colonies in GT1b replicon cells survived selection using ABT-530 at 10-fold over its EC_{50} value. The most frequent GT1a NS5A variant selected by ABT-530 was Y93H, which conferred only 7-fold resistance. When resistant colony selection with ABT-530 at 10- or 100-fold over its EC_{50} value was performed on chimeric replicons containing NS5A from GT2 to GT6, there were either very few or no surviving resistant colonies, indicating that this compound also has very high genetic barriers to resistance in GT2 to GT6 HCV.

Conclusions: ABT-530 is a next generation HCV NS5A inhibitor with potent and broad genotype activity. It exhibits very high genetic barriers to resistance in different HCV GTs, and retains high levels of potency against common variants that confer resistance to other NS5A inhibitors currently in clinical development. ABT-530 is being developed for use in combination with other DAAs for the treatment of chronic infection with HCV of different GTs.

Session P-N3 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

HCV: Prognosis and Impact of Treatment Including Liver Transplantation

640 FIB-4 Outperforms Liver Biopsy in the Assessment of Prognosis in HIV/HCV Coinfection

Juan Berenguer[1], Francisco X. Zamora[2], Ana Carrero[1], Miguel Angel von Wichmann[3], José López-Aldeguer[4], María J. Téllez[5], José Sanz[6], Herminia Esteban[7], José M. Bellón[1], Juan González-García[2], and GESIDA 3603 Study Group

[1]Hospital General Universitario Gregorio Marañón, Madrid, Spain, [2]Hospital Universitario La Paz, Madrid, Spain, [3]Hospital Donostia, San Sebastián, Spain, [4]Hospital La Fe, Valencia, Spain, [5]Hospital Clínico San Carlos, Madrid, Spain, [6]Hospital Príncipe de Asturias, Alcalá de Henares, Spain, [7]Fundación SEIMC/GESIDA, Madrid, Spain

Background: Liver biopsy (LB) is widely considered the gold standard in the assessment of the severity of liver disease. FIB-4 is a non-invasive test (based on platelet count, age, AST, and INR; Hepatology 2006; 43: 1317-25) to estimate fibrosis in HIV/HCV-coinfected patients. We compared the prognostic abilities of LB and FIB-4 in HIV/HCV+ patients.

Methodology: The study sample comprised patients from the GESIDA 3603 Study Cohort with a baseline assessment of fibrosis by both LB (METAVIR) and FIB-4. We assessed overall death (OD) and liver-related events (LRE), defined as decompensation or hepatocellular carcinoma, whichever occurred first. We used ROC curves to determine the ability of LB and FIB-4 to predict outcomes. In order to assess the association between outcome and significant fibrosis and advanced fibrosis (assessed by LB [F≥2 and F≥3] or FIB-4 [≥1 and ≥3.25]), we used Cox regression adjusted for age, sex, prior IDU, CDC clinical category, CD4+ cells, HCV genotype, HCV-RNA, and sustained viral response.

Results: We analyzed 903 patients. The median time (IQR) between LB and FIB-4 was 4.5 (2.2 - 12.0) months. Patients with F≥2, 590; F≥3, 354; FIB-4≥1, 755; FIB-4≥3.25, 158; SVR, 328. After a median follow-up of 63 months, 46 patients died and 71 had an LRE. The AUROCs for OD for LB and FIB-4 were 0.6241 and 0.7932, respectively; P<.001. The AUROCs for LRE for LB and FIB-4 were 0.6760 and 0.7498, respectively; P=.032. The table shows adjusted hazard ratios (95% CI) of OD and LRE according to significant fibrosis and advanced fibrosis assessed by LB and FIB-4.

Conclusions: We found that FIB-4 outperformed LB as a predictor of both OD and LRE. LB makes it possible to evaluate structure but not function, whereas FIB-4 enables us to evaluate function. Our results call into question the role of LB as a gold standard for assessing prognosis in HIV/HCV coinfection.

aHR (95% CI) of OD and LRE according to different stages of fibrosis assessed by LB and FIB-4			
		aHR (95% CI)	P
Overall death			
Significant fibrosis	LB F (≥2 vs. <2)	1.757 (0.837 - 3.686)	.136
	FIB-4 (≥ 1 vs. <1)	4.256 (0.954 - 18.219)	.051
Advanced fibrosis	LB F (≥3 vs. <3)	1.547 (0.836 - 2.860)	.165
	FIB-4 (≥ 3.25 vs. < 3.25)	6.522 (3.517 - 12.095)	<.001
Liver-related events			
Significant fibrosis	LB F (≥2 vs. <2)	2.291 (1.222 - 4.296)	.010
	FIB-4 (≥ 1 vs. <1)	5.178 (1.589 - 16.875)	.006
Advanced fibrosis	LB F (≥3 vs. <3)	2.369 (1.438 - 3.904)	.001
	FIB-4 (≥ 3.25 vs. < 3.25)	4.344 (2.654 - 7.109)	<.001

641 Sustained Virologic Response and the Risk of Liver Decompensation in HCV and HIV/HCV Patients

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Background: Few studies have evaluated the impact of achieving a sustained virologic response (SVR) on liver-related complications among HIV/hepatitis C virus (HCV)-coinfected patients. Our objective was to assess the effect of SVR on rates of hepatic decompensation in patients with HIV/HCV coinfection and HCV monoinfection.

Methodology: We conducted a cohort study among HIV/HCV-coinfected and HCV-monoinfected patients with HCV genotype 1 who were treated with interferon-based therapy in the U.S. Veterans Health Administration between October 2005 and December 2010. SVR was defined as an undetectable HCV RNA in all follow-up measurements 12 weeks after treatment end date. The primary outcome was incident hepatic decompensation (defined by one hospital diagnosis or two or more outpatient diagnoses of ascites, spontaneous bacterial peritonitis, or variceal hemorrhage). Incidence rates of hepatic decompensation (in events/1,000 person years) were calculated from the date of SVR for coinfected and monoinfected patients, by SVR status. Cox regression was used to determine adjusted hazard ratios (HRs) of decompensation associated with SVR for the coinfected and monoinfected groups.

Results: Among 467 HIV/HCV-coinfected (mean age, 55 years; 34% black; mean HCV RNA, 6.4 log IU/mL; 10% cirrhosis) and 11,395 HCV-monoinfected (mean age, 55 years; 13% black; mean HCV RNA, 6.3 log IU/mL; 12% cirrhosis) patients treated with interferon-based therapy, 113 (24%) and 3,527 (31%) achieved SVR, respectively. Incidence rates of hepatic decompensation were lower for patients who achieved SVR compared to those who did not among HIV/HCV-coinfected (4.24 vs. 13.25 events/1,000 person-years; adjusted HR=1.74 [95% CI, 0.21-14.48]) and HCV-monoinfected (3.38 vs. 16.56 events/1,000 person-years; adjusted HR=5.13 [95% CI, 3.34-7.86]) patients. Coinfected patients who achieved an SVR did not have significantly higher rates of decompensation than HCV-monoinfected patients with SVR (adjusted HR=1.67 [95% CI, 0.22-12.47]).

Conclusions: Achievement of SVR following interferon-based treatment decreased the risk of hepatic decompensation among both HIV/HCV-coinfected and HCV-monoinfected patients. Coinfected patients who achieved SVR did not have significantly higher rates of decompensation compared to monoinfected patients with SVR.

642LB GWAS Reveals New Genetic Associations With Liver Fibrosis Progression

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Background: Genetic studies with common variants in HIV mono-infection have mainly revealed associations with HIV non-progression and elite control (notably in the HLA locus). In HCV infection, the main association results were found between IL28B variants and clearance of the virus either under treatment or spontaneously. We took the opportunity of the large French ANRS CO13 HEPAVIH cohort of co-infected HIV/HCV patients to study these signals and search for additional markers associated with various phenotypes related to the course of the co-infection in a genome-wide association study (GWAS)

Methodology: We used the Illumina Omni2.5 BeadChip to genotype 439 Caucasian patients who had given their informed consent for genetic studies. We first performed the usual quality controls (SNP calling >98%, patient calling >95%, HWE >10-6, IBD 1%) and then measured the stratification using the Eigenstrat® software. We report here the early findings of GWAS screening for host genetic determinants of progression of liver fibrosis. The fibrosis stage at baseline was assessed by elastography (Fibroscan®) scoring fibrosis in kilopascal. For each single nucleotide polymorphism (SNP), the genetic association was estimated by linear regression using as covariates the age at baseline, gender, the HCV genotype, the duration of both HIV and HCV infection, alcohol and drug consumption, effective cumulative time on antiretroviral treatment, and the first two principal components of the stratification analysis.

Results: After quality control and stratification analysis, there were 412 patients left to search for genetic associations on 922,971 SNPs. Fibrosis stage was available at baseline in 399 patients . Three SNPs in two regions passed the Bonferroni threshold for genome-wide significance (5x10-8): the rs11790131 SNP located in the locus 9p21.3 in the gene LOC392288 (P=1.8x10-8), the rs73060964 and rs73060937 SNPs (r2=1), located in the locus 3p22.1 in the gene LOC101928135 (P=4x10-8). The previously published genetic markers of HIV and HCV mono-infection did not reach this statistical significance.

Conclusions: : We report new signals, reaching genome-wide significance, associated with liver fibrosis in HIV/HCV co-infected patients. Confirmation in other genetic studies is needed. These potential markers of fibrosis will be studied prospectively in the cohort as well as other phenotypes such as HIV and HCV treatment response and tolerance, HIV progression and occurrence of hepato-cellular carcinoma.

643 Incident HCV Infections in the Swiss HIV Cohort Study: Natural History and Treatment Outcomes

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Background: We recently observed dramatic changes in the hepatitis C virus (HCV) infection epidemic in the Swiss HIV Cohort Study (SHCS), including an 18-fold incidence increase in men who have sex with men (MSM). The long-term trends in outcomes of incident HCV infections are largely unknown. We studied the natural history, treatment uptake and outcomes of incident HCV infections between 1991 and 2012 in a nationwide cohort.

Methodology: We included all patients followed in Swiss tertiary care hospitals with a documented HCV-seroconversion. Detailed information on HCV diagnosis, treatment and outcomes, as well as reasons for not starting HCV treatment was retrieved from the SHCS database and chart review using standardized case report forms. Natural history, treatment uptake and outcomes were compared between risk groups and time periods before and after the first description of the surging HCV epidemic in MSM in 2006 using Fisher's exact test.

Results: Of 121 HCV seroconversions, 2 were excluded due to insufficient information. Among the remaining 119 cases, 46 were MSM, 52 injection drug users, 17 heterosexuals and 4 from other HIV transmission risk groups. The proportion of MSM among patients with incident HCV infections increased from 20% before to 75% after 2006 (p<0.001). Fourteen patients died during follow-up, including 3 liver-related deaths. A spontaneous clearance was observed in 30% of cases. Fibroscan results were available for 45 (38%) individuals. The median liver stiffness was 5.9 kPa (IQR 4.6-7.4) after a median follow-up time of 7.4 years (3.1-11.0), and only 5 patients were above the cut-off for liver cirrhosis (14 kPa). HCV treatment uptake increased from 29% before 2006 to 68% after 2006 (p=0.001). Among those treated, only 22% started treatment during acute infection before 2006, compared to 88% after 2006 (p<0.001). MSM were much more likely to receive HCV therapy compared to patients from other transmission groups (62% vs. 29%, p=0.01). The most frequent reason for not being treated was persistent alcohol or drug abuse (30%), followed by patient's refusal (15%). A sustained virologic response

(SVR) was achieved in 69% and 25% (p=0.05) of those treated during acute and chronic infection, respectively. Finally, four patients experienced a re-infection after spontaneous clearance and three after HCV treatment.

Conclusions: In this nationwide representative cohort of HIV-infected patients with an incident HCV infection, treatment uptake was low, although the proportion of patients treated during the acute phase of infection increased after 2006. MSM were more likely to be treated during acute infection. If treated early, SVR rates were high, underscoring the need of increased efforts towards early diagnosis and treatment.

644 Is There Long-Term Evidence of Advanced Liver Fibrosis After Acute Hepatitis C in HIV Coinfection?

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Background: After ten years, the epidemic of sexually transmitted acute hepatitis C (AHC) infection among HIV-seropositive MSM is still ongoing. The rate of early liver fibrosis progression after AHC is of particular interest as more advanced fibrosis progression has been described in small retrospective case series. Here we evaluate the long-term evolution of liver fibrosis in HIV-patients with persistent viremia after AHC.

Methodology: 41 HIV-infected patients from 3 European countries with diagnosed acute HCV infection since 2003 with at least 12 months of follow-up and persistent HCV viremia (chronic course or unsuccessful treatment) were repeatedly evaluated for liver fibrosis by means of transient elastography. Fisher's exact, chi-square and Mann-Whitney U test were used for statistical analysis.

Results: All patients were male, median age was 43 years. Main routes of transmission were MSM (97.6%) and IVDU (2.4%). In 80% of patients clinical symptoms of an acute hepatic infection were missing. 78% of patients were infected with HCV GT 1 and 22% with GT 4. Median baseline HCV RNA was 1.989.500IU/ml and median CD4 T cell count 491 cells/ul. 95% of all patients received cART, 85% had baseline HIV RNA <200cop/ml. Median ALT was 401 U/l. Median follow-up time was 179 weeks (IQR 120-276). All patients had persistent HCV viremia, 11 (26.8%) due to a chronic course and 30 (73.2%) after unsuccessful early treatment.

Overall, as shown in table 1 there was no significant change in median liver stiffness over a maximum follow-up of 8 years. There was no significant correlation between liver stiffness and reason for HCV persistence (chronic course vs. unsuccessful treatment), follow-up time, BMI, alcohol or drug abuse, diabetes, lipodystrophy, cART duration, or exposure to d-drugs.

Conclusions: An episode of acute hepatitis C in HIV-positive MSM does not appear to lead towards early advanced liver fibrosis. This finding is particularly reassuring for clinicians and patients in whom HCV persists due to a chronic course or unsuccessful early treatment.

Median annual liver stiffness after AHC diagnosis								
Years since AHC diagnosis (# of available measurements)	1 (n=20)	2 (n=23)	3 (n=17)	4 (n=14)	5 (n=10)	6 (n=3)	7 (n=4)	8 (n=3)
Median liver stiffness [kPa] (IQR)	7.7 (6-10)	7.0 (6-10)	6.3 (5-8)	6.4 (5-8)	4.4 (4-5)	7.7 (6-20)	7 (5.1-10)	8 (5-49.6)

645 Hepatic Decompensation in HIV/HBV/HCV Patients and the Impact of HBV Therapy

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Background: Few studies have compared rates of hepatic decompensation in HIV/HBV/HCV and HIV/HCV patients. It is also unclear if anti-HBV nucleos(t)ide analogue therapy is effective at reducing decompensation rates in triply infected patients. Our objectives were to: 1) compare the incidence rates of hepatic decompensation in HIV/HBV/HCV and HIV/HCV patients, and 2) determine the risk of decompensation associated with anti-HBV nucleos(t)ide analogue-untreated and treated HIV/HBV/HCV.

Methodology: We conducted a cohort study among HIV/HBV/HCV and HIV/HCV patients in the US Veterans Health Administration (VHA) between October 2005 and February 2012. All patients had HIV, detectable HCV RNA, and 12 months in the VHA. Chronic HBV was defined by 2 positive HBV surface antigen results and/or chronic HBV diagnoses recorded >6 months apart. Use of an anti-HBV nucleos(t)ide analogue was determined. The main outcome was incident hepatic decompensation (defined by one hospital diagnosis or two or more outpatient diagnoses for ascites, spontaneous bacterial peritonitis, or variceal hemorrhage). Follow-up began after 12 months in the VHA. Rates of decompensation were compared between HIV/HBV/HCV and HIV/HCV patients. Cox regression was used to evaluate adjusted hazard ratios (aHRs) of decompensation between triply and dual infected patients and to determine the risk of decompensation in anti-HBV nucleos(t)ide analogue-untreated and treated HIV/HBV/HCV patients compared to HIV/HCV patients.

Results: Among 149 HIV/HBV/HCV and 4,902 HIV/HCV patients, the incidence rate and risk of decompensation was higher in triply than dual infected patients (24.1 versus 10.8 events/1,000 person-years; aHR=2.40 [95% CI, 1.44-3.99]). The risk of decompensation was substantially increased for HIV/HBV/HCV patients with no anti-HBV nucleos(t)ide analogue use (aHR, 2.48; 95% CI, 1.37-4.49) but not for HIV/HBV/HCV patients receiving an anti-HBV nucleos(t)ide analogue (aHR, 1.09; 95% CI, 0.40-2.97) compared to HIV/HCV patients.

Conclusions: HIV/HBV/HCV patients had higher rates of hepatic decompensation compared to HIV/HCV patients. The risk of decompensation was increased among triply infected patients who did not receive an anti-HBV nucleos(t)ide analogue. Controlling HBV viremia with HBV therapy is important to reduce rates of hepatic decompensation in HIV/HBV/HCV triply infected persons.

646 Short-Term Risk of Decompensation Among HIV/HCV-Coinfected Patients With Significant Fibrosis

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Background: Newer directly acting antivirals against (DAA) HCV are becoming available. Their efficacy and safety profile is better than that of telaprevir or boceprevir. Therefore,clinicians tend to defer therapy for patients at a seemingly low risk of liver decompensation (DC)in the short-term. Thus, individuals with F3-F4 by liver biopsy (LB) are given maximum treatment priority and therapy for those with F≤2 is often appointed for the approval of next generation DAA. However, the risk of DC for HIV/HCV-coinfected patients with F2 and F3 could be similar, not allowing safe delaysin therapy in this setting. Weaimed at evaluating the risk of DC among HIV/HCV-coinfected individuals according to fibrosis stage. We specifically compared the risk of DC for patients with F2 vs. F3.

Methodology: 540 HIV/HCV-coinfected patients with LB, naïve or without sustained viral response to HCV therapy, prospectively followed (1990-2013), were included in this cohort study. The date of LB was baseline (BL). Fibrosis was staged by the Scheuer's score.Survival analyses were carried out.

Results: Median (IQR) age was 47 (43-50) years. 461 (85%) patients were men. Median (IQR) follow-up was 5.6 (3.3-8.4) years. At BL, median (IQR) CD4 cell count was 463(304-639) cells/μL, and 380 (70%) individuals showed plasma HIV RNA<50 c/mL at BL. Fibrosis stage frequencies were: F0, 40 (7.4%); F1, 119 (22%); F2, 116 (22%); F3 129 (24%); F4 136 (25%). DC were observed in: F0, 0; F1, 5 (4.2%); F2, 7 (6%); F3 12 (9%); F4 29 (21%). For F2 and F3, DC during the first year of follow-up were observed. The probability of remaining free of DC by fibrosis stage was: at 1 year:F1, 98% (93%-100%); F298% (93%-100%); F3 98% (93%-100%); F4 85% (78%-91%); at 3 years:F1, 98% (93%-100%); F298% (93%-100%); F3 94% (86%-97%); F4 79% (70%-85%); at 5 years:F1, 91% (79%-97%); F2 86% (72%-93%); F3 78% (63%-88%); F4 66% (53%-77%). The probability of remaining free of DC for F2 was not significantly different from that for F3 (p=0.139). The factors independently associated with DC werefibrosis stage (per stage increase, hazard ratio [HR] 1.9; 95%CI, 1.4-2.6; p<0.0001) andBL platelet count (<100x10^3 vs. ≥100x10^3, HR 2.6; 95%CI, 1.3-4.9; p=0.006).

Conclusions: HIV/HCV-coinfected patients with F2are at a risk of DCnot significantly different from individuals with F3.Consequently, a similar degree of priority for therapy should be given to them.

647 Differential Immune Marker Levels Linked To Liver Fibrosis in HIV/Hepatitis C (HCV) Coinfection

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Background: Liver fibrosis, which can lead to cirrhosis and fatal liver failure, advances faster in HIV/HCV co-infected individuals due in part to an elevated inflammatory profile that persists even with effective cART. Immune markers targeting various stages of the fibrosis process could aid in understanding the etiology and prognosis of HIV-HCV co-infection.

Methodology: A case-cohort study was nested in the prospective multicentre Canadian Co-infection Cohort (n=1119). HCV RNA-positive individuals free of HCV treatment, fibrosis, end-stage liver disease and chronic Hepatitis B at baseline (n=679) were included. A randomly selected subcohort (n=171) served as controls (APRI <1.5 when cases occurred), while cases (n=130) developed an APRI > 1.5 (significant fibrosis) over study follow-up.

Pro-fibrogenic markers (IL-8, MIP-1 α , MIP-1β , MCP-1,TNF- α , RANTES, sICAM-1 and sVCAM-1) were measured from first available plasma or serum in the subcohort and cases. The subcohort was only used to determine median and quartile cutoffs. We used Cox proportional hazards to model time to APRI>

1.5 according to baseline cytokine levels and adjusted for sex, alcohol use, HCV duration, CD4 count, HIV RNA, cART interruption and baseline APRI.

Results: Overall 70% were male with median HCV duration of 19 years. At baseline, 81% were on cART, with median CD4 count of 410. Median (IQR) follow-up was 2.2 years (0.48, 3.45). In univariate analysis, above median levels of IL-8 and sICAM1 were associated with higher rates of liver fibrosis, while higher levels of RANTES had protective effects compared to below median levels. These associations held when examined at the quartile level, with IL-8 and sICAM1 exhibiting a clear dose response.

After adjustment for clinical predictors, IL-8, MIP-1 β , and sICAM1 remained linked to higher risk of fibrosis, while RANTES and MCP-1 were protective. (See table)

Conclusions: Co-infected patients who develop significant liver fibrosis have higher levels of pro-inflammatory IL-8, MIP-1 β , and sICAM1 and lower levels of MCP-1 and HIV-suppressive RANTES, which is a natural ligand of the HIV co-receptor CCR5.

Table 1: Cytokines and Rates of Significant Liver Fibrosis (Hazard ratios (95%CI))

Above median vs. below median					
	IL-8	sICAM-1	MIP-1b	RANTES	MCP-1
Univariate	1.96 (1.28,3.02)	2.42(1.58, 3.70)	1.37(0.91,2.06)	0.61(0.40, 0.92)	1.02 (0.68,1.53)
Multivariate	2.94(1.31, 6.61)	4.28(1.77, 10.38)	3.32(1.33, 8.30)	0.36(0.16, 0.80)	0.38(0.15, 0.97)

Evidence of Dose Response	YES**	YES**	NO	NO	NO
Quartiles (vs. 1st)					
2	1.62**(0.80, 3.28)	4.67**(2.01, 10.82)	1.69(0.90, 3.16)	0.90(0.53,1.54)	2.50(1.36, 4.62)
3	2.01 **(1.03, 3.91)	5.52 **(2.39, 12.77)	1.38(0.72, 2.65)	0.59(0.33, 1.06)	1.58(0.81, 3.09)
4	3.28**(1.72, 6.27)	7.52 **(3.27, 17.27)	2.28(1.25, 4.14)	0.57(0.31, 1.02)	1.94(1.01, 3.70)

648 Outcome of 215 HCV/HIV-Coinfected Liver Transplant Recipients: A Prospective Multicenter Study

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Background: We compared the survival after liver transplantation (LT) between HCV/HIV-coinfected patients and HCV-monoinfected patients. We also identified prognostic factors in HCV/HIV-coinfected LT recipients.

Methodology: Consecutive 215 HCV/HIV-coinfected patients who underwent LT between 2002 and 2012 and followed until June 2013 at 22 Spanish centers were matched with 613 HCV-monoinfected patients who received LT during the same period at the same institutions. Other matched criteria were age (±10 years), gender, HBV infection, and hepatocellular carcinoma. All patients had serum HCV RNA positive at LT.

Results: A total of 90 (42%) HCV/HIV-coinfected and 184 (30%) HCV-monoinfected recipients died during a median (IQR) follow-up of 3 (1-6) years. Retransplantation was performed in 11 (5%) and 43 (7%) patients, respectively. Survival at 1, 3, and 5 years for HCV/HIV-coinfected and HCV-monoinfected patients, according to the different HCV genotypes, is shown in the table. Five-year survival for HCV genotype 1 in HIV-infected recipients was 40% (29-51) in comparison with 68% (63-73) for HIV-negative recipients ($P<0.001$). Survival rates for genotypes 2 and 3 were excellent and similar in both groups ($P=0.172$). In HCV/HIV-coinfected recipients, pre-transplant predictive factors of post-transplant survival (HR, 95% CI) were: HCV genotype 1 (1.94 [1.19-3.14]), MELD score (per unit increase; 1.14 [1.00-1.07]), site LT volume (>1 case/year; 0.58 [0.37-0.94]), HCV viral load (>400,000 units/mL; 1.62 [1.03-2.57]), and plasma HIV suppression on cART (0.47 [0.24-0.90]). Anti-HCV treatment with pegylated-interferon plus ribavirin was administered in 42% of recipients in each group, and sustained virological response (SVR) was achieved in 22% of HCV/HIV-coinfected patients and 37% of HCV-monoinfected patients ($P<0.01$). In patients with SVR, 5-year survival after anti-HCV therapy was 84% and 97%, respectively ($P=0.139$)

Conclusions: 1) LT is a valid option for HCV/HIV-coinfected patients with genotypes 2 and 3, but more challenging for patients with genotypes 1 and 4; however, survival greatly improves in patients with SVR to anti-HCV therapy. The new available direct-acting antiviral agents (DAA) will improve the post-LT rates of SVR and therefore the outcome of coinfected recipients with genotypes 1 and 4; 2) Plasma HIV viral load should be suppressed before LT; and, 3) LT in HCV/HIV coinfected patients should be performed at selected sites.

Table 1

Survival estimates (95% CI)	No	1-year	3-year	5-year	P Value
HCV RNA positive at LT					
- HCV/HIV-coinfected - HCV-monoinfected	215 613	82 (76-87) 87 (84-89)	62 (55-69) 75 (71-78)	51 (43-59) 68 (64-72)	<0.001
HCV genotype 1					
- HCV/HIV-coinfected - HCV-monoinfected	119 437	79 (71-86) 86 (83-89)	53 (44-63) 74 (69-80)	40 (29-51) 68 (63-73)	<0.001
HCV genotype 2/3					
- HCV/HIV-coinfected - HCV-monoinfected	52 82	84 (72-93) 93 (86-97)	69 (55-82) 83 (74-90)	69 (55-82) 77 (66-86)	0.172
HCV genotype 4					
- HCV/HIV-coinfected - HCV-monoinfected	36 33	86 (73-95) 91 (79-98)	77 (61-89) 79 (62-92)	53 (33-72) 68 (48-85)	0.419
Patients with SVR after LT					
- HCV/HIV-coinfected - HCV-monoinfected	23 90	100 (100-100) 100 (100-100)	96 (84-99) 100 (100-100)	84 (63-97) 97 (73-93)	0.139

649 Liver Fibrosis Progression Among Persons With Recently Acquired HCV Infection

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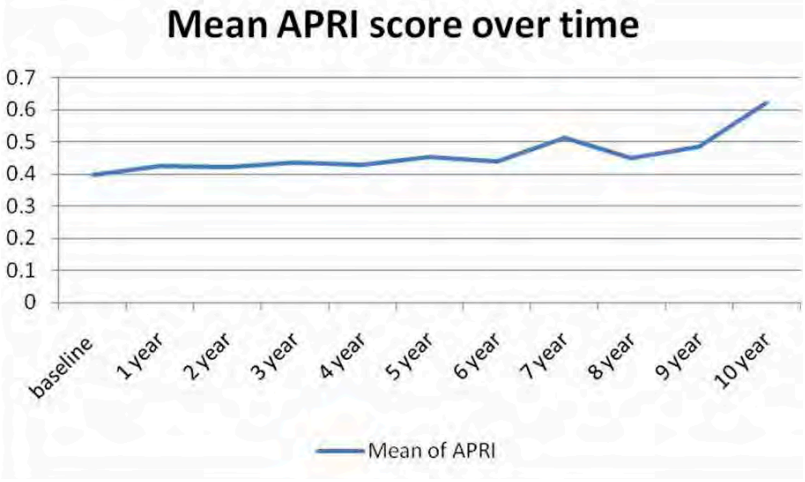
Background: Studies of natural history of HCV infection are often limited by lack of knowledge about time of seroconversion. Serial measurements of HCV antibody can provide a relatively accurate time for seroconversion. Degree and progression of liver fibrosis is a critical element in prognosis, response to treatment and outcomes. We sought to determine liver fibrosis progression in persons with recently acquired HCV infection.

Methodology: We analyzed data from the Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES). Participants were Veterans with an initial negative and a subsequent positive HCV antibody test. We excluded those with a prior history of HCV treatment, HIV coinfection, baseline AST-to-platelet ratio index (APRI) >1.5, and <24 months of follow up. The date of seroconversion was defined as the mid-point between last negative and first positive HCV antibody test. Liver fibrosis was evaluated by APRI, determined prior to and at yearly intervals after seroconversion. We calculated the yearly change in APRI and 10-year cumulative incidence of APRI >1.5, indicating significant hepatic fibrosis.

Results: We identified a total of 4,162 persons who met the above criteria and had complete data to calculate APRI scores. The mean age was 53.9 ± 12 years, 62% were White, 26.3% Black, and 92.6% were male. Mean APRI score was 0.40±0.28 at baseline and 0.60 at 10 years. The average increase in APRI was 0.023 units per year. A total of 271 (6.5%) persons had APRI > 1.5 after 10 years of follow up. Age, race, sex, body mass index and genotype were not associated with APRI>1.5.

Conclusions: Fibrosis progression in persons with recently acquired HCV infection is slow, particularly in the first 5 years. Over 10 years only, 6.5% developed significant fibrosis. These data can help in deciding whether to defer treatment while awaiting more potent and more tolerable newer regimens to treat HCV infection.



650 Predicting Risk of ESLD in HIV/HCV Patients for Individualized HCV Therapy Decisions

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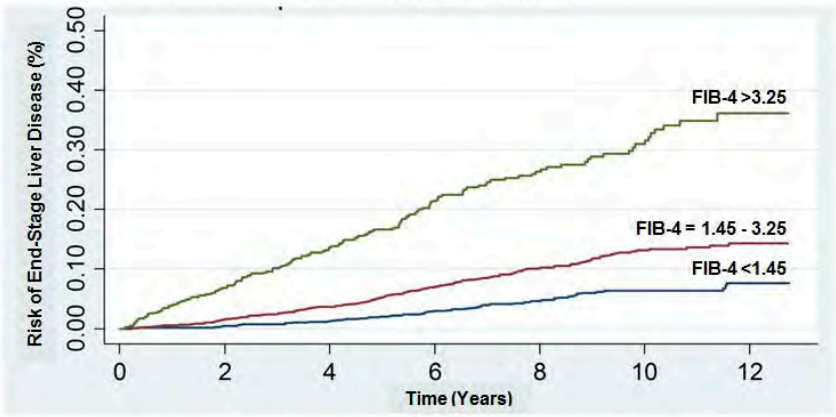
Background: The optimal time to treat hepatitis C virus (HCV) infection in HIV/HCV-coinfected patients is unclear. Improving the ability to identify patients who are more likely to progress to end-stage liver disease (ESLD) would help determine which patients should be targeted for therapy with direct-acting antiviral agents. We evaluated the ability of routinely collected clinical variables to predict the risk of ESLD in HIV/HCV patients.

Methodology: We conducted a cohort study among HIV/HCV-coinfected patients in the Veterans Aging Cohort Study Virtual Cohort between 1997 and 2010. Patients with detectable HCV RNA who were on antiretroviral therapy (ART) were included. The main outcome was incident ESLD, defined by hepatic decompensation, hepatocellular carcinoma, or liver-related death. Baseline variables evaluated as predictors of ESLD included: FIB-4 score (a non-invasive index of hepatic fibrosis calculated using age, platelet count, and alanine and aspartate aminotransferase levels), severe anemia (hemoglobin <10 g/dL), CD4 count <200 cells/mm^3, HIV RNA >400 copies/mL, diabetes mellitus, hepatitis B coinfection, non-black race, and obesity. Cox regression was used to develop prognostic models that determined the risk of

Figure. Cumulative risk of end-stage liver disease among antiretroviral-treated HIV/hepatitis C virus-coinfected patients, by FIB-4 score.



FIB-4 Score	Risk of End-Stage Liver Disease at Specified Time				
	1 Year	3 Years	5 Years	7 Years	9 Years
<1.45	0.1%	1%	2%	4%	6%
1.45 – 3.25	0.6%	4%	5%	9%	12%
>3.25	4%	10%	17%	25%	29%

FIB-4 determined by: (age [years] x AST [U/L])/((platelet count [10^9/L]) x (ALT [U/L])$^{1/2}$)

developing ESLD. Decision curves compared the predictive ability of models. The cumulative risk of ESLD over time was determined from cut-off points of the final model.

Results: Among 4,280 ART-treated HIV/HCV patients, 373 (8.7%) developed ESLD over a median 6.8 (interquartile range, 3.6-10.1) years of follow-up. A predictive model with FIB-4 alone had the highest discriminatory ability for ESLD (c-statistic, 0.73) and performed better across decision-making thresholds compared to other prognostic models that included various combinations of the predictors of interest. Three categories of FIB-4 score (<1.45; 1.45-3.25; >3.25) were able to predict the cumulative risk of ESLD over time (**Figure**).

Conclusions: Baseline FIB-4 score discriminated the risk of developing ESLD over time among ART-treated HIV/HCV patients. This index has prognostic value and could provide useful information to aid HCV treatment decisions.

651 Level of Alcohol Use and Advanced Hepatic Fibrosis in HIV-Infected and Uninfected Patients

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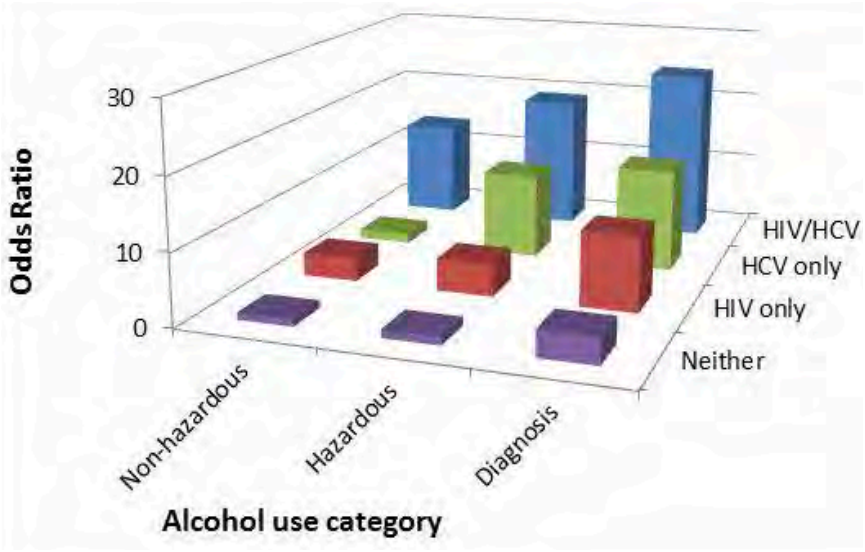
Background: The risk of liver disease associated with level of alcohol consumption is unclear for HIV-infected patients. We evaluated the association between alcohol use categories and advanced hepatic fibrosis by HIV and Hepatitis C virus (HCV) status.

Methodology: In HIV-infected and uninfected subjects reporting alcohol use at enrollment in the Veterans Aging Cohort Study, alcohol use was determined by responses to Alcohol Use Disorders Identification

Test-Consumption (AUDIT-C) questionnaire and alcohol-related diagnoses. Use was classified as non-hazardous, hazardous/binge, or abuse/dependence. Adjusted odds ratios (ORs) of advanced hepatic fibrosis (defined as FIB-4 >3.25) associated with alcohol use categories were determined, stratified by HIV/HCV status.

Results: In 1,454 HIV-infected and 2,111 uninfected, presence of advanced hepatic fibrosis increased with alcohol use category (p-trend <0.001 for both groups). HIV-infected had a higher prevalence of advanced hepatic fibrosis than uninfected (non-hazardous drinking: 6.7% versus 1.4%; hazardous/binge drinking: 9.5% versus 3.0%; abuse/dependence: 19.0% versus 8.6%; p<0.01). In HIV infected, as level of alcohol increased so did the proportion with CD4 count <200 cells/mm3 (non-hazardous: 20%; hazardous/binge: 23%; abuse/dependence: 29%; test for trend, p<0.001) and HIV RNA >400 copies/mL (non-hazardous: 52%; hazardous/binge: 56%; abuse/dependence: 60%; test for trend, p<0.001). Both HIV and HCV increased the strength of association between alcohol use and advanced hepatic fibrosis with strongest associations seen in HIV/HCV-coinfected patients with non-hazardous drinking (OR, 13.7 [5.7-33.3]), hazardous/binge drinking (OR, 19.1 [8.0-45.8]), and alcohol abuse/dependence (OR, 24.5 [10.3-58.5]) compared to uninfected non-hazardous drinkers (Figure).



Conclusions: Advanced hepatic fibrosis was present at low levels of alcohol consumption, increased with alcohol use categories, and was greater in HIV-infected than uninfected individuals. For all categories of alcohol use, associations with advanced hepatic fibrosis were particularly strong in HIV/HCV-coinfected patients.

652 Liver-Related Death in HIV/HCV Coinfected Individuals: Who Should Be Targeted for HCV Treatment?

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Background: The arrival of potent and less toxic directly acting agents (DAA) for treatment of HCV infection may see improved outcomes and less toxicity among HIV coinfected patients. The costs of treatment may necessitate prioritisation of those at greatest risk of liver-related death (LRD) for therapy. Further understanding of LRD among HIV/HCV coinfected individuals is urgently required.

Methodology: EuroSIDA patients with HCV coinfection and follow-up after 1/1/2000 were included. Causes of death were classified using CoDe methodology. Kaplan-Meier (KM) estimation was used to calculate probabilities of liver-related death (LRD) and competing risks Cox proportional hazards models were used to describe factors associated with LRD and non-LRD (excluding unknown causes).

Results: 470 deaths with known causes were recorded (126 liver-related) from 4204 coinfected patients during 23,621 PYFU to June 2012. Patients were mostly male (68%) IDUs (69%); fibrosis data was available in 80%. LRD rates peaked at age 35-45 (7.2/1000 PYFU; 95% CI 5.6-8.8) and were lower, 2.0 (0.9-3.1)/1000 PYFU and 4.9 (0.1-14.6)/1000 PYFU in those aged <35 and >65 respectively. In contrast, non-LRD increased with age from 14.1 (11.1-17.1) to 29.6 (6.3-52.9) in those aged <35 and >65 respectively. The KM 5-year probability of LRD increased from 0.03% (0.01-0.07) in those with <F2 fibrosis and CD4≥200cells/mm^3, to 0.10% (0.02-0.20), 6.7% (4.5-9.9) and 9.2% (5.4-15.4) in those with <F2/CD4<200cells/mm^3, ≥F2/CD4≥200cells/mm^3 and ≥F2/CD4<200cells/mm^3, respectively (p<0.0001). In multivariable Cox models (Table 1), ≥F2 fibrosis was associated with 25-fold increased risk of LRD. Other predictors of LRD were lower current CD4 count, higher current HIV-RNA, raised ALT, HBsAg positivity and on-going HCV viral replication. Predictors of non-LRD were increasing age at baseline, lower current CD4 cell count and on-going HCV viral replication, ≥F2 fibrosis was not a predictor of non-LRD. After adjustment, ≥F2 fibrosis was associated with a 27-fold increased risk of LRD (sHR: 27.2 (11.9-61.9)) in those with CD4≥200cells/mm^3 and 50-fold when CD4<200cells/mm^3 (sHR: 50.7 (6.6-386.7), p=0.0012 test for interaction).

Conclusions: Untreated HIV is associated with a high risk of LRD in HCV coinfected patients, in particular in those with ≥F2 fibrosis, hepatitis B coinfection and raised ALT. Our findings support guidelines to improve CD4 cell counts prior to starting HCV treatment in patients at risk of LRD.

Table 1: Competing Risks Cox Regression Models for Factors Associated with LRD and Non-LRD

Endpoint (N=Events)		*LRD (N=126)*	*Non-LRD (N=344)*
Parameter		*sHR (95% C.I.)*	*sHR (95% C.I.)*
Baseline Age: 35-40	Vs. <35	1.31 (0.81 - 2.12)	1.35 (0.97 – 1.87)
Baseline Age: 40-45	Vs. <35	1.16 (0.65 - 2.07)	1.49 (1.03 – 2.16)
Baseline Age: >45	Vs. <35	1.21 (0.65 - 2.24)	2.62 (1.80 – 3.81)
IDU	Vs. MSM	1.22 (0.55 - 2.70)	1.06 (0.68 – 1.65)
Heterosexual	Vs. MSM	0.71 (0.24 - 2.10)	1.01 (0.58 – 1.76)
South	Vs. West Central	0.75 (0.43 - 1.32)	1.02 (0.66 - 1.57)
North	Vs. West Central	1.26 (0.70 - 2.28)	1.79 (1.16 – 2.76)
East Central	Vs. West Central	0.53 (0.23 - 1.22)	1.72 (1.03 – 2.86)
East	Vs. West Central	0.23 (0.07 - 0.70)	1.91 (1.05 – 3.49)
CD4 Cell Count*	Per Doubling	0.71 (0.61 - 0.84)	0.66 (0.60 - 0.73)
HIV RNA*	Per Log_{10}	1.36 (1.18 - 1.56)	1.04 (0.95 – 1.15)
Viremic HCV*	Vs. Resolved Infection†	2.27 (1.10 - 4.67)	1.44 (1.00 – 2.08)
Unknown Viremia*	Vs. Resolved Infection†	2.36 (1.05 - 5.30)	1.38 (0.91 – 2.10)
Genotype 2 or 3	Vs. Genotype 1 or 4	0.79 (0.46 - 1.33)	1.27 (0.91 – 1.79)
HBsAg Positive*	Vs. HBsAg Negative	4.27 (1.22 - 14.97)	1.50 (0.74 – 3.04)
HBsAg Unknown*	Vs. HBsAg Negative	2.47 (0.75 – 8.08)	1.21 (0.65 – 2.24)
ALT: uNR - 3x uNR*	Vs. uNR	1.94 (1.26 - 3.00)	0.76 (0.57 – 1.02)
ALT: >3x uNR*	Vs. uNR	2.23 (1.11 - 4.48)	0.90 (0.55 – 1.49)
≥F2 Fibrosis*	Vs. <F2 Fibrosis	24.62 (11.68 - 51.91)	1.15 (0.82 – 1.61)
Unknown Fibrosis*	Vs. <F2 Fibrosis	3.07 (1.41 – 6.66)	2.91 (2.15 – 3.93)

Model additionally adjusted for: sex, race, other transmission risk groups, baseline year, CD4 nadir, unknown ALT
*Time updated variable; LRD: liver-related death; sHR: sub-hazard ratio from the Fine and Gray competing risk method; IDU: injection drug user; HBsAg: hepatitis B surface antigen; ALT: alanine transaminase; uNR: upper normal range; 3x uNR: 3x upper limit of normal range.
†Resolved infection via treatment for HCV or spontaneous clearance

653 Significant Decrease of Liver Fibrosis in HIV-HCV Coinfected Patients Treated for HCV Infection

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Background: To evaluate prospectively the regression of liver stiffness and the kinetics of two biochemical tests of liver fibrosis (FIB-4 and APRI) in HIV/HCV co-infected patients treated for their hepatitis C.

Methodology: In the ANRS CO13 HEPAVIH Cohort, patients with HIV and chronic hepatitis C who (1) received anti-HCV treatment with pegylated interferon-α and ribavirin and (2) had a liver stiffness measurement by transient elastometry before and after anti-HCV treatment were included. The kinetics of liver stiffness, FIB-4 and APRI were characterized during therapy and thereafter in patients with sustained virological response (SVR) and in patients with treatment failure.

Results: Among the 160 patients included, 69 (43%) had a SVR while 91 were non responders (NR). After a median follow-up duration of 36 months (IQR: 23.4-46.3), a significant liver stiffness decrease was observed after treatment in patients who achieved a SVR. In this group, the median decrease of liver stiffness was 19% after 1 to 2 years (p=0.007), 31% after 2 to 3 years (p=0.002), and 25% after 3 to 4 years (p=0.009). Similar dynamics were observed with APRI and FIB-4 and the liver stiffness decrease was observed in cirrhotic as well as in non-cirrhotic patients. In the NR group, there was a transient but non sustained decrease in the first year following the end of treatment. In the multivariate analysis, only the SVR was associated with long-term improvement of liver stiffness (odds ratio: 2.79; 95% confidence interval: 1.19-6.51, p=0.017).

Conclusions: In HIV/HCV co-infected patients, liver stiffness is significantly reduced after treatment, and this improvement continues off treatment in patients who achieve a SVR.

Session P-N4 Poster Session
Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

HCV Treatment: Real-World Experience

654LB On-Treatment Viral Response To MK-5172/MK-8742 ± RBV for 12 Weeks in HCV/HIV-Coinfected Patients

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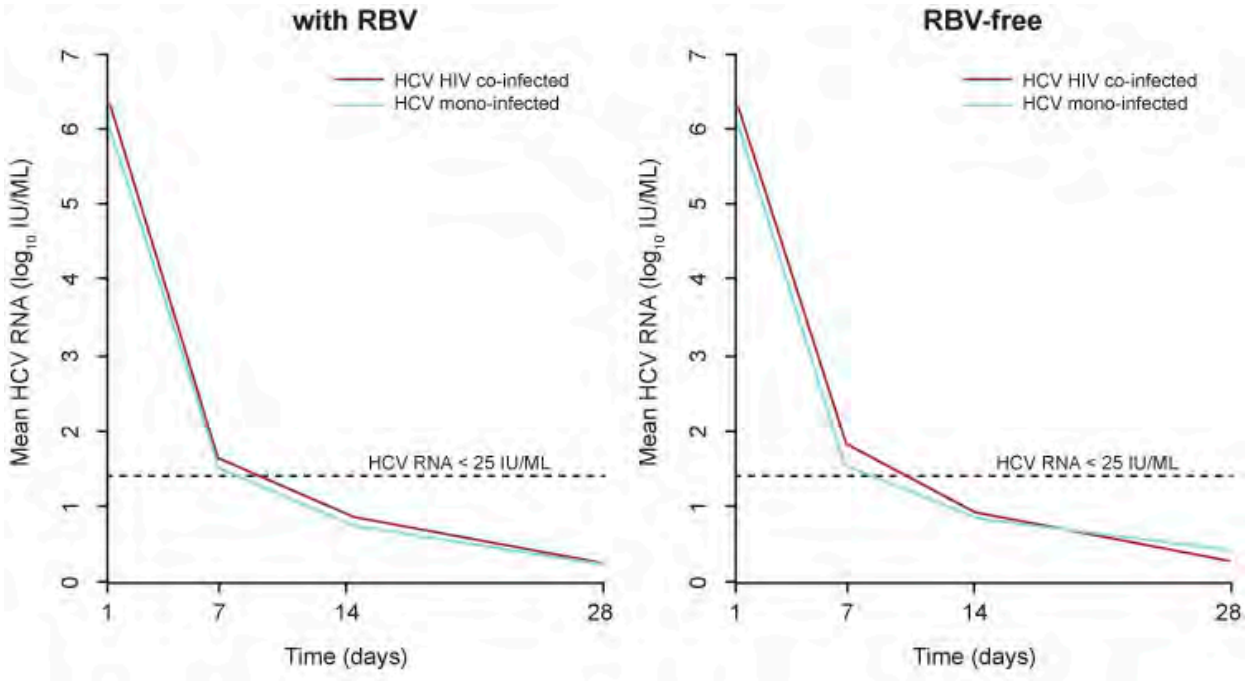
Background: The combination of MK-5172 (a highly potent second-generation HCV NS3/4 protease inhibitor) and MK-8742 (a highly potent HCV NS5A replication complex inhibitor) has demonstrated a high barrier to resistance. In part A of C-WORTHY, 62 of 63 treatment-naive, noncirrhotic patients with chronic HCV GT1 infection treated for 4-12 weeks with this combination ± ribavirin (RBV) achieved SVR12. In this study, on-treatment viral responses in an HIV/HCV GT1-coinfected population treated in part B of C-WORTHY are compared with those of the HCV-monoinfected patients treated in part A.

Methodology: Treatment-naive, noncirrhotic HIV/HCV GT1-coinfected patients on a stable antiretroviral regimen (raltegravir + tenofovir or abacavir with either 3TC or FTC) with undetectable HIV RNA were randomized to receive MK-5172 100 mg QD + MK-8742 50 mg QD ± weight-based RBV for 12 weeks. Virologic response was assessed using COBAS TaqMan v2.0 (lower limit of quantitation <25 IU/mL).



Results: 59 coinfected patients were enrolled (male, 82%; black, 18%; subtype 1a, 78%) and compared with 63 monoinfected patients enrolled in part A (male, 45%; black, 11%; subtype 1a, 58%). At baseline, coinfected patients had a mean HCV RNA of 6.4 $\log_{10}$ IU/mL compared with a baseline viral load of 6.2 $\log_{10}$ IU/mL in the monoinfected patients. After 4 weeks of therapy all coinfected and monoinfected patients had an HCV RNA <25 IU/mL independent of RBV. Among coinfected patients, the mean decline was 6.2 with RBV and 6.1 without RBV. The HCV kinetics over the first 4 weeks of therapy were similar in patients with and without HIV coinfection (Figure 1A, RBV; 1B, no RBV). Mean viral decline in GT1a- and GT1b-coinfected patients was similar (6.1 and 6.1, respectively). The most common adverse events (AEs) were fatigue (8%; 4/50) and headache (8%; 4/50); no AE was increased in patients with HIV compared with monoinfected patients. No HIV breakthrough was detected during HCV treatment. No coinfected patient discontinued. Full on-treatment data will be available in March 2014.

Conclusions: Among HCV GT1-infected patients with and without HIV, the combination of MK-5172/MK-8742 ± RBV was associated with robust HCV suppression. All HIV/HCV coinfected patients had HCV RNA levels <25 IU/mL after 4 weeks of treatment. The safety profile was similar in HIV/HCV-coinfected and HCV-monoinfected patients.

655 Slow HCV-RNA Decay and Early Resistance Predict the Risk of Failure To TVR/BOC Treatment

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Background: Triple therapy with telaprevir (TVR)/boceprevir (BOC)+peg-IFN+RBV can achieve excellent results in terms of antiviral efficacy, but it can be burdened by failures with the development of resistance mutations (RAVs). Aim of this study was to evaluate, in clinical practice, the kinetics of HCV-RNA decay and the early appearance of RAVs, in order to identify as soon as possible patients at highest risk of virological failure under triple therapy.

Methodology: 126 patients (GT1a/1b/1g=46/79/1; previously non-responders/relapsers/naive=75/31/20; cirrhotic=61 [48.4%], 2 HIV-1 co-infected) received pegIFN+RBV+TVR (N=89) or +BOC (N=37). The presence of RAVs was evaluated by population sequencing (PS) at baseline, at early time points (48h-2 weeks) and at failure. HCV-RNA was determined at early time points and then according to the standard treatment protocol.

Results: In this ad interim analysis, the median [IQR] time follow-up was 33 [17-62] weeks with BOC and 23 [9-44] weeks with TVR. Virological failure was observed in 31 (25%) patients (23 previously non-responders), in the 89% of cases associated with appearance of RAVs. Among patients who have completed treatment (N=64), RAVs at baseline/early time-points (48h-2weeks) were observed in 9 patients (14%); 7/9 (78%) subsequently failed treatment vs. 19/55 (35%) of patients without early RAVs (p=0.025). Among the 7 failures, 1 with T54S baseline failed without further RAVs, while 6 showed the development of complex mutational patterns (1=R155RT+A156AV, 2=V36M+R155K, 1=T54S+R155KR, 1=V36L+R155M, 1=A156T+T54S), probably as a result of viral evolution under therapy pressure. Other 2 patients had early RAVs only in quasispecies (T54AT; A156AT), and are currently SVR8.

Patients with baseline/early RAVs also showed a suboptimal HCV-RNA decay: only 10% achieved a rapid virologic response vs 49% of patients without RAVs (p=0.021). The median [IQR] decay of HCV-RNA after 48h of TVR administration was substantial (-3.0 [-3.4;-2.6] logUI/ml) and independent from the subsequent failure (p=0.941). On the contrary, 2 weeks HCV-RNA decay was significantly lower in failing patients than in those who reached the end of treatment (-3.7 [-4.3;-3.2] vs -4.6 [-5.2;-4.0] logUI/ml, p=0.007). None of the 11 patients with undetectable HCV-RNA at 2 weeks subsequently failed treatment, vs 2/27 patients with detectable HCV-RNA 100 IU/ml (p<0.001).

Conclusions: In the context of a PI-regimen, especially for patients with advanced disease and/or previous non response to peg-IFN/RBV, early detection of RAVs combined with a suboptimal HCV-RNA decay in the first 2 weeks of treatment, may identify patients with higher risk of viral failure and thus requiring a closer monitoring during therapy.

656LB Global Origin of HCV NS3 Substitution Q80K That Is Associated With Lower Simeprevir Susceptibility

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Background: The substitution Q80K in HCV serine protease (NS3) is associated with reduced susceptibility to the protease inhibitor Simeprevir. Q80K has been observed predominantly in HCV genotype 1a with a prevalence of 16% in Europe and 50% in the US. Thus, FDA approval for Simeprevir has stipulated screening for Q80K. We conducted a phylogenetic analysis of HCV NS3 sequences to reconstruct the evolutionary origins of Q80K, which has significant implications for its transmission between hosts and future impact.

Methodology: We retrieved all published HCV NS3 sequences from the Genbank database and used pairwise alignment against H77 to trim sequences to the first 543 nucleotides. We screened for genotype 1a (n = 5,021) based on phylogenetic reconstruction. Sequences were annotated with country and year of sample collection, or discarded if these data were not available. To remove repeated samples from the same host in the absence of consistent annotation, the sequences were re-aligned and highly similar sequences were pruned from the resulting phylogeny based on a branch length cutoff of 0.01 expected nucleotide substitutions per site. We used a modified version of Path-O-Gen to root the phylogeny relating the remaining n = 794 sequences, and a penalized likelihood method to estimate ancestral divergence times. A model of codon evolution was fit to the final tree using HyPhy to reconstruct ancestral sequences.

Results: We observed Q80K in 172 out of 794 (22%) HCV 1a NS3 sequences; in particular, in 115 out of 256 (45%) sequences obtained in the US. The phylogeny comprised two major clades relating sequences derived predominantly in the US or Europe, respectively. Consistent with previous estimates, the root of our phylogeny implied that genotype 1a emerged in the early 1910's. As expected, the ancestral 1a sequence reconstructed at the root encoded the wild-type Q at NS3 position 80. We mapped only seven ancestral Q80K substitution events in the phylogeny; one of these occurred deep in the US clade in a lineage ancestral to 292 observed sequences (165 of which inherited this Q80K). Thus, the vast majority (96%) of HCV 1a carrying Q80K have descended from a single substitution event from over 50 years ago. Reversions to wild-type occurred in 13 descendant lineages of this sub-clade. Five minor Q80K substitution events mapped to terminal branches leading directly to observed sequences, while a sixth mapped to a lineage relating only two observed sequences.

Conclusions: Our results suggest that the Q80K substitution that confers decreased Simeprevir susceptibility has a deep origin within the HCV genotype 1a clade and is readily transmitted between hosts. This evolutionary history may explain the currently observed differences in the prevalence of Q80K in European and US populations.

658 Protease Inhibitors To Treat Hepatitis C in the Swiss HIV Cohort Study: High Efficacy But Low Uptake

Sebastian Haubitz[1], Verena Schaerer[2], Juan Ambrosioni[3], Matthias Cavassini[4], Marcel Stoeckle[5], Patrick Schmid[6], Laurent Decosterd[4], Karin Metzner[2], Jan Fehr[2], **Andri Rauch[1]**

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Background: Combination therapy with pegylated interferon, ribavirin and protease inhibitors (PI) has become the standard of care for chronic hepatitis C virus (HCV) genotype 1 infection. However, there is limited information on treatment outcomes in HIV/HCV coinfected patients in clinical routine settings. We assessed PI treatment uptake and efficacy in the Swiss HIV Cohort Study (SHCS).

Methodology: Information on drug regimens, side effects and virological outcomes were collected prospectively in all SHCS participants starting PI treatment followed in one of 7 SHCS centers until July 2013. Treatment uptake and efficacy were compared to treatment outcomes before the availability of PI in September 2011.

Results: Upon approval of PI treatment, there were 717 patients with chronic HCV genotype 1 infection. Of those, 44 (6%) started PI treatment. Thirty-four patients were infected with HCV genotype 1a and 10 with 1b. The majority were male (82%) and IDU (59%). Median CD4 count at treatment start was 536 cells/µl and 91% had an HIV-RNA <50 cp/ml. Twenty-six (59%) started telaprevir, 11 (25%) faldaprevir and 7 (16%) boceprevir, and 10 (22%) had pre-treatment with intravenous silibinin. Twenty (45%) were treatment-naïve, 9 (20%) prior relapser and 15 (34%) prior partial or null-responder. Assessment of liver fibrosis by biopsy and/or fibroscan was available in 40 patients: 32 (80%) had significant fibrosis (≥ Metavir F2), and 9 (23%) had cirrhosis. Two patients stopped therapy due to side effects and 4 because of virological failure. The proportion of patients who achieved a rapid virological response (RVR) was 77% for telaprevir, 82% for faldaprevir and 71% for boceprevir. Extended virological response rates (EVR) were 85%, 100% and 86%, respectively. RVR were higher in treatment naïve and relapser compared to previous partial or null-responder (80%, 89% and 67%, respectively), while EVR were above 80% irrespective of previous treatment history. End-of-treatment (EOTR) and sustained virological response rates (SVR) available to date were 86% (in 21 patients) and 67% (in 15 patients), compared to EOTR of 43% and SVR of 28% in those treated before the availability of PI. Treatment uptake increased from 4.3 per 100 patient-years before to 7.5 per 100 patient-years (P=0.02) after the introduction of PI.

Conclusions: Protease-inhibitor based hepatitis C treatment in HIV-infected patients resulted in high virological response rates. Although treatment uptake increased after the introduction of PI, less than 10% of patients with chronic HCV genotype 1 infection started therapy. Therefore, the introduction of PI in clinical routine was beneficial at the individual level, but had only a modest effect on the disease burden at the population level.

659LB Boceprevir for Previously Treated HCV-HIV Coinfected Patients: The ANRS-HC27 BocepreVIH Trial

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Background: Boceprevir (BOC) added to pegylated-interferon (P) and ribavirin (R) increases sustained virological response (SVR) rates in naive hepatitis C virus (HCV) genotype 1/HIV-co-infected patients. There is no data in HCV/HIV-co-infected patients who previously failed PR treatment.

Methodology: In this multicenter single arm open-label phase 2 trial, patients received a 4-week lead-in of PR (peg-IFNα2b:1.5 µg/kg/wk;weight based R 800-1400 mg/day), followed by PR+BOC (800 mg tid) for 44 weeks, with additional 24 weeks PR for patients with HCV RNA (VL) >15 and ≤1000 IU/mL at W8. BOC was stopped if HCV RNA was >1000 IU/mL at W8 or W12. ART regimens had to include 2 NRTI (TDF or ABC + FTC or 3TC) with atazanavir/r (ATVr) or raltegravir (RAL). Null-responders with cirrhosis were excluded.

Results: 69 patients were enrolled, 64 started HCV therapy (31% prior relapsers, 8% with prior breakthrough, 28% partial and 33% null responders). ART regimen was 2 NRTI+ ATVr (50%), or RAL (42%) or other combinations (8%). HCV genotype was 1a in 78% of cases. METAVIR fibrosis stage was F3 in 22% and F4 in 17%. Median CD4 cell count was 728/mm3 and plasma HIV RNA was <50 cp/mL in 95%. Sixty-two patients started BOC after the lead-in phase. The W8-VL was less than 15 IU/mL in 26 patients, between 15 and 1000 IU/mL in 21 and above 1000 in 17, including patients who

stopped HCV therapy. The W12-SVR was achieved in 34/64 patients (53%), varying according to ART regimen (ATVr: 41%, RAL: 70%, others: 40%), previous response (relapse: 90%, breakthrough: 0%, partial response: 61%, null response: 24%), HCV subtype (1a: 46%, 1b: 79%), but not to IL28 polymorphism (CC: 55%, CT: 45%, TT: 60%) nor fibrosis stage (F0-F2: 56%, F3: 43%, F4: 55%). HCV treatment was discontinued in 35 patients (55%) due to virological non response in 9 (14%), breakthrough in 7 (11%), patient's decision in 8 (13%; 7 before W16), investigator's decision in 1, infections in 3 (5%), general disorders in 4 (6%), acute pancreatitis in 1, neutropenia in 1 and thrombopenia in 1. Grade 4 AEs occurred in 20 patients including leuconeutropenia (6%), infections (6%), anemia (3%) and general disorders (3%). W12-SVR was achieved in 7 patients who stopped prematurely HCV treatment for AEs or patient/investigator's decision. P or R dose reduction was required in 3 and 9 patients, respectively, EPO in 38, blood transfusions in 8 and G-CSF in 7. No HIV breakthrough or death was observed. HCV NS3 protease could be sequenced in 13 patients exhibited virological failure on BOC+PR and relevant mutations (mostly R155K and V36M/A) were detected in 7, whereas absent at baseline.

Conclusions: W12 SVR rate to BOC+PR in treatment-experienced patients was similar to that described in HCV-1-mono-infected treatment-experienced patients with a low discontinuation rate for toxicity.

660 Boceprevir/Telaprevir-Based Therapy in HIV-Infection: Interim Analysis of a Multicenter Cohort

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Background: Clinical trials on triple therapy against HCV infection including telaprevir (TVR) or boceprevir (BOC) plus pegylated interferon and ribavirin (PR) have reported considerably higher response rates than with PR alone. However, there is little information about the response to triple therapy used in clinical practice in these patients. This study was aimed to evaluate the efficacy and safety of triple therapy including TVR or BOC in HIV/HCV-coinfected patients in real-life conditions.

Methodology: HIV/HCV genotype 1-coinfected patients seen at 20 centers throughout Germany and Spain who received therapy including TVR or BOC plus PR for at least 4 weeks were included in this study. In patients with a lead-in phase, treatment week (TW)4 and TW12 response was evaluated 8 and 16 weeks after treatment initiation.

Results: 166 patients have been included in this study so far: 84.3% were male, 71.3% were IL28B rs12979860 genotype CT or TT and 48% individuals presented cirrhosis. Infection with HCV genotype 1a was observed in 69.9% and 75.8% showed a baseline HCV RNA load >600000 IU/mL. The most commonly used ARV drugs were tenofovir/emtricitabine [117 (70.5%) patients], boosted atazanavir [44 (26.5%) patients] and raltegravir [82 (49.4%) patients)]. Of the 117 (75.5%) patients who had received previous HCV treatment, 36.8% had been null responders, 14.5% partial responders and 29.1% had relapsed. 134 subjects (80.7%) initiated treatment based on TVR and 32 (19.3%) on BOC. In an intention-to-treat approach, proportions of patients with undetectable HCV RNA, according to the time-point of follow-up were 72.1% (106/147) at TW4, and 87.5% (126/144) at TW12, 73.8% (104/141) at TW24 and 64.3% (74/115) at TW48. 41 (24.7%) patients discontinued HCV therapy [30 (18.1%) because they fulfilled stopping rules, 5 (3%) individuals due to adverse events, 5 (3%) were lost to follow-up and 1 (0.6%) patient died due to hepatic decompensations]. Rash associated with TVR was observed in 8 cases (4.8%) and 27 (30.7%) individuals showed hemoglobin levels below 10mg/dl at some point of treatment. In an analysis restricted to 39 patients who had a 60 week or longer follow-up after starting therapy, sustained virological response 12 weeks after treatment discontinuation was observed in 27 (69.2%) patients. 3 (10%) out of 30 who had response at end of therapy and reached W12 after treatment, relapsed.

Conclusions: Response rates to triple therapy with TVR or BOC plus PR in HIV/HCV-coinfected patients under real-life conditions, and therefore, including a high proportion of poor responders, pretreated patients and of subjects with cirrhosis, are similar to that found in naïve patients in clinical trials. The safety profile of BOC and TVR-based therapy is comparable to that shown in clinical trials.

661 Favorable Adverse Event Profile of Sofosbuvir/Ribavirin Versus Standard of Care for Hepatitis C

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Background: The treatment of

Hepatitis C virus (HCV) infection is rapidly evolving from the current standard of care comprised of interferon (IFN)- based triple therapy to IFN free treatment with directly acting antiviral agents (DAAs). Triple therapy with Boceprevir (BOC) or Telaprevir has resulted in improved SVR rates, however adverse events (AEs), pill burden and drug interactions remain significant barriers to successful completion of treatment. The aim of this study was to evaluate the AEs experienced with the present standard of care compared to sofosbuvir + ribavirin (SOF/RBV) in HCV monoinfected, genotype-1 (GT-1) individuals.

Methodology: We retrospectively evaluated HCV monoinfected, treatment naive, GT-1 individuals treated with either BOC/IFN/RBV at the Veterans Affairs Medical Center, Baltimore (n=97) or SOF/RBV in the SPARE clinical trial at the National Institute of Allergy and Infectious Disease (n=60). AEs namely hematologic (hemoglobin, neutrophil and platelet counts); hepatic (alanine transaminase or bilirubin) and renal (eGFR) were measured and graded from 1 (mild) to 4 (severe) according to the DAIDS toxicity table (version 1.0). Comparisons were carried out using the nonparametric Wilcoxon rank sum and Chi square tests using GraphPad Prism 6.0.

Table 1: Proportion of people who developed a Graded Adverse Event

No. (%)	VA	SPARE	p-values
HGB			
Baseline Abnormal HGB	1 (1)	0	
Baseline Median (IQR)	14.5 (13.8-15.5)	13.8 (12.4-14.9)	
Any Grade AE	73 (75)	16 (27)	**p = 0.0048**
1	23 (23)	10 (17)	
2	37 (38)	5 (8)	
3	13 (13)	1 (2)	
4	0	0	
Ribavirin dose reduction	64 (64)	9 (15)	
Erythropoietin use	25 (26)	0	
ANC			
Baseline Abnormal ANC	4 (4)	5 (9)	
Baseline Median (IQR)	3.0 (2.2-3.9)	2.4 (1.5-3.6)	
Any Grade AE	81 (87)	1 (2)	**p = 0.0179**
1	29 (30)	0	
2	17 (17)	0	
3	14 (14)	1 (2)	
4	11 (11)	0	
G-CSF use	12 (13)	0	
Platelets			
Baseline Abnormal Plt	27 (28)	2 (3)	
Baseline Median (IQR)	169.0 (118-210)	205.5 (163.3-260.5)	
Any Grade AE	62 (64)	0	**p = 0.0002**
1	12 (12)	0	
2	33 (34)	0	
3	14 (14)	0	
4	3 (3)	0	
Creatinine			
Baseline Abnormal Cr	5 (5)	3 (5)	
Baseline Median (IQR)	0.9 (0.82-1.1)	0.81 (0.7-0.9)	
Any Grade AE	8 (8)	1 (2)	**p < 0.0001**
1	5 (6)	0	
2	3 (3)	1(2)	
3	0	0	
4	0	0	
ALT			
Baseline Abnormal ALT	41 (39)	32 (53)	
Baseline Median (IQR)	72.0 (39.5-96.8)	52.5 (38.3-87.8)	
Any Grade AE	8 (8)	2 (3)	p = 0.2138
1	3 (3)	1 (2)	
2	5 (5)	1 (2)	
3	0	0	
4	0	0	
Tbili			
Baseline Abnormal Tbili	10 (10)	4 (7)	
Baseline Median (IQR)	0.8 (0.6-1.1)	0.50 (0.40-0.68)	
Any Grade AE	15 (15)	13 (21)	**p < 0.0001**
1	13 (14)	7 (12)	
2	1 (1)	5 (8)	
3	1 (1)	1 (2)	
4	0	0	

Grading was measured from 1 (mild) to 4 (severe) according to the DAIDS toxicity table (version 1.0). http://rsc.tech-res.com/Document/safetyandpharmacovigilance/Table_for_Grading_Severity_of_Adult_Pediatric_Adverse_Events.pdf

Results: The BOC/IFN/RBV cohort was older (58 vs. 55, p=0.0006) male (96% vs. 62%, p<0.0001) and had more advanced liver disease (59% vs. 23%, p<0.0001) (Table 1). The SOF/RBV group had a higher proportion of African Americans (83% vs. 65%, p=0.001). The combination of SOF/RBV was well tolerated, while BOC/IFN/RBV was associated with significantly more AEs, most commonly neutropenia, anemia and low platelets. (Table 1). In the SOF/RBV cohort, 5(8%) patients discontinued treatment early but none (0%) were for AEs while 34 (35%) patients on triple therapy discontinued treatment due to AEs.

Conclusions: SOF/RBV treatment was associated with much fewer side effects than BOC-based triple therapy appearing to be a safer and more tolerable alternative for HCV GT-1 subjects. These results show that emerging IFN/RBV free therapies may enhance patient compliance, allowing treatment of larger numbers of patients.

662LB IFN-Free 3 DAA Regimen in HCV Genotype 1-Infected Patients On Methadone or Buprenorphine

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Background: ABT-450 is an HCV NS3/4A protease inhibitor (dosed with ritonavir 100mg, ABT-450/r) identified by AbbVie and Enanta. ABT-267 is an NS5A inhibitor, and ABT-333 is an NS5B RNA polymerase inhibitor. This 3D regimen, dosed with ribavirin (RBV) in treatment-naïve and -experienced HCV-infected genotype 1 (GT1) patients, has demonstrated SVR12 rates of 96% after 12 weeks of treatment. We evaluated the safety and efficacy of 3D+RBV in patients receiving chronic opioid replacement therapy, a challenging population with a high prevalence of HCV.

Methodology: Non-cirrhotic patients with chronic HCV GT1 infection who were on stable methadone or buprenorphine +/- naloxone therapy were enrolled in this open-label study. Patients were treated for 12 weeks with co-formulated ABT-450/r/267 (2 tabs QD), ABT-333 (1 tab BID), and weight-based RBV. The percentage of patients achieving SVR4 (HCV RNA < LLOQ 4 weeks post-treatment) was assessed in an intent-to-treat analysis.

Results: 38 patients were enrolled (19 on methadone, 19 on buprenorphine). Mean age was 48.2 years, 66% were male, 95% were treatment-naïve, 84% had GT1a infection, and 68% had IL28b non-CC genotype. One subject prematurely discontinued due to a serious adverse event unrelated to study drug (cerebrovascular accident). The remaining 37 subjects all achieved SVR4. Complete SVR12 data will be presented. There were no virologic failures. The most frequent adverse events were nausea (50%), fatigue (47.4%), and headache (31.6%); 8 patients experienced hemoglobin < 10 g/dL while on treatment.

Conclusions: The 3D+RBV regimen was well tolerated in this population; patients achieved SVR4 rates comparable with previous trials.

663 Telaprevir Treatment of HIV/HCV G1 Patients With Severe Fibrosis: Efficacy Results To Week 16

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Background: HEP3005 is an ongoing, open-label, international clinical trial of telaprevir for patients with genotype 1 hepatitis C, HIV co-infection, and either severe fibrosis or compensated cirrhosis.

Methodology: One-hundred and eighteen patients were treated with telaprevir, pegylated interferon-alpha and ribavirin (PR) for 12 weeks, followed by PR for 36 weeks. Liver biopsy or non-invasive tests showing severe fibrosis (Metavir F3 or Ishak 3-4) or cirrhosis (Metavir F4 or Ishak 5-6) and platelet count >90,000/mm^3 were required at entry. This interim (ITT) analysis included 16 week data from the first 102 patients who had the potential to reach Week 16 (12 weeks of TVR + PR and 4 weeks of follow up on PR alone).

Results: Mean age was 44 years and mean weight 75kg; 82% were male and 100% Caucasian, 67% had HCV RNA levels ≥800,000 IU/mL, 59%/41% had severe fibrosis/cirrhosis, 61% had genotype 1a, 34% were treatment naïve, 16% prior relapsers, 45% prior non-responders and 4% had prior viral breakthrough. Baseline HIV RNA was <50 copies/mL in 96% of patients; mean baseline CD4 count was 644 cells/uL. The ribavirin dose was 1000 to 1200 mg/day in 92% of patients. Overall, 99/102 patients continued antiretroviral treatment during the trial, while 3 were untreated. NRTIs were TDF/FTC for 62% and ABC/3TC for 34% of patients. In addition patients received either raltegravir (37%), efavirenz (21%) or atazanavir/ritonavir (46%). By Week 4, 65/102 patients (64%) had undetectable HCV RNA, rising to 86/102 (84%) by Week 12. Of the other 16 patients at Week 12, 3 discontinued for a virological endpoint, 2 had detectable HCV RNA levels (<25 IU/mL), 6 had HCV RNA levels >1000 IU/mL, 2 discontinued for adverse events and 3 discontinued for other reasons. The most common Grade 1-4 adverse events were thrombocytopenia (27%), anaemia (26%), rash (22%), and neutropenia (16%). The most common Grade 3-4 adverse events were thrombocytopenia (4%), anaemia (3%), rash (1%), and neutropenia (5%). Five patients discontinued telaprevir for adverse events (2 for anaemia, 2 for rash, 1 for asthenia). The mean reduction in CD4 count to Week 12 was 267 cells/mm^3. At Week 12, 78 out of 81 patients (96%) had HIV RNA <50 copies/mL (On treatment analysis).

Conclusions: In this telaprevir early access program for HIV-HCV co-infected patients with severe fibrosis or compensated cirrhosis, 84% of patients had undetectable HCV RNA by week 12 (ITT). HIV RNA remained suppressed in patients continuing on HCV treatment. The most common adverse events were haematological; discontinuation for adverse events was uncommon (5%).

664LB Telaprevir Increases Ribavirin Toxicity Through eGFR Decrease in HIV-HCV Coinfected Patients

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Background: A significant hematological toxicity (HT) was observed during the retreatment of HIV-HCV genotype 1 coinfected patients in the ANRS HC26 TelapreVIH study. Alterations in renal function have been described with telaprevir (TVR). We examined the relationship between ribavirin (RBV) trough concentration (C), estimated glomerular filtration rate (eGFR) and hemoglobin (Hb) level, before and after introduction of TVR in the TelapreVIH study.

Methodology: 69 HIV-HCV genotype 1 coinfected patients received PegIFN α2a (180µg/week) + RBV (1000-1200mg/day) for 4 weeks, followed by TVR (750/1125mg tid without/with efavirenz) + PegIFN-RBV for 12 weeks and finally PegIFN-RBV for 32 to 56 weeks. RBV C was determined by HPLC at W4 and W8, before and after TVR introduction. eGFR was estimated by the MDRD equation. Hb level and eGFR were determined at baseline (BL) and monthly. Factors associated with HT (defined by RBV dose reduction, prescription of EPO or blood transfusion) were analyzed by uni- and multivariate analysis. All data are presented as median [IQR].

Results: 67/69 patients were analyzed (female 21%, severe fibrosis/cirrhosis 40%, inosine triphosphatase (ITPA) CC 81%). Hb level was 154 g/L [145-160] at BL and declined to 131 g/L [119-143] at W4 and 116 g/L [104-129] at W8 ($p<0.0001$). eGFR remained normal between BL (97.9 mL/mn [81.4-110]) and W4 (103.4 mL/mn [87.4-122.1]), then declined to 86.3 mL/mn [74.8-104.5] at W8 ($p<0.0001$). eGFR stabilized until W16 and increased back to BL level at W20 (98.4 mL/mn [84.1-112.2]). The proportion of patients with stage 1 / stage 2 chronic kidney disease increased from 36% / 0% at BL to 50% / 6% at W8 ($p=0.001$) and 40% / 15% at W16 ($p=0.001$), then decreased to 35% / 0% at W20.

RBV C increased from 1.88 mg/L (1.48 - 2.29) at W4 to 2.88 mg/L (2.16 - 3.71) at W8 ($p<0.0001$). RBV C was ≥3 mg/L in 12% of patients at W4 and in 45% at W8 ($p<0.0001$). Female gender was marginally associated with RBV C ≥3 mg/L at W4 ($p=0.05$). Female gender ($p=0.02$) and W8 eGFR ($p=0.0001$) were significantly associated with RBV C ≥3 mg/L at W8.

HT was observed in 23.9% of patients at W4, 45.3% at W8 and 70% at W48. Female gender, BL Hb, BL eGFR, W8 eGFR and RBV C ≥3 mg/L at W8 were associated with W8 HT in the univariate analysis while body weight, CDC stage, CD4 cells count, type of antiretrovirals, liver fibrosis, HCV sub-genotype, ITPA genotype and SVR24 were not. In multivariate analysis, RBV C ≥3 mg/L at W8 (OR 7.7 [2.2-27.4]) and BL Hb <150 g/L (OR 6.4 [1.7-23.8]) were independently associated with W8 HT while gender, type of antiretrovirals, BL eGFR and W8 eGFR were not.

Conclusions: Association of TVR to PegIFN+RBV was associated with a decrease in eGFR and a significant increase in RBV C, leading to RBV over-exposure in 45% of the patients.

665LB Safety and Efficacy of IFN-Free, Sofosbuvir/RBV Therapy in HIV/HCV Liver Transplanted Patients

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Background: Long-term outcome in HCV/HIV-coinfected subjects undergoing liver transplantation (LT) relies on the management of HCV recurrence. Currently available peg-IFN-based therapies are associated to high toxicity and low antiviral efficacy, leading to worse outcomes in comparison to HCV monoinfected subjects.

Methodology: To describe for the first time the on-treatment safety and efficacy of the combination of 400mg/day of sofosbuvir (SFB) -a new direct antiviral agent against HCV targeting the HCV-NS5B polymerase- plus ribavirin (RBV) in 7 HIV/HCV-coinfected patients with HCV recurrence after LT.

Results: Mean age 49±7, male 57%, 71% prior AIDS, 100% undetectable HIV-RNA, median CD4 counts 160 cells/ml (47-451). 71% HCV-G1 (n=5), HCV-G3 (n=1), HCV-G4 (n=1). Most subjects (71%) were IL28B non-CC. Only P2 was completely naïve to anti-HCV therapy (14%). Previously to SFB/RBV 57% (n=4) had already received post-LT antiviral therapy, with standard peg-IFN/RBV (n=2, null response in both), or triple therapy with boceprevir (n=1) or telaprevir (n=1), in both with premature discontinuation due to life threatening toxicity despite negative HCV-RNA. All subjects showed histological severity: cirrhosis 71% (n=5, 60% CHILD-PUGH ≥6 and prior decompensation in 40%), 29% (n=2) fibrosing cholestatic hepatitis (FCH), both female with HCV-G1. Overall 86% were on tacrolimus-based immunosuppresive therapy, 43% were currently on steroids. All patients were on raltegravir-based HAART: 4 with KIVEXA™ (fixed dose 3TC/Abacavir), 3 with TRUVADA™ (fixed dose FTC/Tenofovir), P7 also received maraviroc. Median time from LT to therapy was 900 days (88-1932). To date, the median time on SFB/RBV is 7 weeks (2-40) and three (43%) have completed at least 12 weeks. Median baseline HCV-RNA was 5.73$\log_{10}$ IU/ml. Median HCV-RNA decreases during therapy: w+2, -3,94$\log_{10}$IU/ml, w+4, -4,15$\log_{10}$IU/ml; 100% of patients with at least 4 weeks of therapy (n=6) reached RVR (<15 IU/ml at w4). During therapy there were no cases of HCV-RNA or HIV-RNA rebound. Median initial dose of RBV was 800mg/d, with dose adjustments needed in 4 subjects (57%), all of them within the first 8 weeks, in three with blood transfusions. EPO was transiently used only in P3 (FCH). Liver transaminases reached normal vales within the fist two weeks in 100%. There were not premature discontinuations, infections, or SFB-related adverse events.

Conclusions: An IFN-free, SFB/RBV regimen showed an excellent safety and efficacy profile in HIV/HCV-coinfected patients with severe liver damage related to HCV recurrence after LT. 100% reached RVR, with rapid normalization of liver function tests. Viral response was the rule regardless baseline HCV-RNA, IL28B or HCV genotype, or previous pattern of response to peg-IFN based therapy.

666 ss469415590 Variant Is a Better Predictor Than IL28B rs12979860 of PegIFN-α/RBV Therapy Failure

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Background: Recently, it has been discovered, upstream of the interferon-λ3 protein (IFNL3) (also termed IL28B) on chromosome 19, a new transiently induced region that harbors a dinucleotide variant ss469415590 (TT or ΔG), which is in high linkage disequilibrium with rs12979860. ss469415590 (ΔG) is a frameshift variant that creates a novel gene, designated IFNL4, which is moderately similar to IFNL3. Importantly, ss469415590 may have a functional role in the innate immune response to HCV. Since there are no data about the impact of IFNL4 ss469415590 polymorphisms on treatment outcomes in HCV/HIV-1 coinfected patients, we decide to investigate the role of the ss469415590 SNP in a well characterized cohort of HCV/HIV-1 coinfected patients that were treated with pegIFN-α/RBV.

Methodology: The prevalence of the ss469415590 TT/ΔG substitution, as well as the rs12979860 polymorphism, was analyzed in a cohort of 207 patients from our clinic with chronic HCV and HIV-1 coinfection and with a known response to treatment with pegIFN-α/RBV at 24 weeks post-treatment. ss469415590 and rs12979860 genotyping was performed using the ABI TaqMan allelic discrimination kit and the ABI7500HT Sequence Detection System. The association of ss469415590 and rs12979860 polymorphisms with response to treatment was performed by univariate and multivariate logistic regression as implemented in the SNPStats software.

Results: ss469415590 and rs12979860 polymorphisms were in strong linkage disequilibrium (R2 = 0.95) and both had a minor allele frequency of 0.32. The ss469415590 minor allele frequency was identical to that found for Europeans in the HapMap samples (0.07 frequency in Asians, 0.32 frequency in Europeans and 0.73 frequency in Africans). We next correlated the ss469415590 and rs12979860 genotypes with the HCV pegIFN-α/RBV treatment response. Both polymorphisms were associated with response to treatment. However, ss469415590 had a more significant association with response to treatment (OR = 3.12, 95% CI 1.1.72-5.67, P = 0.0001) than rs12979860 (OR = 2.60, 95% CI 1.45-4.69, P = 0.0012). Remarkably, ss469415590 had also a stronger association in a multivariate model, after adjustment for age, sex, HCV RNA load and fibrosis stage (OR = 3.56, 95% CI 1.80-7.03, P = 0.0002) than rs12979860 (OR = 2.99, 95% CI 1.53-5.84, P = 0.001).

Conclusions: These results demonstrate that ss469415590 is a better marker of sustained viral response than rs12979860.

667 Pill Burden & Treatment Length Reduce Adherence To IFN-Free Hepatitis C Therapy in an Urban Cohort

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Background: Potent oral directly acting antiviral (DAA) HCV therapy with low pill burdens and short therapeutic courses are promising replacements for interferon and ribavirin based regimens. The impact of these improvements on patient adherence and virologic outcomes has not been described.

Methodology: Sixty HCV infected, treatment naïve, genotype 1 patients were enrolled into 3 arms of a phase 2 clinical trial and received: sofosbuvir + ledipasvir (400/90mg one pill once daily in a fixed dose combination (FDC)) for 12 weeks, FDC + GS-9451 (80mg/day), two pills, once daily for 6 weeks, or FDC + GS-9669 (500mg/day), three pills, once daily for 6 weeks. Serial measurements of virologic correlates (HCV RNA; deep sequencing of viral mutations) were performed. Adherence was measured using three tools: MEMS caps (MEMS), pill counts (PC) and patient report (PR). Demographics and modified ACTG questionnaires were used to determine risk factors for non-adherence. Adherence tools, treatment arms, and risk factors were compared using Pearson correlations, T-tests/ANOVA and Chi-squared tests respectively.

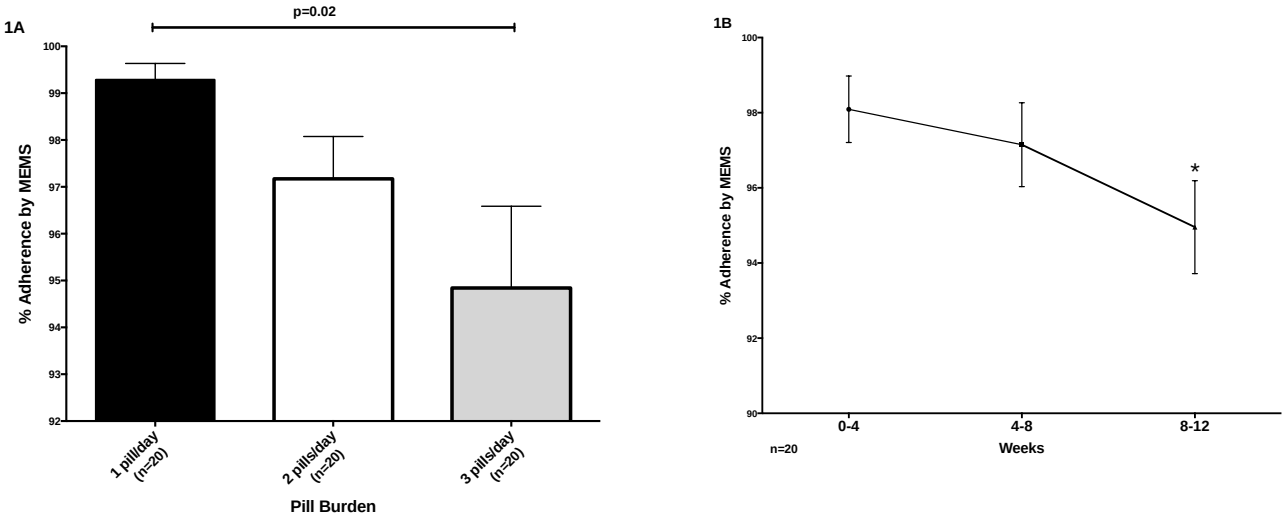

Figure 1: A: Adherence declines with increasing pill burden (p=0.02). B: Adherence declines during 12-week treatment duration (*p=0.04, Week 0-4 vs. Week 8-12)

Results: Patients enrolled were African American (88%), male (72%) with ≤ 12th grade education (61%). Psychiatric disease (43%) and recent history of drug/ETOH abuse (37.5%) were common.

Adherence to DAA regimens declined with increasing pill burden (99.3 ± 1.6% vs. 97.2 ± 3.6% vs. 94.8 ± 7.4%, one, two & three pills/day respectively, p=0.02 (Fig 1A)). Adherence to therapy declined significantly during the 12-week treatment course (98.1 ± 0.9% vs. 95.0 ± 1.2% weeks 0-4 vs. weeks 8-12, p=0.04 (Fig1B).) Missed doses by MEMS correlated with PC (R2=0.24, p<0.0002), but neither with PR (p=0.14 & p=0.84 respectively). Three patients missed ≥2 consecutive doses. Adherence was similar in patients with and without early viral suppression (<LLOQ at week 4) and time to viral suppression similar between adherent and non-adherent (defined as 0.05). Risk factors for non-adherence were feeling inconvenienced (p=0.03) and children living at home (p=0.01). Common reasons for non-adherence were feeling that drugs were working (39%), forgetting (35%) and absence from home (32%).

Conclusions: Adherence to short courses of DAA therapy with 1-3 pills once a day was excellent in an urban population with multiple risk factors for non-adherence. Increased pill burden and duration of treatment decreased adherence. Continued education regarding adherence despite on-therapy viral load decline may improve outcomes.

668 Telaprevir in Treatment-Experienced HIV-HCV G1 Coinfected Patients (ANRS HC26 TelapreVIH)

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Background: Retreatment with PegInterferon (PegIFN) + Ribavirin (RBV) results in poor SVR rates in HIV-HCV coinfected patients. There is no data regarding the use of Telaprevir (TVR) + PegIFN-RBV in this population

Methodology: HIV-1 infected patients who had previously failed ≥12 weeks PegIFN-RBV for HCV genotype 1 coinfection were enrolled in a single-arm, phase 2 trial. Authorized antiretrovirals (ART) were tenofovir (TDF), emtricitabine (FTC), efavirenz (EFV), boosted atazanavir (ATVr) and raltegravir (RAL). Null-responders with cirrhosis were excluded. All patients received PegIFN α2a (180µg/week) + RBV (1000-1200mg/day) for 4 weeks (lead-in phase (LI)), followed by TVR (750 mg or 1125mg tid if EFV-based ART) + PegIFN-RBV for 12 weeks and finally PegIFN-RBV for an additional 32 to 56 weeks according to their virological response at week 8 (RVR8). Primary endpoint was the sustained virological response at 24 weeks post-treatment (SVR24) by ITT analysis.

Results: Among 70 screened patients, 69 (39% relapsers (RR), 9% breakthroughs (VB), 22% partial (PR) and 30% null responders (NR)) started treatment. Median [IQR] CD4 cell count was 630 cells/mm3 [459-736]. ART regimen was TDF-FTC with ATVr in 49%, EFV in 19%, RAL in 17% and other combinations in 14%. HCV genotype was 1a in 70% of cases. METAVIR fibrosis stage was F3 in 16% and F4 in 23%. IL28B genotype was CC in 31%, CT in 50% and TT in 19%. SVR24 was achieved in 55/69 patients (79.7%, 95% CI: 68.3%-88.4%). SVR24 was not influenced by fibrosis stage (F1-2 81%, F3-4 78%), ART regimen (ATVr 81%, EFV 75%, RAL 71%), HCV subtype (1a 75%, 1b 90%), baseline CD4 cell count (<350/mm3 60%, ≥350/mm3 83%), type of previous response (RR 74%, VB 83%, PR 100%, NR 71%), baseline HCV-RNA (<5.9 Log UI/mL 71%, ≥5.9 Log UI/ml 83%), HCV-RNA decline at the end of LI (<1 log UI/mL 74%, ≥1 log UI/ml 82%) or IL28B genotype (CC 81%, CT 76%, TT 85%). Only 3 patients with a partial RVR8 were assigned to 72 weeks of treatment, the remaining patients were assigned to a 48 weeks treatment.

HCV treatment was prematurely discontinued for toxicity in 20% of patients, including cutaneous adverse events (AE) 4%, psychiatric AE 4%, hematological AE 6%, other AE 6%. Grade 4 AEs occurred in 20% of cases, including anemia (10%), leuconeutropenia (6%), thrombocytopenia (1%) and infections (3%). PegIFN or RBV dose reduction was required in 23 and 43%, respectively. 65% of the patients required EPO, 23% blood transfusions, 6% G-CSF and 1% platelet transfusions and TPO-R agonist. Two patients died during the study, 1 from an intracerebral hemorrhage at week 40 and 1 from an upper gastrointestinal hemorrhage at week 55.

Conclusions: Despite a high discontinuation rate related to toxicity, a high proportion of treatment-experienced HIV-coinfected patients achieved SVR24 with a TVR-based regimen.

Session P-N5 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

HCV: The Cascade

669 The Treatment Cascade for People With Chronic Hepatitis C Virus Infection in the United States

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Background: As antiviral therapy for chronic hepatitis C virus (HCV) advances to become more convenient, effective, and better-tolerated, identifying gaps in HCV care will become increasingly important to clinicians, public health officials, and federal agencies. The objective of this study was to review the literature to estimate the number of chronic HCV-infected persons living in the United States (US) completing each step along a proposed HCV treatment cascade.

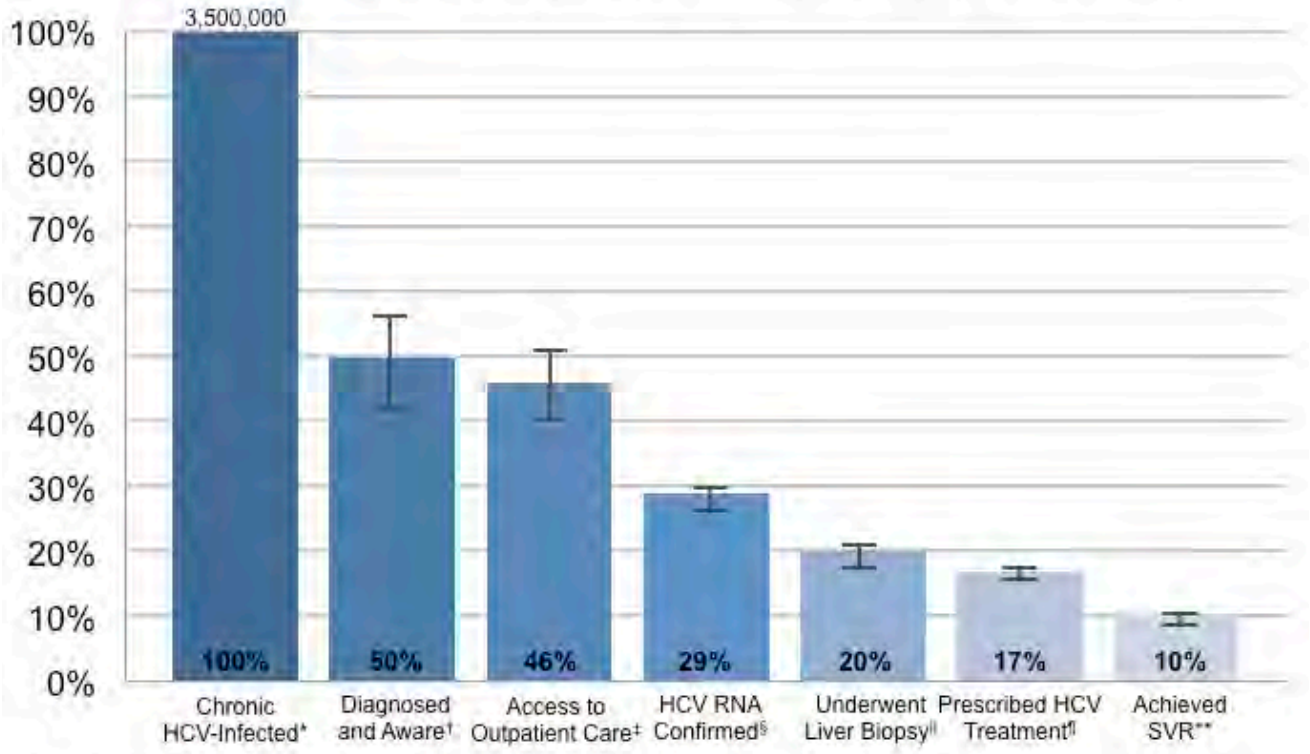
Methodology: We searched MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews for English language articles published between January 2003 and July 2013 addressing the following key questions: (1) number of people with chronic HCV infection; and the proportion of chronic

HCV-infected individuals: (2) diagnosed and aware of their infection; (3) with access to outpatient care; (4) HCV RNA confirmed; (5) disease staged by liver biopsy; (6) prescribed HCV treatment; and who (7) achieved sustained viral response (SVR). Studies were excluded if they were not relevant to study questions, focused on specific populations, did not present original data, involved only a single site, were conducted outside of the US, or only included data collected prior to 2000. Bibliographies of included studies were reviewed for additional studies, and experts were contacted to ensure no relevant studies were missed. For each key question for which multiple studies were identified, we used meta-analytic techniques to quantitatively summarize the estimates.

Results: Of the 9,581 articles identified, 120 were retrieved for full text review and 7 met inclusion criteria (1 study for questions 1-5, 2 for question 6, and 3 for question 7). Overall, 3.5 million people have chronic HCV infection in the US. Fifty percent (95% Confidence Interval 43-57%) are diagnosed and aware of their infection; 46% (41-51%) are able to access outpatient care. Twenty-nine percent (28-30%) receive confirmatory HCV RNA testing, 20% (19-21%) undergo fibrosis staging, 17% (16-17%) are prescribed antiviral therapy, and 9% (9-10%) achieve SVR. (Figure)

Conclusions: The proposed HCV treatment cascade provides a framework for identifying gaps in HCV care, indicating that continued efforts are needed to improve diagnosis and awareness of infection, liver fibrosis staging, prescription of antiviral therapy, and achievement of SVR.

Figure. Treatment Cascade for People with Chronic Hepatitis C Virus (HCV) Infection



* Chronic HCV-Infected: N=3,500,000.
† Calculated as estimated number chronic HCV-infected (3,500,000) x estimated percentage diagnosed and aware of their infection (50%); n=1,750,000.
‡ Calculated as estimated number diagnosed and aware (1,750,000) x estimated percentage with access to outpatient care (91.0%); n=1,592,500.
§ Calculated as estimated number with access to outpatient care (1,592,500) x estimated percentage HCV RNA confirmed (62.9%); n=1,001,683.
|| Calculated as estimated number with access to outpatient care (1,592,500) x estimated percentage who underwent liver biopsy (44.3%); n=705,478.
¶ Calculated as estimated number with access to outpatient care (1,592,500) x estimated percentage prescribed HCV treatment (36.7%); n=584,448.
** Calculated as estimated number prescribed HCV treatment (584,448) x estimated percentage who achieved SVR (58.8%); n=343,655.

670 Initial Results of a Community-Based Rapid Hepatitis C Testing and Linkage To Care Program

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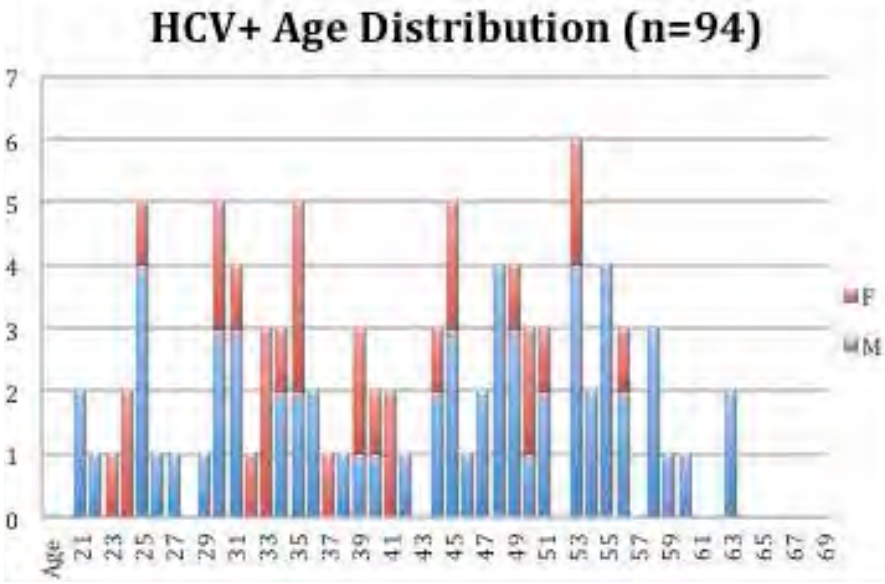
Background: Chronic Hepatitis C virus (HCV) is a major public health concern and the leading chronic viral cause of death in the United States. Some estimates suggest that less than 50% of those infected with HCV are aware of their infection. Community-based testing strategies are needed, but uncertainty exists surrounding the implementation of HCV testing, linkage to care, and treatment.

Methodology: 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 cross-trained on HCV testing and counseling. Demographic and risk-factor data was collected prospectively. Rapid HCV Antibody testing was followed immediately by post-test counseling, phlebotomy for confirmatory viral load testing, and linkage to care.

Results: Between 4/23/13 and 9/5/13 we conducted 453 rapid tests at 3 clinic sites and 6 residential alcohol and drug treatment programs. 94 rapid tests (21%) were positive. Of those patients with positive rapid HCV Ab tests, 12 (12.7%) refused confirmatory testing. 82 patients had confirmatory viral loads drawn with 59 (71.9%) positive and 23 (28%) undetectable indicating resolved infection. Of the 94 HCV Ab positive patients, 63 (67%) were male and 38 (40.4%) fell within the 'baby boomer' birth cohort of birth year between 1945-1965. 47 (50%) disclosed a prior history of injection drug use. The median age was 44 (range 22-64). Only 25 of 94 (26.5%) had insurance, and of these, all but 2 were publicly funded (Medicaid or Low Income health insurance). Overall, 67 (71.2%) were linked to care and one started treatment.



Conclusions: This demonstration project reports a very high seroprevalence of HCV in urban community health centers and alcohol and drug rehabilitation centers. Many patients refused confirmatory blood draws, and only half reported prior injection drug use. Only one quarter of all HCV Ab positive patients had insurance at the time of testing, and of those who were insured, their plans would generally not cover HCV treatment. Stigma, denial, lack of healthcare insurance, and lack of coverage for HCV treatment are significant obstacles to the effort to address the HCV epidemic.

671 The CORE HCV Cascade a Decade Later: Looking Ahead To an IFN-Free Era

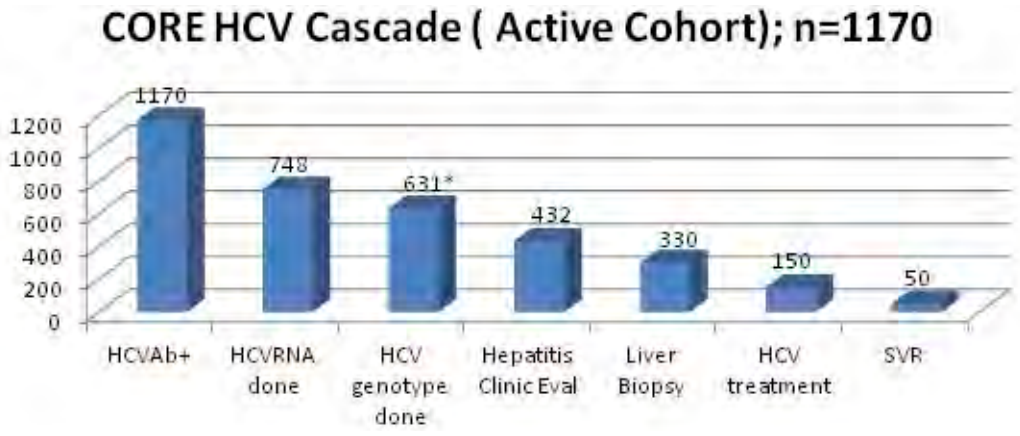
Oluwatoyin M. Adeyemi, Stephon Effinger, Benjamin Go, Sonia Vibhakar, Maureen Gallagher, Deborah Wolen, Becky Goldberg, Mike Demetria, David Barker, Gregory Huhn
Ruth M Rothstein CORE Center, Cook County Health and Hospitals System, Chicago, IL, United States

Background: One of the goals of the US National Viral Hepatitis Plan is to increase testing, linkage to care and treatment of HCV. Our HIV center has had an on-site multidisciplinary hepatitis clinic since 2001 and patients (pts) have access to all approved HCV medications regardless of ability to pay. In this study, we determined HCV evaluation and treatment rates in HIV/HCV co-infected pts through 2013.

Methodology: Retrospective electronic chart review of all HIV+/HCV ab+ pts with ≥1clinic visit at the CORE center Chicago from Jan 2006- July2013. HIV+/HCV+ pts were classified into 2 cohorts: Lost to Care (LTC) cohort;Last primary care clinic visit between Jan 2006-Dec 2010 and Active cohort (AC);most recent clinic visit between Jan 2011- July 2013.

Results: Since Jan 1 2006, 1905 HIV+/HCV+ pts have had ≥ 1 HIV primary care clinic(PCC) visit at CORE. There were 735 pts in the LTC cohort and 1170 in the active cohort. The LTC cohort had a median age of 54 yrs, 72% were male, 70 % AA, 18% white and 12% Hisp. Median CD4 at last visit was 337 and 55% had undetectable HIVRNA. Only 16% of the LTC cohort had ≥1 hepatitis(hep) clinic visit while in care and this ranged from 9% of pts with last PCC visit in 2006 to 28% of those with last PCC visit in 2009. The AC (n=1170) have a median age of 52 years and 73% are male,69% AA, 18% Hisp and 12% white. 762 (65%) have had ≥1 PCC visit through July 2013; for 238 (20%) last PCC visit was in 2012 and for 170 (15%)last PCC visit was in 2011. Median CD4 of the AC is 428 cells/mm3 and 71% have undetectable HIVRNA. 37% of the AC have had ≥1 hep clinic visit (median=7).The HCV cascade for the AC is shown in the table. *Of 631 pts with HCV genotype done; 514 (81%) were genotype1. 87% of the active cohort is ≤federal poverty level (FPL). 60% are uninsured, 29% on Medicaid, 5.5% on Medicare and <2% have private insurance.

Conclusions: The vast majority of HIV/HCV co-infected Pts in our clinic have not been evaluated in the hepatitis clinic and only a minority have been treated for HCV. Limitations of the current HCV therapies (tolerability and patient/provider issues) remain major barriers to HCV treatment in our co-infected pts. we expect that the numbers evaluated and treated will increase with improved treatment options in the near future. Many co-infected pts are≤FPL thus, ready coverage of approved HCV medications by publicly and privately funded health plans need to be advocated for.



672 The Hepatitis C Cascade of Care Among HIV-Infected Patients Following Diagnosis of HCV Infection

Edward R. Cachay[1], Lucas Hill[2], David Wyles[1], Francesca Torriani[1], Bradford Colwell[2], Craig Ballard[2], William Christopher Mathews[1]
[1]Medicine, University of California San Diego, La Jolla, CA, United States, [2]Pharmacy, University of California San Diego, La Jolla, CA, United States

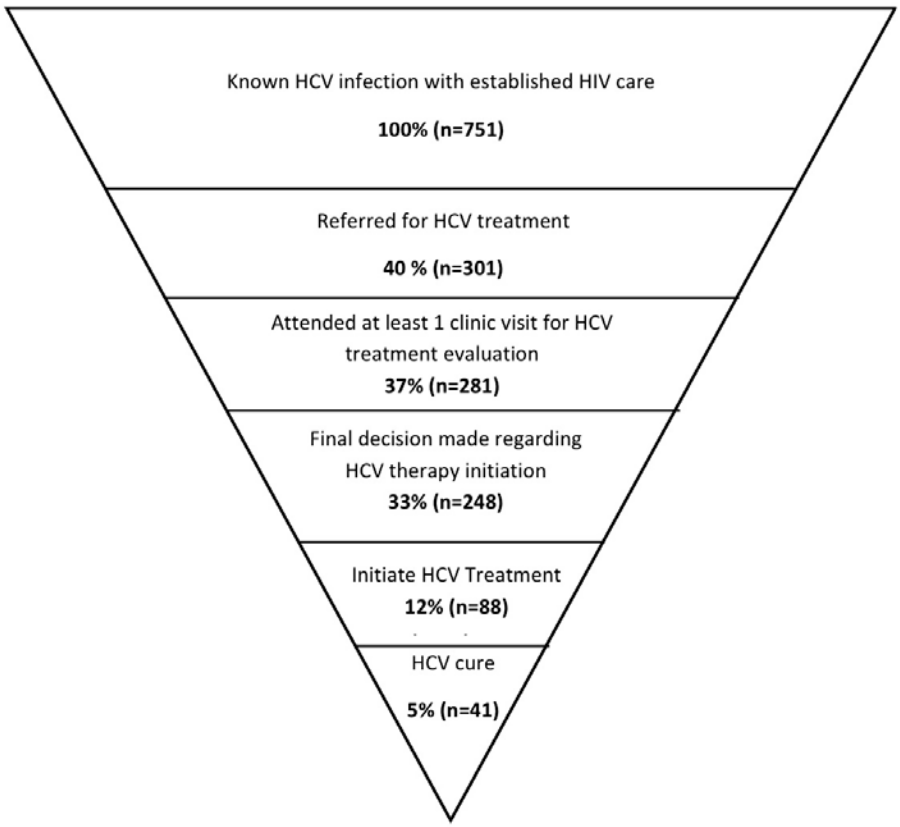
Background: Guidelines recommend screening for hepatitis (HCV) in all HIV-infected individuals, but little is known about factors influencing HCV treatment referral and disposition following HCV diagnosis. We therefore conducted this study to investigate the HCV cascade of care for HIV patients with known HCV diagnosis and to identify reasons for not starting HCV therapy after completion of HCV treatment staging.

Methodology: Retrospective cohort analysis of HIV-infected patients under care at UCSD Owen Clinic between 2008_2012. HCV-infected patients (HCV+ antibody and/or detectable HCV viral load) were categorized based on HCV treatment referral status. Bivariate analyses were conducted to investigate factors associated with lack of referral for HCV therapy. Definitions of barriers to care included: ongoing alcohol and/or drug use, uncompensated neuropsychiatry disease, uncontrolled AIDS and/or lost to follow-up attributed to alcohol or drug use.

Results: The cohort included 751 HIV/HCV+ infected patients: 84% male, 33% non-white, 20% Hispanics, 63% HIV viral load < 40 copies/ml. Median age (range) in years was 48 (19-75) and CD4+ count/mm^3 was 397 (5-1777). The main routes of HIV acquisition included 30% MSM, 20% MSM + IDU, 14% heterosexual + IDU, 10% heterosexual not IDU and 3% hemophiliacs. Of the 301 (40%) patients who were referred for HCV treatment, 281 attended at least 1 HCV clinic visit. In comparison to the HCV referred group, patients who were not referred for HCV therapy had a higher proportion of non-white patients (36 vs. 28%, p=0.019) and detectable (>40 copies/ml) HIV viral load (39 vs. 32%, p=0.047). There were no differences between HCV groups in gender distribution, median age or CD4+ count. A total of 88 patients initiated HCV therapy. Of those, 22 were treated with HCV triple therapy (pegylated interferon, ribavirin and telaprevir), and 41 patients were cured of HCV (figure 1). The main reasons for not starting HCV treatment after evaluation (n=193) were: ongoing barriers to care [78(40%)]; patient choice to wait for interferon-sparing regimens [43(22%)]; decompensated cirrhosis [33(17%)]; prior HCV treatment failure with low chances of eradication with available HCV therapies [16(8%)].

HCV Cascade of care in HIV-infected patients following HCV infection diagnosis

UCSD Owen clinic: 2008-2012



Conclusions: Most HIV-infected patients with known HCV infection are not referred for HCV therapy, with minorities being referred least. The most frequent reason for not initiating HCV therapy among those assessed is the presence of ongoing barriers to care.

Session P-N6 Poster Session
Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Acute HCV Infection: Pathogenesis

674 Assessing HCV Acquisition Routes in HIV-Infected MSM Using Single Genome Sequencing-A Pilot Study

Daniel S. Fierer[1], Andrew H. Talal[2], Kristen M. Marks[3], Wouter O. van Seggelen[1], Andrea D. Branch[4], Shirish Huprikar[1], Shuyi Wang[5], George M. Shaw[5], Hui Li[5]
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Background: The international epidemic of hepatitis C virus (HCV) infection is in its second decade among HIV-infected men who have sex with men (MSM) but little is known about mechanisms of transmission. Our prior case control study in New York City found unprotected receptive anal intercourse as the main risk factor for acquisition, but studies in England and Germany suggest that group sex or anal trauma are the main risk factors. We sought to understand whether significant disruption of the anorectum is required for HCV acquisition among HIV-infected MSM.

Methodology: We used single genome sequencing (SGS) to identify and enumerate transmitted HCV genomes to test the hypothesis that sexual transmission would be associated with few transmitted genomes, parenteral infection through injection would be associated with many, and bloody or

traumatic sex would be associated with an intermediate number of transmitted genomes. Detailed sex and drug histories and plasma were obtained during acute HCV infection in HIV-infected MSM.

Results: Eight men with acute HCV underwent SGS of their plasma virus RNA from the earliest available visits. All had precise and unambiguous identification and enumeration of transmitted HCV genomes. Six of 8 men were productively infected by single HCV genomes; none had rectal bleeding associated with sex nor were they exposed to blood of others; one had injected methamphetamine but without sharing injection equipment, and then had sex. Two men were infected by >10 genomes; one had shared injection equipment and then had sex, and the other denied any injection, rectal trauma, or bleeding with sex. None had an intermediate number of infecting genomes.

Conclusions: Most HCV infections of HIV-infected men were caused by a single transmitted virus, suggesting that HCV infection of MSM is due to a limited exposure to infecting virus across a relatively intact mucosal barrier. In contrast, the one man who had shared injection equipment was infected by a high number of viruses. These patterns of HCV infection parallel both sexual and parenteral acquisition of HIV, where most infections are caused by a single versus a higher number of transmitted HIV genomes, respectively. Larger prospective risk factor studies are needed using SGS to provide novel epidemiological insights to better characterize HCV acquisition in HIV-infected MSM.

675 Higher Risk of Sexually Acquired HCV Coinfection in MSM With Wide HIV Transmission Bottleneck

Roger D. Kouyos[1], Andri Rauch[2], Dominique Braun[1], Sabine Yerly[3], Jürg Böni[4], Thomas Klimkait[5], Vincent Aubert[6], Bruno Ledergerber[1], Hulrdrych Günthard[1], The Swiss HIV Cohort Study (SHCS)

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Background: Even though the mechanisms responsible for the recent dramatic increase of sexually transmitted HCV among HIV-infected MSM remain largely unknown, an important contribution by high-risk sexual behaviors has been suggested. At the same time such high-risk behaviors have been linked with a broad transmission bottleneck in HIV as they might lead to mucosal breaches, which could facilitate the transmission of several genetically distinct viruses in one transmission event.

Methodology: We assessed the association between the width of the HIV transmission bottleneck and the incidence of HCV coinfections in HIV-infected MSMs from the Swiss HIV Cohort Study. As a proxy for the width of the transmission bottleneck we used the fraction of ambiguous nucleotides in Genotypic Resistance Tests (GRT) from recently infected MSMs. We have previously shown that a high fraction (>0.5%) of ambiguous nucleotides during recent infection corresponded to a high viral diversity, which in turn indicated a broad transmission bottleneck. Accordingly, the HIV transmission bottleneck was considered to be broad if the fraction of ambiguous nucleotides exceeded 0.5% in GRTs from recent (less than one-year-old) infections and narrow otherwise. Recent infection was determined by Acute Retroviral Syndrome and by negative and positive HIV-serology less than 1 year apart. The impact of the HIV-transmission bottleneck on HCV incidence was quantified as Hazard Ratios (HR) determined from uni- and multivariable Cox-proportional hazards models.

Results: We considered 543 MSMs, who were HCV-negative at baseline and for which a GRT sampled during recent infection (<1 year post seroconversion or ARS) was available. Of those individuals, 119 (21.9%) exhibited a broad transmission bottleneck and 22 (4.1%) had an incident HCV infection. The total incidence rate of HCV infections was 7.6/1000 person-years. Individuals with a broad HIV-transmission bottleneck exhibited an over fourfold higher hazard of an incident HCV infection than individuals with a narrow HIV transmission bottleneck (HR[95%CI]=4.7[2.0,10.8] , p<0.001). This effect remained robust when adjusting for time (year of enrolment), geography (lab performing the GRT), and age: In the corresponding multivariable model the hazard of an HCV coinfection was increased by an HR of 4.8[2.0,11.4] if the HIV-transmission bottleneck was broad.

Conclusions: Our results indicate that the currently occurring sexual spread of HCV is focused on those MSMs that are also prone to exhibit a broad transmission bottleneck at HIV transmission. This suggests that high-risk behavior and mucosal barrier impairment may play an important role in the sexual transmission of HCV.

676 Seminal HCV RNA Level May Mirror Dynamics of Plasma HCV RNA in HIV-Positive Men With Acute HCV

Daniel Bradshaw[1], Francois Lamoury[1], Beth Catlett[2], Tanya L. Applegate[1], John Mcallister[2], Gregory J. Dore[1], Gail Matthews[1], Mark Danta[3]

[1]Kirby Institute, University of New South Wales, Sydney, Australia, [2]St Vincent's Hospital, Sydney, Australia, [3]Faculty of Medicine, University of New South Wales, Sydney, Australia

Background: We hypothesise that sexual transmission of HCV in HIV-positive men who have sex with men may be due to raised semen HCV RNA in acute or recent HCV (AHCV) infection.

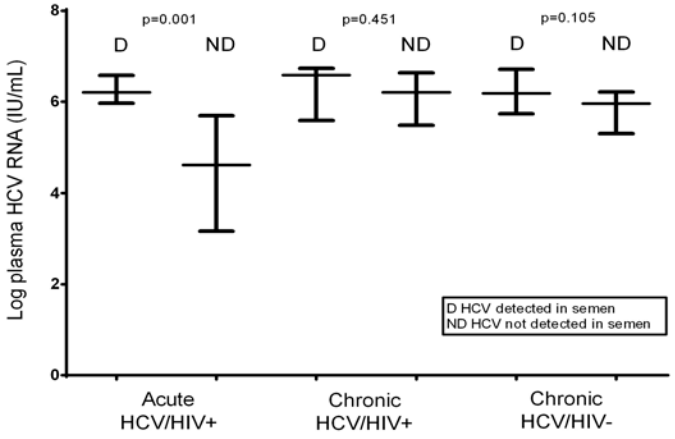
Methodology: The M2000 RT-PCR was optimised for quantification of HCV RNA in semen with lower limit of detection of 60 IU/mL. Men with AHCV (duration ≤12 months) or chronic HCV (CHCV, >12 months) not on anti-HCV therapy were prospectively recruited. An STI screen was performed. Paired semen and EDTA plasma samples were assayed for HCV RNA. Data were analysed with Chi^2, Fishers Exact, Mann-Whitney U and Kruskal-Wallis tests.

Results: Of 66 HCV RNA-positive men, median age 49, IQR 44-53 years, 18 (27.3%) were infected with AHCV/HIV, 22 (33.3%) CHCV/HIV and 26 (39.4%) CHCV. In men with AHCV, median duration of infection was 3.5, IQR 2.0-6.3 months. Of 40 HIV-positive men, 35 (87.5%) were on antiretrovirals with undetectable plasma HIV RNA; median CD4 count was 598, IQR 410-788 cells/mm^3. HCV genotypes were 1a (38, 57.6%), 1b (5, 7.6%), 3a (18, 27.2%), other (5, 7.6%). Semen HCV RNA was detected in 29/66 (43.9%) men at baseline. There was a similar proportion of men with detectable semen HCV comparing AHCV with CHCV (p=0.613), or HIV-positive with -negative (p=0.191). Median plasma HCV RNA was 6.1, IQR 5.5-6.5 log IU/mL and not significantly different comparing AHCV/HIV, CHCV/HIV and CHCV (p=0.055). When detected, median semen HCV RNA was 2.1, IQR 1.8-2.6 log IU/mL. HCV RNA levels in semen and plasma were correlated (r^2=0.142). Median plasma HCV RNA was higher in men with detected versus undetected

semen HCV RNA for AHCV/HIV (6.2, IQR 6.0-6.7 versus 4.6, IQR 3.2-5.7 log IU/mL p=0.001) but not for CHCV/HIV or CHCV (Fig. 1). Of 35 men attending a follow up visit (at median 18, IQR 15-26 weeks), semen HCV RNA was detected for 26 (74.3%) in ≥ 1 sample, including for 12 (34.3%) in both. Median plasma HCV RNA was higher in men with 2 samples positive (p=0.009). Presence of STI was not significant for shedding (p=0.271).

Conclusions: Semen HCV RNA was detected in 43.9% of men at baseline, at median 4.0 log IU/mL less than plasma. In 40.0% of men followed up, shedding was intermittent. For men with AHCV/HIV, detectable semen HCV RNA was more likely with higher plasma HCV RNA, implying a possible relationship between HCV dynamics in plasma and semen in the acute phase. If, as previously described, HIV-coinfected individuals in early acute HCV have a higher plasma HCV RNA, this could lead to raised semen levels, facilitating sexual transmission.

Figure 1. Detection of HCV RNA in semen according to log plasma HCV RNA (error bars indicate median and IQR)



677 HCV Viral Load Kinetics During Acute Hepatitis C in HIV-Infected Patients: A Model-Based Analysis

Romain Ragonnet[1], Christoph Boesecke[2], Marguerite Guiguet[3], Karine Lacombe[4,5], Jeremie Guedj[1], Jürgen K. Rockstroh[2], **Yazdan Yazdanpanah[1,6]**, Sylvie Deuffic-Burban[1,7]
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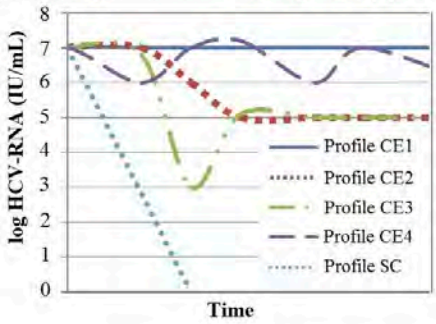
Background: The timing of treatment initiation in case of acute hepatitis C (AHC) occurrence is unclear. Indeed, patients may have spontaneous clearance (SC) but time at which SC may occur is imprecise since infection can rarely be dated. Besides, no study explored the relationship between viral kinetics and chance to achieve SC. Objectives of this study are first to model HCV viral load kinetic during the acute phase of hepatitis C in HIV-infected patients in the absence of HCV treatment; and second to use this model to determine frequency of SC occurrence over time, in order to help physicians in treatment decision making.

a) Distributions and estimated parameters of HCV RNA kinetic

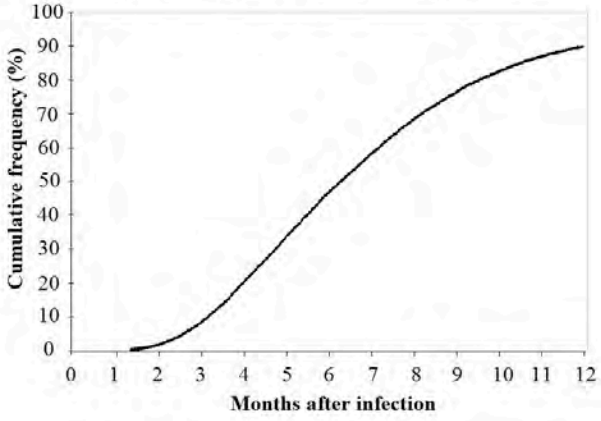
Phase	Parameters	Distribution *
Ramp-up	Doubling time of HCV RNA (in hours)	Uniform on [8-10]
	Maximal viral load in log (IU/mL)	Normal (mean=6.37, sd=0.75)
Plateau	Duration in days	
	Early drop (12%)	Uniform on [0-90]
	Delayed drop (76%)	Weibull (shape=1.71, scale=128.97)
Drop		
CE2	Loss rate in log (IU/mL) /day	Uniform on [0.01-0.05]
	Final level in log (IU/mL)	Uniform on [2.75-5.5]
CE3	Loss rate in log (IU/mL) /day	Uniform on [0.015-0.055]
	Lowest level in log (IU/mL)	Uniform on [2.5-4.2]
	Rise rate in log (IU/mL) /day	Weibull (shape=0.85, scale=0.04)
	Final level in log (IU/mL)	Normal (mean=5.72, sd=1.05)
CE4	Amplitude of fluctuations in log (IU/mL)	Uniform on [0.4-1.6]
	Half-period in days	Uniform on [75-150]
SC	Loss rate in log (IU/mL) /day	Weibull (shape=1.64, scale=0.12)

* when applicable, range is given in brackets; otherwise estimated parameters to specify the distribution

b) Different profiles identified during the drop phase



c) Cumulative frequency of SC over time among spontaneous clearers



Methodology: Based on available medical literature, we considered four phases for HCV RNA kinetic during AHC: ramp-up, plateau, drop and stabilization; the two last phases being different according to whether the patient is a spontaneous clearer (SC) or a chronic evolver (CE). We first characterized each phase using individual HCV RNA data from 261 HIV-HCV co-infected patients in acute phase of HCV where 33% of untreated patients were SC, and using data available in the literature. For each phase, random distributions were determined and Kolmogorov-Smirnov and Shapiro-Wilk tests were used to provide reliability. Second, we simulated the trajectory of 50,000 virtual patients to obtain cumulative frequency of SC over time. Time of SC occurrence is defined as first undetectable HCV RNA.

Results: Data were fitted according to distributions and estimated parameters reported in the table (Figure a). For the drop phase, we identified five different profiles: four for CE (CE1 to CE4) and one for SC (Figure b). The model estimated a median time from infection to SC occurrence of 187 days (IQ 130-263); no SC was observed before 35 days and 10% occurred after one year (Figure c).

Conclusions: This model brings knowledge about time of SC occurrence. It also highlights the diversity of HCV viral loads evolution profiles after infection in HIV-infected individuals. These predictions could help optimize the timing of treatment initiation during acute hepatitis C.

Session P-N7 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

HCV Infection and Cellular and Humoral Immune Responses

678 Impaired CD8+ T Cell IL-7 Activity in HCV Infection: Implications for HIV-HCV Co-Infection

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Background: Effective immune responses against hepatitis C virus (HCV) are dependent on CD8+ T cells, yet their function is impaired in chronic infection, which is also a feature of chronic HIV infection. HCV is the most prevalent co-morbidity in HIV, yet the effect of HCV on HIV infection remains largely unknown. This study will determine how CD8+ T cell activity (specifically IL-7 activity) is impaired in chronic HCV infection. IL-7 is critical for CD8+ T cell development, and important for T cell homeostasis, memory cell generation, and cytolytic function. CD8+ T cell responses to IL-7 are dependent on the expression of IL-7 receptor alpha on the cell membrane (mCD127). Reduced mCD127 expression, increased plasma soluble CD127 (sCD127) levels, or cellular deficiencies in IL-7 signalling may contribute to impairment, as we reported in HIV infection. The hypothesis of this study is that HCV infection decreases CD8+ T cell activity, specifically IL-7 responsiveness, in both HCV and HIV-HCV infection.

Methodology: CD8+ T cells were isolated from healthy donors (controls) as well as individuals with untreated HCV infection and HAART-controlled (< 40 copies/ml HIV RNA) HIV-HCV co-infection. Expression of mCD127 on CD8+ T cells and plasma sCD127 levels were measured by flow cytometry and immunobead assays, respectively. IL-7-induced signalling (STAT5 phosphorylation), proliferation, and production of the anti-apoptotic molecule Bcl-2 were measured by flow cytometry. Dose responses were assessed by regression analysis ($P < 0.05$).

Results: There was no significant difference in mCD127 expression on blood-derived bulk CD8+ T cells or plasma sCD127 levels between control, HCV and HIV-HCV infection. IL-7-induced STAT5 phosphorylation was significantly reduced ($p = 0.005$) in CD8+ T cells from HCV infection compared to controls, and similar to HIV-HCV co-infected individuals. Cell division of CD8+ T cells cultured with suboptimal amounts of T cell stimulator (PHA) was of lower magnitude in HCV infection than controls. Lastly, the production of Bcl-2 in response to IL-7 was significantly reduced in CD8+ T cells of HCV and HIV-HCV infected individuals compared to controls ($p<0.001$ and 0.04, respectively).

Conclusions: These results suggest that CD8+ T cell impairment in HCV infection is characterized by decreased responsiveness to IL-7, independent of mCD127 expression, in contrast to what is observed in HIV infection. The mechanism of CD8+ T cell impairment may be through IL-7-stimulated signalling, since we know Bcl-2 production is STAT5 dependent. Identifying the mechanisms of CD8+ T cell impairment in HCV infection has implications in the design of novel treatments, namely cytokine directed immunotherapies, to help reduce the burden of HCV effects on HIV infection.

679 HCV and GBV-C NS5A Proteins Inhibit TCR-Mediated Activation of Human CD4+ T Cells

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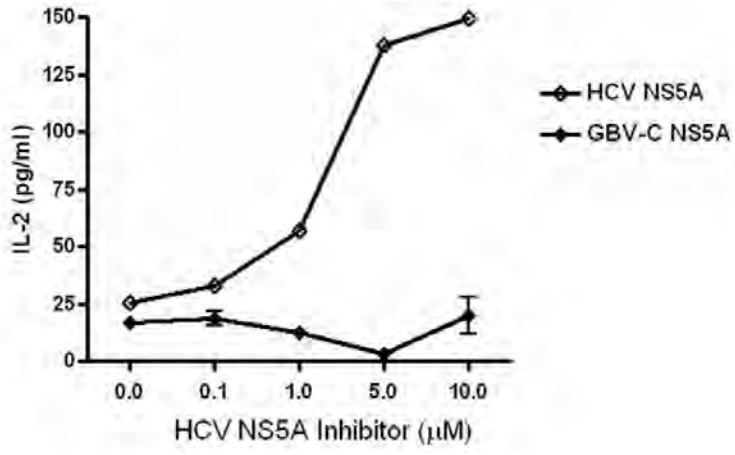
Background: Hepatitis C virus (HCV) and GB virus C (GBV-C) are closely related members of the family *Flaviviridae*, and both viruses are capable of establishing persistent infection. In clinical studies, HCV and GBV-C infections are characterized by reduced immune activation, delayed antibody response and altered T cell function. Although T cells are not the primary site of HCV replication, numerous studies demonstrate the presence HCV RNA in T cells and there is some evidence of viral replication in these cells. Previously, we demonstrated that the GBV-C envelope protein E2 inhibits T cell receptor (TCR) signaling and contributes to reduced immune activation by competing for activation of the lymphocyte-specific protein tyrosine kinase (Lck). Here, we studied the effects of HCV and GBV-C NS5A protein on T cell activation.

Methodology: Previously described Jurkat cell lines stably expressing HCV and GBV-C NS5A protein were studied. TCR signaling was monitored by measuring IL-2 release (ELISA) and CD69 expression by flow cytometry after stimulation with anti-CD3/CD28 or PMA-ionomycin. The effect of MSD HCV NS5A inhibitor on the NS5A-mediated modulation was examined.

Results: T cell activation was inhibited in Jurkat cells expressing either HCV or GBV-C NS5A protein following TCR stimulation with anti-CD3/soluble CD28 when compared to controls ($p<0.01$ for both IL-2 release and CD69 upregulation). Maintenance of cells in the presence of a potent NS5A inhibitor (provided by Merck) rescued HCV NS5A-mediated TCR inhibition, but not GBV-C NS5A-mediated TCR inhibition following TCR stimulation ($IC_{50} \simeq 2.5\mu M$; See Figure). NS5A proteins inhibited TCR-signaling upstream of NFAT and PKC activation, as PMA-ionomycin-mediated activation was not inhibited by HCV or GBV-C NS5A.



Conclusions: TCR signaling pathways are modulated by HCV and GBV-C NS5A protein expression in vitro. The HCV NS5A inhibitor blocked the TCR signaling defect induced by NS5A for HCV, but not GBV-C, thus this molecule appears specific for the HCV-NS5A protein, despite considerable amino acid sequence and predicted structural homology with GBV-C NS5A. Studies are underway to characterize the mechanism(s) by which HCV and GBV-C NS5A reduces TCR signaling. Since TCR activation is required for T cell proliferation and function during viral infection; these data may provide insight into HCV and GBV-C pathogenesis and persistence.

680 Impact of HCV Coinfection On T-Cell Dynamics in Long-Term HIV Suppressors Under cART

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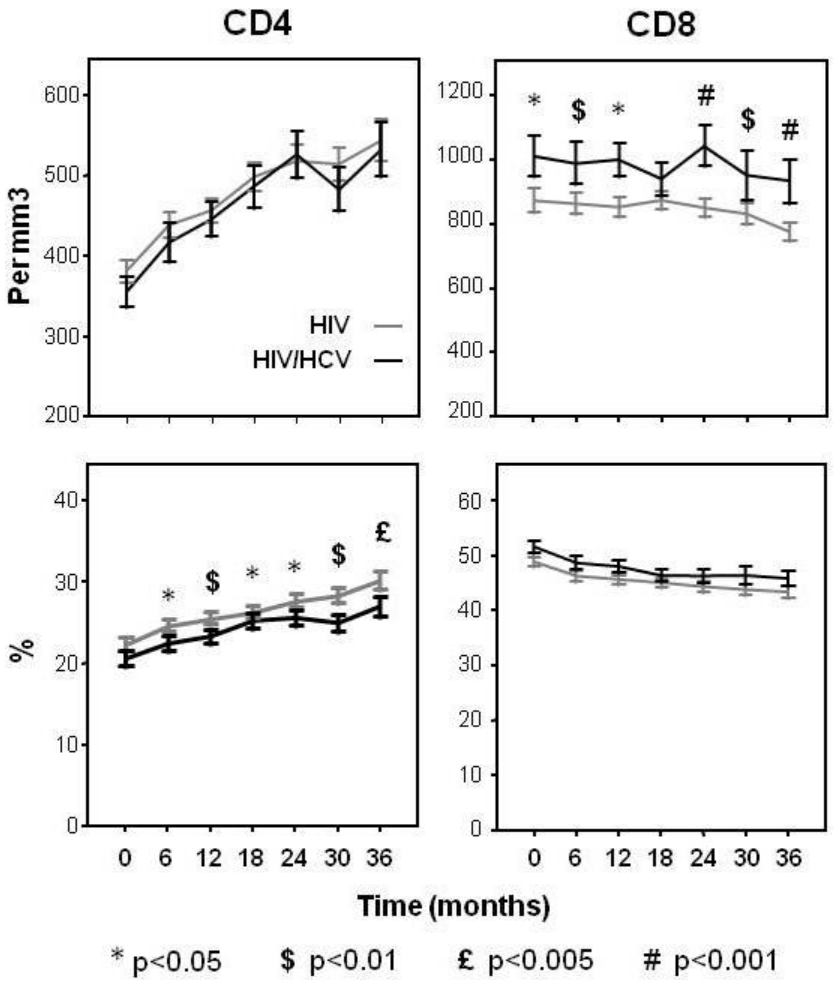
Background: HCV co-infection affects a fifth of HIV-infected subjects in the western world. The benefit provided by the cART revolution in HIV care is challenged by the eventual drawbacks inherent to the hepatitis C pathology. The full extent of HCV impact on the evolution of T cell compartments in patients that achieve long term HIV-suppression under cART is yet to be determined.

Methodology: A prospective study performed in an out-door HIV care unit following 1495 HIV-infected patients. Data of patients that achieved undetectable HIV load for at least 3 years were collected retrospectively from the Nadis® electronic database from January 1997 to April 2005. This period was defined in order to select patients that were naives of IFN-based hepatitis treatment. T cell counts were assessed from the first undetectable HIV load and every 6 months during the study period.

Results: Screening yielded data of 356 long term HIV suppressors, of which 130 were HCV co-infected. Most patients were male with median age of 36y for HCV coinfected vs 39 y ($p=0.001$). Median follow-up for HIV was longer in HCV coinfected (10y vs 4 y, $p<0.001$). cART regimens were no different between the two groups. As shown in the figure, HIV-infected (group 1) and HCV co-infected patients (group 2) displayed similar positive patterns of reconstitution of CD4 counts, though the mean fraction of CD4 cells was slightly higher in group 1 (30.3±1.1 vs. 27±1.1% after 3 yrs in groups 1 and 2, respectively, $p<0.001$). Regarding CD8 cells, HIV suppression led to a modest drop of median CD8 counts in group 1 ($p=0.027$), but not in group 2. More strikingly, group 2 displayed higher mean CD8 counts compared to group 1 (mean diff. = 135.71 ± 26.89 CD8/mm3, $p<0.001$).



Conclusions: In spite of long lasting successful HIV suppression under cART, HCV co-infection appeared to be detrimental to immune restoration. Outstandingly, the CD8 compartment is amplified in HCV co-infected patients, and this CD8 hyperlymphocytosis is refractory to otherwise successful HIV treatment. Further studies will determine the nature (activated, memory, exhausted) of CD8 cells amplified during HCV co-infection as well as the impact of PEG-IFN/RBV and new generation antiviral agents against HCV on the CD8 pool. The knowledge of CD8 cells behavior upon hepatitis treatment will contribute to determine the interest of early HCV-targeted therapy in HIV/HCV co-infected patients.

681 CD3+CD56+ Natural Killer-Like T Cells in HIV(+) Patients With Acute Hepatitis C

Pavlos Kokordelis[1,2], Benjamin Krämer[1,2], Christoph Boesecke[1,2], Esther Voigt[3], Patrick Ingiliz[4], Andreas Glässner[1,2], Ulrich Spengler[1,2], Jürgen K. Rockstroh[1,2], Jacob Nattermann[1]

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Background: In Western Europe and the US approximately 30% of HIV (+) patients are co-infected with the hepatitis C virus (HCV), which has become a major cause of morbidity and mortality in HIV(+) patients.

We recently showed that natural killer cells are able to recognize HCV-containing target cells via the NK cell receptors NKG2D- and NKp46 and to effectively block HCV replication in vitro. Moreover, we presented first data suggesting NK cells to critically affect outcome of acute hepatitis C in HIV(+) patients.

CD3+CD56+ natural killer-like T cells represent a subset of T lymphocytes that also express natural killer cell receptors.

Here, we studied phenotype and function of CD3+CD56+ natural killer-like T cells in HIV(+) patients with acute hepatitis C.

Methodology: 36 HIV(+) patients with acute hepatitis C, including 13 patients with spontaneous clearance and 23 patients that subsequently developed chronic hepatitis C, were studied. As a control HIV mono-infected patients (n=8), HIV(+) patients with chronic hepatitis C (n=12), HIV(-) patients with chronic HCV infection (n=8) as well as 12 healthy individuals were analyzed. 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 HuH7A2 HCV replicon system.

Results: Frequency of CD3+CD56+ NK-like T cells did not differ significantly between the study groups.

However, we observed a significant higher expression of the maturation markers CD27, CD127, and CD161 on CD3+CD56+ NK-like T cells in healthy controls than in HIV mono-infected patients and HIV patients with an acute HCV infection, respectively.

Interestingly, CD3+CD56+ NK-like T cells from HIV patients with acute hepatitis C displayed a higher expression of CD69, indicating a more activated status as compared to healthy controls. Of note, a high CD69 expression was associated with spontaneous clearance of acute hepatitis C, suggesting a role for CD3+CD56+ NK-like T cells in anti-HCV immune responses.

Accordingly, we found IL12/IL15-activated CD3+CD56+ NK-like T cells to effectively block HCV replication in an IFN-γ dependent fashion. However, CD3+CD56+ NK-like T cells from HIV patients with acute HCV infection displayed a significantly impaired capacity to secrete IFN-γ compared to both HIV mono-infected as well as healthy individuals.

Conclusions: Our results indicate that CD3+CD56+ NK-like T cells have the potential to block HCV replication but are functionally impaired in HIV(+) patients with acute hepatitis C.

682 The Effect of Hepatitis C (HCV) Clearance On Macrophage Activation in HIV/HCV Coinfection

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Background: Macrophage activation may contribute to accelerated atherosclerosis in HIV-infected persons. We hypothesized that HCV coinfection increases macrophage activation and cardiovascular disease (CVD) risk, and that successful HCV treatment in coinfected persons reduces CVD risk through reduction in macrophage activation.

Methodology: Of 54 coinfected subjects who received up to 72 weeks of pegylated interferon/ribavirin (PEG/RBV), 27 with and 27 without sustained virologic response (SVR, HCV RNA<60 IU/mL 24 weeks after end of treatment [EOT]) matched by race/ethnicity and sex, stored plasma before treatment and 24 weeks after EOT were tested for soluble CD14 (sCD14) and CD163 (sCD163). Baseline characteristics and biomarkers were compared between SVRs and non-SVRs by Fisher's exact and Wilcoxon tests and associations between biomarkers and baseline variables by simple regression. Changes in each biomarker were examined within and between groups by t-test and regression models adjusting for race/ethnicity, sex, and with backward selection of baseline variables significant at 0.10 level (HCV RNA, fibrosis stage, HCV treatment history, AST and ALT level) (Model 1), and further controlling for change in ALT (Model 2) and PEG/RBV duration (Model 3).

Results: Of 54 subjects, 30 white, 24 black, and 44 male, 78% had HIV-1 RNA<50 copies/mL. Median [Q1, Q3] CD4 was 544 [370, 734] cells/μL. 3 SVR and 4 non-SVR subjects had baseline CVD; none had a CVD event on study. The Table describes baseline and change in markers. Baseline sCD163 was associated with fibrosis stage (P<0.001) and baseline ALT (P<0.001). Controlling for fibrosis, there was no difference in baseline sCD163 by SVR status (P=0.094). In Model 1 adjusting for race/ethnicity, sex and baseline AST after backward selection, SVR was associated with decrease in log10 sCD163 (p=0.042), but not after further adjusting for change in ALT (Model 2, P=0.096, change in ALT P=0.002) or PEG/RBV duration (Model 3, P=0.071, PEG/RBV P=0.052).

Conclusions: SVR was associated with decrease in plasma sCD163 but not sCD14 levels. Adjustment for change in ALT attenuated the association between SVR and sCD163, suggesting hepatic inflammation may mediate this association. HCV treatment may reduce hepatically-driven macrophage activation, with greater sensitivity of sCD163 as compared to sCD14 to hepatic inflammation. Degree of liver disease must be considered in the interpretation of macrophage activation markers in HIV-infected persons.

Marker	SVR Median [Q1, Q3]	P*	Non-SVR Median [Q1, Q3]	P*	P**
Baseline sCD163 (ng/mL)	2056 [1172, 3006]	-	2933 [2094, 4129]	-	0.013
Change in log10 sCD163	-0.13 [-0.25, 0.05]	0.009	-0.06 [-0.10, 0.01]	0.20	0.162
Baseline sCD14 (ng/mL)	2032 [1622, 2484]	-	1866 [1724, 2591]	-	0.950
Change in sCD14 (ng/mL)	56 [-255, 244]	1.0	110 [-146, 329]	0.50	0.642

Table. Baseline and change in macrophage activation markers by SVR status. Unadjusted P-values: *within group; **between group

683 HIV Patients Develop High Levels of Broadly Neutralizing Antibodies Against Hepatitis C Virus

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Background: Hepatitis C virus (HCV) infection is a major health issue for HIV-infected patients. The high cost of new direct-acting antivirals against HCV limit their use in countries with poor income, underscoring the urgent medical need of an HCV vaccine. The impact of HIV infection on the HCV-humoral response remains unknown although it might greatly influence the design and the effectiveness of an HCV vaccine in HIV-infected patients. The aim of this study is to analyze the HCV-specific neutralizing response in HIV-infected patients.

Methodology: HCV-specific neutralizing antibody-mediated response was assessed in a cohort of 299 patients including 136 HIV-/HCV+, 70 HIV+/HCV-, and 63 HIV+/HCV+. Thirty healthy HCV-unexposed controls were used to define neutralization assay cutoff. Neutralization experiments were performed with patients' sera and purified immunoglobulins G (IgG) using HCV pseudoparticles (HCVpp) and cell-culture derived HCV (HCVcc) model systems.

Results: Mean age of HIV-/HCV+ and HIV+ patients was 49 and 43 years, respectively. Sixty-five (49%) HIV+ patients have detectable HIV RNA in plasma with a mean viral load at 3.96 (1.72- 5.83) log10 copies/mL. Mean CD4+ cell count in all HIV+ patients were 490 (41-1770) cell/mm3. HCV RNA was detectable in 70% of HIV-/HCV+ and 57% of HIV+/HCV+ patients, with a mean HCV RNA load at 5.96 (4.38-7.15) and 5.83 (1.51-7.24) log10 copies/mL, respectively ($p=0.59$). High levels of neutralizing antibodies (nAbs) were detected in 97% of HCV-viremic HIV+/HCV+, among them 69% harbored nAbs against the three HCVpp genotypes 1a, 1b, and 3a, similarly to HCV-viremic HIV-/HCV+ patients (95% and 65%, respectively, $p>0.05$). In HCV-aviremic patients, high levels of nAbs were more frequently noticed in HIV+/HCV+ (85% against at least one genotype and 15% against the three genotypes) than in HIV-/HCV+ individuals (44% and 7%, respectively), ($p<0.001$). Moreover, broadly nAbs anti-HCV were detected in 13% of HIV+/HCV- individuals. All the data were confirmed using HCVcc model system. No correlation was observed between nAbs and HIV RNA load or CD4+ cell count.

Conclusions: Our results indicate that HIV-infected patients are able to develop high levels of HCV-specific broadly nAbs. Persistence of nAbs in HCV-aviremic HIV+/HCV+, and the detection of neutralizing activity in HIV+/HCV- patients suggest that they may have experienced frequent exposure to HCV as observed in HIV-negative individuals (e.g injection drug users) with the immune capacity to clear HCV. These data suggest that HCV-humoral response is not impaired during HIV-infection. The persistence of a broad HCV-neutralizing response in HIV+ patients may forecast promising achievement of HCV vaccination in HIV-infected persons.

684 Activation and Senescence Markers in HCV-Infected Patients On PegIFN/RBV/Telaprevir Tritherapy

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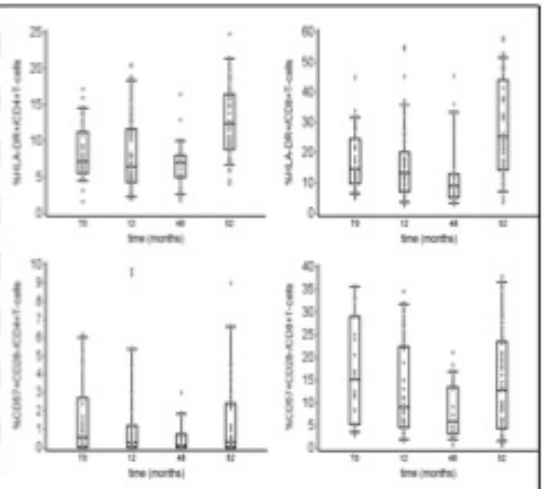
Background: Immune activation and senescence described in chronic viral infections is associated with an increase in morbidity and mortality. No data were reported in HCV-infected patients (pts). We describe the immunological markers of activation, senescence and exhaustion in pts initiating PegIFN/RBV/Telaprevir tritherapy.

Methodology: Pts with a prior PegIFN/RBV failure who initiated tritherapy (D0) and obtained SVR24 were included. CD4 and CD8 activation (DR+), maturation (naive, memory T cells), senescence (CD57+CD28-), regulatory T cells, and PD1+T cells were measured at D0, W12, W48 and W52-72. Kinetics was described during the 3 periods: D0-W12 tritherapy; W12-W48 bitherapy; W48-W72 off treatment. D0 data were compared with 20 healthy donors (HD).

Results: 83 pts were included: 66% males, median age=57 years, infection duration=30 years, HCVRNA=1643000 IU/mL, fibroscan =10 kPa (36% F4). There is no significant difference for CD4+ and CD8+ senescence or maturation between pts at D0 and HD. CD4+ and CD8+ activation was higher in patients (p=10-3 and 0.07) than in HD, although within the normal range. D0-W12 period: significant decrease in senescent (P =10-4) and memory cells (P=10-2 to 10-4) without variation in activated CD4+ and CD8+; increase in Treg (P=10-3) without variation in % PD-1+CD4+ or CD8+. W12-W48 period: No variation occurred. W48-W72 period: increase in memory (P<10-4 to P<10-2), senescent (P=10-2) and activated (P<10-4) CD4+ and CD8+, while naive T cells decreased (P<10-4).

Conclusions: Chronic HCV replication for more than 30 years is associated neither with a CD8+ clonal expansion, nor with lymphocyte activation or senescent status in the peripheral blood. No association was found between activation and fibrosis. We speculated that the immunological variables kinetics on successful IFN-based therapy may be due to variations in lymphocytes homing: decrease in memory and senescent lymphocyte subsets on suppressive tritherapy, increase in memory, senescent and activated lymphocytes after the end of IFN exposure without detectable HCV. The intrahepatic immune response does exist and may be under the regulation of lymphocytes and Treg homeostasis. It seems relevant to follow the persistence of this activated status at the end of IFN exposure and to evaluate its clinical impact, notably in terms of fibrosis evolution and comorbidities. This observed immune paradox may be of interest for the deciphering of new (IFN-free) therapeutic strategies.

Variables, median (IQR)	D0 (n=35)*		W12 (n=43)		W48 (n=21)		W52-72 (n=48)	
CD4 /µl	733	(540 ; 976)	310	(182 ; 460)	378	(299 ; 419)	466	(323 ; 625)
CD4 (%)	46,6	(41,7 ; 52,8)	54,8	(44,8 ; 62,7)	47,1	(40,1 ; 59,5)	44,2	(38,7 ; 51,7)
TN amongCD4+, %	36	(16,8 ; 48)	42,2	(25 ; 54)	39	(28,4 ; 51,3)	35,2	(19,2 ; 45,1)
TEMRA among CD4+, %	0,8	(0,2 ; 2,2)	0,3	(0,1 ; 0,9)	0,4	(0,2 ; 1,8)	0,5	(0,2 ; 1,4)
HLA-DR+ among CD4+, %	7,2	(5,5 ; 11,2)	6,4	(4,3 ; 11,6)	7	(5 ; 8)	12,4	(8,8 ; 16,5)
CD57+CD28- among CD4+, %	0,6	(0 ; 2,7)	0,3	(0 ; 1,2)	0,1	(0 ; 0,7)	0,3	(0 ; 2,4)
PD-1+ among CD4+, %	23.7	(21.2 ; 28.9)	25.3	(21.3 ; 30.4)	26.4	(18.9 ; 36.2)	24.9	(21.5 ; 32.2)
CD8 /µl	320	(249 ; 544)	104	(65 ; 175)	110	(69 ; 151)	200	(110 ; 311)
CD8 (%)	20,4	(17,4 ; 27,6)	17,4	(14,1 ; 22)	15,8	(12,4 ; 19,4)	19,6	(15,2 ; 25,7)
TN among CD8+, %	46,4	(36,2 ; 63,1)	58,9	(44,7 ; 72)	69,1	(50,9 ; 78,2)	51,7	(37 ; 62,9)
TEMRA among CD8+, %	15,1	(6,5 ; 29,3)	7,5	(4,5 ; 19)	7,6	(4,7 ; 14)	10,1	(3,8 ; 26,4)
HLA-DR+ among CD8+, %	14,5	(9,8 ; 24,5)	13,3	(7,3 ; 20)	9	(5,3 ; 12,9)	25,3	(14,2 ; 44)
CD57+CD28- among CD8+, %	15,1	(5,2 ; 29)	9,1	(4,6 ; 22,4)	5,9	(3,2 ; 13,5)	12,7	(4,3 ; 23,5)
PD-1+ among CD8+, %	25.1	(20.3 ; 30.4)	24.8	(20 ; 31.7)	24.8	(18.5 ; 29.4)	25.2	(18 ; 35)
CD4/CD8 ratio	2,1	(1,6 ; 3)	3,3	(2,3 ; 4,7)	3	(2,4 ; 3,9)	2,4	(1,8 ; 3,4)
Treg among CD3+, %	2,8	(2 ; 3,4)	3,8	(2,3 ; 4,9)	3,8	(2,6 ; 5,4)	3,9	(3,1 ; 5,8)



Description of immunological parameters during the 3 periods of treatment: W0-W12 on PegIFN/RBV/Telaprevir tritherapy. W12-W48 on PegIFN/RBV bitherapy and W48-W52/72 after stop of treatment at D0 (n=35) . W12 (n=43). W48 (n=21). and W52-72 (n=48).

Session P-N8 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

HCV-Related Outcomes: Cardiac and Non-Liver

685 HCV Viremia and the Risk of Acute Myocardial Infarction at Various Lipid Levels

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Background: Studies have shown an association between HCV infection and cardiovascular disease (CVD) events. The role of HCV viremia upon the risk of acute myocardial infarction (AMI) at varying lipid levels is unknown.

Methodology: We used Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES) to determine the risk of AMI at various lipid levels for HCV antibody positive persons with detectable and undetectable HCV RNA. All subjects were HCV treatment naïve. We excluded females (due to small numbers), smokers, and those with HIV, diabetes, prior cardiovascular disease, chronic kidney disease, chronic obstructive lung disease or hypertension at baseline. Lipid categories were based on National Cholesterol Education Program risk profile levels. Risk of AMI by lipid level was determined by Cox regression analyses.

Results: We compared 5,979 HCVRNA+ and 167 HCVRNA- subjects. After adjusting for age, race, body mass index and other lipids, the risk of AMI was progressively higher with higher total cholesterol, LDL-cholesterol and triglyceride levels among HCVRNA+ subjects, while the association among HCVRNA- subjects was not statistically significant at any level. (Table) At the highest levels within the lipid category, the risk of AMI increased between 22-64% compared with desirable levels.

Conclusions: In HCV viremic subjects, higher lipid levels were associated with higher risk of AMI. This association was not seen in non-viremic persons, possibly due to small sample size with few incident AMI events, The effect of lipid lowering therapy and viral eradication through HCV therapy upon the risk of future AMI needs further study.

Table. Hazard ratios of myocardial infarction by HCVRNA status at various lipid levels

	Category	HCVRNA+ (N=5,979)		HCV RNA – (N=167)	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Total cholesterol, mg/dL	<200: Ref	1.00(.,.)	-	1.00(.,.)	-
	200-239	1.02(0.91,1.14)	0.73	0.58(0.11,2.97)	0.51
	>240	1.22(1.06,1.40)	0.01	0.66(0.08,5.66)	0.70
LDL cholesterol, mg/dL	<100: Ref	1.00(.,.)	-	1.00(.,.)	-
	100-129	0.95(0.84,1.07)	0.40	5.85(0.67,51.48)	0.11
	130-159	1.01(0.89,1.16)	0.85	1.25(0.08,20.21)	0.87
	160-189	1.06(0.89,1.26)	0.52	4.12(0.25,67.30)	0.32
	>=190	1.64(1.30,2.07)	0.00	13.36(0.81,220.16)	0.07
HDL cholesterol, mg/dL	<40: Ref	1.00(.,.)	-	1.00(.,.)	-
	40-59	0.73(0.65,0.81)	0.00	0.29(0.06,1.43)	0.13
	>=60	0.63(0.53,0.74)	0.00	*	1.00
Triglycerides, mg/dL	<150: Ref	1.00(.,.)	-	1.00(.,.)	-
	150-199	1.25(1.09,1.43)	0.00	2.09(0.39,11.01)	0.39
	200-499	1.28(1.12,1.45)	0.00	0.92(0.17,5.03)	0.92
	>=500	1.43(0.96,2.13)	0.08	*	1.00

*Number too small for the cell

686 Association of Coinfection With HBV, HCV, or Both On Survival Among HIV-Infected Adults

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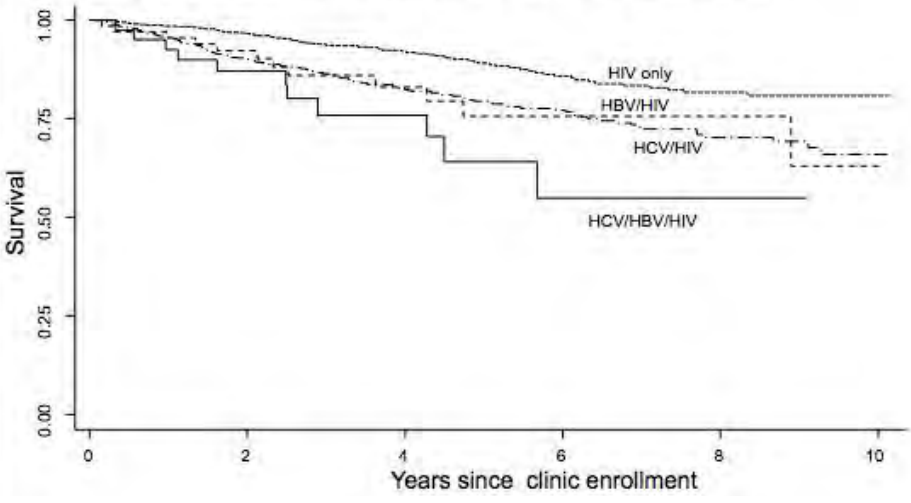
Background: HBV and/or HCV coinfection is associated with increased morbidity and, in some studies, with increased mortality in HIV-infected patients. The impact of antiretroviral therapy (ART) on this relationship is incompletely defined. We examined survival among adults who were infected with HIV alone or in conjunction with HBV, HCV, or both in the era of tenofovir containing ART.

Methodology: We used data from a prospective clinical cohort of 1603 patients with HIV and known HBV and HCV status receiving care at the Johns Hopkins HIV Clinic from January 2002 to March 2012. Chronic HBV infection was defined as a single HBsAg positive result. HCV infection was defined as HCV antibody positive or detectable HCV RNA. The primary outcome was all-cause mortality rates per 1000 person years according to infection status: HIV alone (n=844),HBV/HIV (n=67),HCV/HIV (n=652)and HCV/HBV/HIV (n=40). Multivariable negative binomial regression was performed.

Results: At enrollment, patients with HCV alone or with HBV were older (median age, 45 years vs. 40 years), had lower CD4 cell count (median 349/mm3 vs. 443/mm3), and were more likely to have a history of injection drug use (73% vs. 8%) than those with HIV alone. Patients with HBV alone were similar to those with HIV alone. Crude mortality rates (per 1000 person-years) were higher in patients with HBV/HIV (45.7, 95% CI 25.9-80.4), HCV/HIV (45.6, 95%

Figure 1. Cumulative Survival After Clinic Enrollment



CI 38.4-54.2) and HCV/HBV/HIV (78.9, 95% CI 43.7-142.5) compared to those with HIV monoinfection (22.2 ; 95% CI 17.8-27.8; Figure 1). Coinfection with HBV (adjusted incidence rate ratio [IRR] 1.85, 95% CI 0.93-3.69), HCV (IRR 1.87, 95% CI 1.22-2.86), and both HCV and HBV (IRR 3.21, 95% CI 1.41-7.31) significantly remained associated with elevated mortality after adjusting for age, race, sex, history of injection drug use, CD4 cell count, and use of ART at clinic enrollment.

Conclusions: In the ART era, patients coinfected with HCV and HBV continue to experience excess mortality compared to those with HIV alone even after considering HIV disease parameters and ART exposure. While this observation may be due to increased liver-related mortality as persons survive longer on ART, further research to elucidate the underlying reasons for this difference is needed.

687 Incidence Rates and Risk Factors for Severe Bacterial Infections in HIV/HCV-Coinfected Patients

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Background: HIV/HCV co-infection is placing an increasing burden on the health care system. Due to comorbidities and more rapid progression of liver disease associated with co-infection, infectious complications may contribute to excess morbidity. We measured the incidence and identified predictors of severe bacterial infections requiring health service use or leading to death among HIV/HCV co-infected patients.

Methodology: Data were analyzed from a Canadian multicentre prospective cohort of 1151 HIV/HCV co-infected patients with at least 2 consecutive visits between 2003-13. Every 6 months, patients self-reported reasons for walk-in clinic and emergency room visits and overnight hospitalizations. Causes of death were available from detailed case reports and linkage to vital statistics. The primary outcome was a first episode of severe bacterial infection (overall). We also examined specific subgroups: pneumonia, invasive bacterial infections [osteomyelitis, endocarditis, peritonitis, pyelonephritis, bacteremia, meningitis, septic arthritis] and skin and soft tissue (SST) infections. We used discrete-time proportional hazards models adjusted for age, sex, baseline BMI (as a marker for risk of insulin resistance) and hemoglobin and time-updated intravenous drug use (IDU), cigarette smoking, CD4 cell count, HIVRNA and APRI (≥1.5=significant fibrosis).

Results: At baseline, median age was 45 years, 26% were female, 16% Aboriginal, 35% active IDU, 76% smoked cigarettes and median BMI was 24. Median CD4 was 440 cells/μL and 81% were on cART. During 2063 person-years (PY) of follow-up, 113(13%) patients reported any severe bacterial infection [IR=5.5/100 PY; 95% CI, 4.5-6.5]. 61(7%) developed at least one episode of pneumonia [IR=2.9; 2.1-3.6], 26(3%) invasive infection [IR=1.2; 0.7-1.6], and 37(4%) SST infection [IR=1.7; 1.2-2.2]. Of 133 deaths, 13(10%) were attributable to infection. Factors associated with severe bacterial infections are shown in the table below. Inclusion of HCV therapy in the models had no effect on the results.

Conclusions: Severe bacterial infections represent common causes of death and health service use among HIV/HCV coinfected patients. Risk for these infections is driven primarily by low CD4 and IDU rather than stage of liver disease. Insulin resistance and anemia may also be contributory. Efforts to address comorbidities and improve ART uptake and adherence in this population are warranted to limit the burden of severe infections.

	Overall (N= 113/904)		Invasive infection (N= 26/916)		SST infection (N= 37/914)		Pneumonia (N= 61/908)	
Independent Variables	aHR	95% CI	aHR	95% CI	aHR	95% CI	aHR	95% CI
Female sex	0.85	(0.49, 1.48)	0.64	(0.22, 1.85)	1.39	(0.63, 3.05)	0.84	(0.38, 1.88)
Aboriginal ethnicity	1.39	(0.78, 2.48)	1.40	(0.47, 4.13)	2.12	(0.97, 4.62)	0.88	(0.33, 2.37)
Baseline								
Age (per 5 years)	1.11	(0.96, 1.28)	0.92	(0.68, 1.26)	1.05	(0.82, 1.35)	1.23	(1.03, 1.48)
BMI (per 5 kg/m^2)	1.01	(0.85, 1.20)	0.96	(0.55, 1.67)	1.19	(1.00, 1.40)	0.91	(0.69, 1.19)
Hemoglobin (per 10 g/L)	0.83	(0.73, 0.95)	0.78	(0.63, 0.96)	0.88	(0.71, 1.09)	0.85	(0.70, 1.03)
Time-updated								
IDU	1.06	(0.65, 1.73)	1.80	(0.76, 4.27)	2.53	(1.15, 5.54)	0.55	(0.26, 1.15)
Cigarette consumption	1.17	(0.69, 2.00)	1.44	(0.41, 5.07)	0.63	(0.27, 1.47)	1.49	(0.72, 3.06)
CD4 count (per 100 cells/μL)	0.87	(0.79, 0.96)	1.00	(0.89, 1.12)	0.92	(0.80, 1.05)	0.77	(0.65, 0.92)
HIVRNA (per log10 copies/mL)	1.15	(0.94, 1.40)	1.07	(0.67, 1.70)	0.91	(0.62, 1.33)	1.27	(0.99, 1.62)
APRI ≥1.5	0.78	(0.47, 1.30)	0.79	(0.29, 2.18)	1.45	(0.64, 3.28)	0.69	(0.35, 1.35)

Note: Sample size varies by outcome as risk set of 2 consecutive visits were necessary for the analysis.

688 Association of HIV and HCV Coinfection With Cardiovascular Disease Outcomes Among US Veterans

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Background: Human Immunodeficiency Virus and Hepatitis C (HIV/HCV) co-infection is associated with increased risk of acute myocardial infarction (AMI). However, associations with other cardiovascular disease (CVD) outcomes have not been adequately characterized. We aimed to determine the association of HIV/HCV co-infection with various CVD outcomes.

Methodology: We conducted a retrospective cohort study using the databases of Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES). HCV and HIV infections were ascertained using antibody testing at baseline. CVD data was obtained using ICD-9 codes as per our previously published work, and outcomes studied included: AMI, congestive heart failure (CHF), stroke, peripheral vascular disease (PVD) and venous thromboembolism (VTE). Multivariate Cox-regression models were used to determine the risk of CVD outcomes among veterans with HIV/HCV co-infection compared to those without HIV or HCV infection. Adjustment was made for traditional CVD risk factors.

Results: Among the HCV- Veterans, 2620 (1.3%) individuals had HIV infection, while among the HCV+ Veterans, 4896 (2.4%) had HIV infection. Veterans with HIV/HCV co-infection, compared to those without HIV or HCV infection were younger (mean age 50 vs 53 years), were more likely to be Blacks (59% vs 29%), and smokers (20% vs 17%). They were less likely to have diabetes (13% vs 16%), had lower body mass index (BMI, 25 vs 29 kg/m2), and low-density lipoprotein (LDL) cholesterol (91 vs 117 mg/dL) (p-value<0.0001, for all comparisons). The hazard ratios (95% confidence intervals) for MI, stroke, CHF, PVD and VTE for veterans with HIV/HCV co-infection compared to those without HIV or HCV infection, after adjustment for age, sex, smoking, diabetes, and BMI were 1.24 (1.01-1.51), 1.59 (1.25-2.03), 2.05 (1.69-2.48), 1.19 (0.99-1.44), and 2.35 (1.19-4.61), respectively. The corresponding HRs (95% CIs) after further adjustment for LDL-cholesterol, high-density lipoprotein cholesterol and triglycerides were 1.14 (0.94-1.40), 1.53 (1.20-1.95), 1.87 (1.55-2.26), 1.12 (0.93-1.35) and 2.46 (1.24-4.85), respectively.

Conclusions: In a retrospective cohort study of HCV+ and HCV- veterans, individuals with HIV/HCV co-infection had increased risk of stroke, CHF and VTE compared to those without HIV or HCV infection, after adjustment for traditional CVD risk factors.

Table: Risk ratios of cardiovascular diseases by HCV and HIV status in multivariable model

Outcome	Adjusted for	N total	N event	HIV- HCV+ vs. HCV-		HIV+ HCV- vs. HCV-		HIV+ HCV+ vs. HCV-	
				HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
MI	Model 1	274778	9392	0.95(0.91,0.99)	0.016	0.86(0.65,1.13)	0.279	1.02(0.84,1.25)	0.821
MI	Model 2	274778	9392	0.97(0.93,1.01)	0.095	1.06(0.80,1.41)	0.664	1.24(1.01,1.51)	0.036
MI	Model 3	274778	9392	0.98(0.94,1.03)	0.443	0.96(0.73,1.28)	0.799	1.14(0.94,1.40)	0.189
Stroke	Model 1	274785	4216	1.26(1.18,1.34)	<0.0001	0.87(0.55,1.38)	0.548	1.93(1.51,2.45)	<0.0001
Stroke	Model 2	274785	4216	1.20(1.13,1.27)	<0.0001	0.82(0.51,1.30)	0.389	1.59(1.25,2.03)	<0.0001
Stroke	Model 3	274785	4216	1.19(1.12,1.26)	<0.0001	0.79(0.50,1.26)	0.326	1.53(1.20,1.95)	0.001
CHF	Model 1	274784	8288	1.14(1.09,1.19)	<0.0001	1.05(0.77,1.43)	0.753	1.63(1.35,1.97)	<0.0001
CHF	Model 2	274784	8288	1.21(1.16,1.26)	<0.0001	1.41(1.03,1.92)	0.03	2.05(1.69,2.48)	<0.0001
CHF	Model 3	274784	8288	1.17(1.12,1.22)	<0.0001	1.35(0.99,1.83)	0.059	1.87(1.55,2.26)	<0.0001
PVD	Model 1	274778	11078	1.14(1.09,1.18)	<0.0001	0.95(0.72,1.25)	0.728	1.19(0.99,1.44)	0.068
PVD	Model 2	274778	11078	1.09(1.05,1.13)	<0.0001	1.05(0.80,1.39)	0.724	1.22(1.01,1.47)	0.042
PVD	Model 3	274778	11078	1.10(1.06,1.14)	<0.0001	0.96(0.73,1.27)	0.769	1.12(0.93,1.35)	0.235
VTE	Model 1	274786	391	0.91(0.74,1.12)	0.369	0.38(0.05,2.74)	0.34	2.05(1.05,4.01)	0.035
VTE	Model 2	274786	391	0.95(0.77,1.16)	0.614	0.44(0.06,3.17)	0.418	2.35(1.19,4.61)	0.013
VTE	Model 3	274786	391	0.95(0.77,1.17)	0.648	0.46(0.06,3.31)	0.443	2.46(1.24,4.85)	0.01

Model1 – age, sex
Model 2 – Model 1+ smoking history, diabetes history, body mass index
Model 3 – Model 2+ LDL-c, HDL-c, triglycerides
MI- myocardial infarction; CHF - congestive heart failure; PVD - peripheral vascular disease; VTE - venous thromboembolism

Note: individuals with CAD, PVD, stroke or VTE at baseline were excluded

689 Performance of the Framingham Risk Score in Hepatitis C-infected Persons

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Background: Hepatitis C (HCV) infection may confer increased risk for cardiovascular disease (CVD). The Framingham Risk Score (FRS) is commonly used to predict 10-year coronary heart disease (CHD) risk, but its performance in HCV-infected persons is not well known.

Methodology: We utilized the Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES), a national cohort of HCV-infected and age, sex, and race-matched uninfected subjects from 2001-2009. Male subjects ages 20-79 with calculable FRS for Hard CHD (calculated using age, sex, systolic blood pressure, antihypertensive treatment, smoking status, high-density lipoprotein and total cholesterol level) and without baseline CVD, diabetes, HIV and

chronic hepatitis B were included. Incident myocardial infarction (MI) rates were calculated and Cox regression used to determine the hazard ratio (HR) for MI by HCV status, adjusting for age and race. C-statistics were used to determine risk discrimination by the FRS, by HCV status and race/ethnicity.

Results: Of 316,514 eligible subjects, 232,816 had calculable FRS: 111,436 HCV-infected and 121,380 uninfected. The table summarizes baseline characteristics and FRS. Age, race/ethnicity, BMI, and baseline FRS (in 10-year CHD risk percent) were similar between HCV-infected and uninfected groups. HCV-infected subjects had higher rates of drug and alcohol abuse and lower LDL-cholesterol. Median (IQR) follow-up was 1437 (758-2059) days in the HCV group and 1547 (824-2159) days in the uninfected. Incident MI rate in the HCV and uninfected groups was 7.11 and 7.70 per 1,000 person years, respectively. Adjusted for age and race, the HR for incident MI in HCV vs uninfected persons was 0.92 (95% CI 0.87-0.96, p<0.001). C-statistics were 0.62 (HCV) and 0.61 (uninfected), and by racial/ethnic group, 0.61 (White), 0.61 (Black), and 0.62 (Hispanic).

Conclusions: There was no difference in FRS performance by HCV status. The FRS performed similarly poorly across HCV status and racial/ethnic groups in this Veteran Affairs cohort. Because we used incident MI as the CHD outcome measurement and hard CHD includes not only acute MI but also non-MI coronary insufficiency and coronary death, the event rate measured likely underestimates the true CHD event rate and the degree to which FRS under-predicts incident CHD may be even greater. FRS performance in this cohort may be confounded by risk modifying variables and competing risk of non-MI death over the follow-up period.

Variable	HCV-infected N=111, 436	Uninfected N=121,380
Age, mean (SD) years	52.7 (8.7)	52.4 (8.8)
Race/Ethnicity		
White, n (%)	62,659 (56.2)	66,699 (55.0)
Black, n (%)	30,039 (27.0)	33,723 (27.8)
Hispanic, n (%)	6,365 (5.7)	7,376 (6.1)
Other/Unknown, n (%)	12,373 (11.1)	13,582 (11.2)
Body Mass Index (BMI), mean (SD)	27.6 (5.3)	28.9 (5.6)
On lipid lowering medication at baseline, n (%)	18,313 (15.8)	36,994 (30.2)
History of drug abuse, n (%)	29,552 (25.5)	15,007 (12.3)
History of alcohol abuse, n (%)	30,161 (26.1)	20,593 (16.8)
LDL-cholesterol, median (IQR) mg/dL	105 (83-130)	119 (95-144)
Baseline predicted 10-year CHD risk by FRS, median (IQR) %	12 (6-16)	12 (6-20)

Table. Baseline characteristics and 10-year Hard CHD Framingham Risk Score (FRS) by HCV status.

690 HCV Accelerates Non-Liver Mortality in HIV-Infected Patients: A Nationwide Cohort Study

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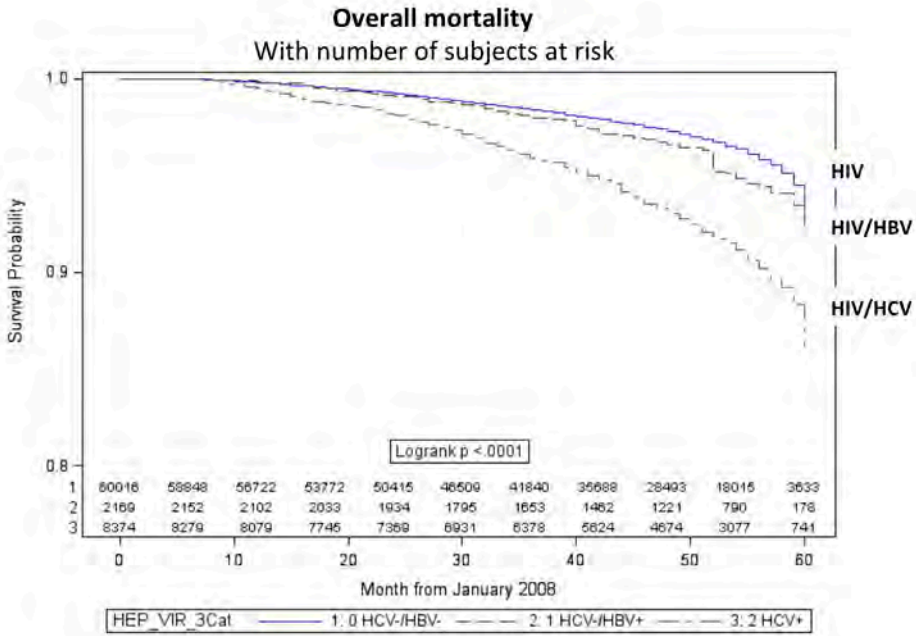
Background: HIV worsens the course of HCV infection. Whether HCV infection accelerates HIV progression and non-liver mortality is controversial. HBV treatment guidelines recommend that it be administered to all HIV/HBV patients regardless of liver fibrosis. HCV treatment guidelines recommend that it be administered to HIV/HCV patients with significant (≥F2) liver fibrosis. The aim of this nationwide study was to assess whether HCV hastens overall and non-liver mortality in HIV-infected patients.

Methodology: We conducted a retrospective, longitudinal analysis of the French National Hospital database. All HIV-infected patients receiving hospital care from January 2008 to December 2012 were included, and their medical trajectory was tracked in all French hospitals with use of the International Classification of Diseases (ICD-10), medical procedures, and in-hospital mortality as recorded per stay. Exclusion criteria involved: age below 18 years, non-resident in Metropolitan France; triple infection (HIV/HCV/HBV; HIV/HBV/HDV); autoimmune, genetic, biliary and vascular liver diseases; and patients identified at cohort inception with AIDS-defining conditions, liver-related events (end-stage liver disease, hepatocellular carcinoma, liver transplant),



hemophilia, dialysis, organ transplant, and a Charlson Comorbidity Index>0. A Cox model was initially used to estimate the overall risk of death adjusted for gender, age, and alcoholism; time-dependent covariates were then incorporated to control for the competitive risks of liver-related events or AIDS-defining conditions.

Results: Of 70,559HIV-infected patients (male 65.2%; mean age 42.8 years), 2,385 deaths occurred in 248,885 patient-years. Overall mortality was higher in 8,374 (7.5%) HIV/HCV patients as compared to 60,016 (2.8%) HIV patients (HR 1.79, P<0.0001),while it did not differ in 2,169 (3.9%) HIV/HBV patients (HR 1.22,P=0.08). When competitive risks were taken into account, non-liver-related mortality as well as non-liver, non-AIDS-related mortality remained higher in HIV/HCV coinfected patients (HR 1.40, P<0.0001 and HR 1.47, P<0.0001, respectively).

Conclusions: HCV infection increases overall and non-liver-related mortality in HIV-infected patients. This was not found in HIV/HBV infected patients, suggesting that viral suppression should be recommended for HCV coinfection as it is for HBV coinfection.

Session P-N9 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

HBV and HDV

691 The Role of HBV Quasispecies Diversity & Other Factors in Residual HBV Viremia On TDF-Based cART

Jennifer Audsley[1,2], **Anchalee Avihingsanon[3]**, Gail Matthews[4], Margaret Littlejohn[5], Stephen Bent[6], Lilly Yuen[5], Fabio Luciani[7], Stephen Locarnini[5], Sharon Lewin[1,2], Joe Sasadeusz[2]

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Background: Tenofovir (TDF) is effective in suppressing HIV and HBV replication in HIV-HBV co-infection. HBV DNA can persist in some individuals on TDF-based combination antiretroviral therapy (cART) but HBV resistance to TDF has not been reported to date. We initiated this study to determine risk factors associated with detectable HBV DNA beyond 6 months on TDF and to examine HBV polymerase in HIV-HBV co-infected individuals receiving TDF.

Methodology: We enrolled 92 HIV-HBV co-infected participants on, or about to commence, TDF-containing ART in a prospective longitudinal study. Subjects were followed every 6 months for 2 years with clinical and laboratory assessments. HBV polymerase sequencing was performed on plasma samples with an HBV DNA >400 IU/ml by both population-based methods and ultra-deep pyrosequencing (UDPS). Quasispecies diversity was assessed using Shannon entropy (SE) values from 55 pre-TDF samples that underwent UDPS.

Results: Most of the cohort (92.4%) was on TDF at study entry (median duration on TDF of 2.03 (IQR 1.0-4.4) years). Over 24 months of f/up, HBV DNA was >15 IU/ml once in 10.9% (n=10); and on >1 occasion in 7.6% (n=7; median number of occasions = 3 (IQR 2-5). Eight patients with detectable HBV DNA once during follow up had HBV DNA <15 IU/ml at enrolment. Three patients (3.3%) had persistently detectable HBV DNA during f/up despite adherence to ART. Detectable HBV DNA at study entry, positive HBeAg, country of recruitment, HBV genotype, lower platelets, urea, phosphate and albumin, and higher GGT were associated at the univariate level with detectable HBV DNA on-TDF. HBV DNA at study entry was the only factor that remained significant in a series of multivariate models. Novel HBV pol mutations were not identified in any on-TDF plasma samples that underwent HBV sequencing (n=19). There was no statistical difference in median SE values between the always HBV aviremic on-TDF (n=41) and the ever viremic on-TDF (n=14) groups, at both site-by-site and haplotype levels.

Conclusions: Detection of HBV DNA on more than one occasion in HIV-HBV co-infected patients on TDF containing cART is common, however, drug resistance did not occur in this setting. HBV DNA positive status at study entry but not preTDF HBV quasispecies diversity was associated with detectable HBV DNA on-TDF. Prolonged follow up will be needed to determine the clinical significance of detectable HBV DNA on HBV-active ART.

692 Therapeutic Management and Evolution of Chronic Hepatitis B: Does HIV Coinfection Still Matter?

Lionel Piroth[1], Stanislas Pol[2], Patrick Miailhes[3], Karine Lacombe[4], Amanda Lopes[5], Françoise Borsa-Lebas[6], Dominique Salmon[7], Eric Rosenthal[8], Fabrice Carrat[9], Patrice Cacoub[10]

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Background: The EPIB 2012 study was conducted to compare the management of chronic hepatitis B (CHB) in HIV-positive and HIV-negative patients, its evolution over time and the relationship with the current presentation of CHB.

Methodology: 755 consecutive patients with past or present CHB were seen in October 2012 in 19 French participating centers. All of their data were retrospectively collected from the first visit onwards through a standardized questionnaire. Out of these, 709 with known HIV status and with at least two HBV serological evaluations were analyzed.

Results: The 299 HIV-positive patients were less likely to have full initial evaluation of CHB (9.7% vs. 42.9%, $p<10^{-3}$), were followed for a longer duration (11.3+/-8.8 vs. 8.6+/-6.9 years, $p<10^{-3}$) and more frequently treated for HBV (95.3% vs. 56.8%, $p<10^{-3}$) than the 410 HBV-mono infected ones. Undetectable HBV at the last visit (80.8% in HIV-positive vs. 55.1% in HIV-negative patients, $p<10^{-3}$) was positively associated in multivariate analysis with

older age (OR + 1 year 1.03, 95%CI 1.01-1.05, $p<10^{-3}$), lower baseline HBV DNA (OR + 1 $\log_{10}$IU/mL 0.87, 95%CI 0.80-0.95, $p=0.001$), longer duration of HBV therapy (OR + 1 month 1.03, 95%CI 1.02-1.03, $p<10^{-3}$)and negatively with previous lamivudine monotherapy (OR 0.31, 95%CI 0.15-0.66, $p=0.002$), but not with HIV status. Similar efficacy was observed for tenofovir and entecavir, whatever the HIV serostatus. Renal impairment (creatinine clearance<60 ml/mn) was associated with older age and low baseline creatinine clearance, but not with HIV status. Cirrhosis was associated with age (OR + 1 year 1.06, 95%CI 1.04-1.09, $p<10^{-3}$), male gender (OR 1.78, 95% CI: 0.93-3.41, $p=0.08$), daily alcohol intake>40g (OR 1.78, 95% CI: 1.14-2.78, $p=0.01$), and co-infection with HCV (OR 2.61, 95% CI: 1.11-6.26, $p=0.03$), HDV (OR 2.61, 95% CI: 1.07-6.36, $p=0.03$), but not with HIV. Hepatocellular carcinoma (HCC) was less frequent in HIV-positive patients (2/297, 0.7% vs 19/410, 4.7%, p=0.002), and was associated with older age (OR + 1 year 1.05, 95%CI 1.01-1.09, $p=0.01$), male gender (OR 10.00, 95%CI 1.27-78.60, $p=0.03$), and cirrhosis (OR 10.11, 95%CI 3.43 - 29.82, $p<10^{-3}$), and negatively with HIV-positive status (OR 0.15, 95%CI 0.03-0.67, $p=0.01$).

Conclusions: Even though the assessment of CHB still has to be improved, the negative impact of HIV on CHB seems to be disappearing probably due to the immunovirological impact of HAART and the more frequent and longer use of HBV therapy. The unexpected lower rate of HCC in HIV-positive patients suggests that a higher rate of viral suppression on long-term HBV therapy could reduce the risk. In light of these results, the management of chronic hepatitis B in HBV mono-infected patients and that in HIV-HBV co-infected patients could become closer in the near future.

693 Increased Hepatitis B Virus Coinfection Screening Following a Change in Zambian HIV Guidelines

Kalo Musukuma[1], Arianna Zanolini[1,2], Lloyd Mulenga[1,3], Carolyn Bolton-Moore[1,4], Samuel Zuercher[5], **Izukanji Sikazwe[1]**, Aggrey Mweemba[3], Gilles Wandeler[6], Benjamin H. Chi[1,4], Michael J. Vinikoor[1,2]

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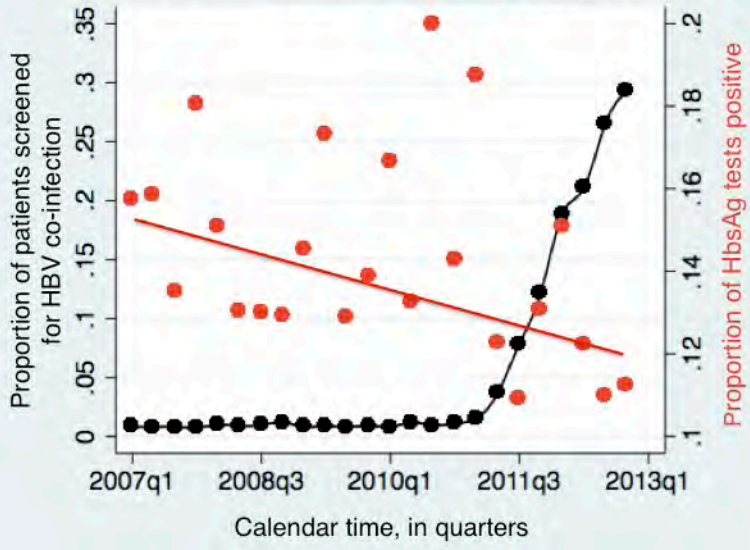
Background: Screening all HIV-infected adults for hepatitis B virus (HBV) co-infection is recommended by the World Health Organization but is not commonly practiced in sub-Saharan Africa. In 2010, the Zambian Ministry of Health (MoH) recommended a change from targeted screening, based on clinical suspicion of liver disease, to universal HBV screening at enrollment. We describe changes in HBV screening practices in the Lusaka public-sector HIV treatment and care program following dissemination of the new guidelines in 2011.

Methodology: Using central laboratory testing data from Lusaka public-sector HIV care facilities, across quarters of calendar time, we analyzed the proportion of HIV-infected patients who were screened for HBV co-infection with hepatitis B surface antigen (HBsAg). Using multivariable logistic regression, we assessed predictors of being screened including age, sex, liver transaminases (AST and ALT), and CD4+ T-cell count as well as factors associated with being HBV co-infected.

Results: From 2007 to 2012, 183,413 HIV-infected individuals enrolled across 23 Lusaka clinics. Prior to 2011, 0.9% of enrollees were screened for HBV, of which 170 (14.9%) had positive tests. Having an abnormal ALT was associated with being tested (adjusted odds ratio [AOR] 1.50; 95% confidence interval [CI], 1.26-1.78). Following dissemination of the new guidelines, the proportion of enrollees screened increased rapidly to 29.3% in 2012, and the proportion with positive HBsAg tests decreased to 12.4% (both P<0.001 for trend; Figure 1). Post-guideline change the predictors of being tested included male sex (AOR 1.07; 95% CI, 1.02-1.13), abnormal baseline ALT (AOR 1.12; 95% CI, 1.05-1.20), and baseline CD4+ T-cell count <200 cells/mm3 (AOR 1.25; 95% CI, 1.19-1.32). Testing patterns also varied across facilities due to a lag in the roll out of the guidelines and due to constrained resources. Among those screened, age <40 years (AOR 1.21), male sex (AOR 1.61), abnormal baseline ALT (AOR 2.20), and enrollment CD4+ T-cell count <200 cells/mm3 (AOR 1.61) were associated with HBV co-infection (all P<0.05).

Figure 1. Changes in HBV testing and proportion of HbsAg tests positive in Lusaka public-sector HIV program, 2007-2012



Conclusions: Implementation of new Zambian HIV guidelines was associated with a large increase in HBV screening; however, overall screening rates remain low. In resource-constrained settings, the cost effectiveness of universal HBV screening policies should be determined.

694 HBsAg Genetic Elements Critical for Immune Escape Drive HBV Reactivation Upon Immunosuppression

Romina Salpini[1], Claudia Alteri[1], Maria-Concetta Bellocchi[1], Emanuela Balestra[1], Claudio Mastroianni[2], Aldo Marrone[3], Massimo Andreoni[1], Mario Angelico[1], Carlo-Federico Perno[1], **Valentina Svicher[1]**

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Background: HBV reactivation is defined as an abrupt reappearance or rise of serum HBV DNA in patients (pts) with resolved or inactive HBV infection. The role of HBsAg genetic diversity in this phenomenon is still anecdotic. Here, we investigate HBsAg genetic signatures underlying HBV reactivation under immunosuppression.

Methodology: This study included 129 HBV D Genotype HBsAg sequences from 29 pts with HBV reactivation triggered by immunosuppressive therapy (55.2% received rituximab, 20.7% other immunosuppressive chemotherapeutics and 24.1% corticosteroids), and 100 chronically HBV infected drug-naïve pts as control. For 21/29 HBV-reactivating pts, HBsAg ultra-deep sequencing (UDPS) was also performed. After applying a correction pipeline and error rate estimation using an HBV plasmid, mutations in both forward and reverse primers in >5 reads were considered. Association of mutations with HBV reactivation was assessed by Fisher test with Benjamini-Hochberg correction for multiple comparison.

Results: At HBV reactivation, median serum HBV DNA is 6.1 (4.6-7.9) IU/ml and median ALT is 193 (37-560) IU/L. Among 9 HBV reactivating pts despite lamivudine prophylaxis, lamivudine resistance is detected in 7 pts.

A significantly higher mean HBsAg genetic divergence is observed in HBV-reactivating pts than controls (0.058 vs 0.017, P<0.001). Independently from drug resistance presence, specific HBsAg mutations tightly correlate with HBV reactivation (M103I, T123N, S143L, D144E, S154L, V190A) (P from 0.039 to 0.002). At least 1 of them occurs in 55.2% HBV reactivating pts, while they are absent (0/100 for M103I, T123N, D144E, S154L), or nearly absent (1/100 for S143L and 2/100 for V190A) in controls. By UDPS, the intra-patient prevalence of these HBsAg mutations ranges from 81.6% to 100%, supporting their full fixation in viral population.

M103I, T123N, S143L, D144E reside in the a-determinant and are known to hamper HBsAg recognition by neutralizing antibodies. Among them, T123N introduces an N-linked glycosylation-site, potentially reducing HBsAg immunogenic surface. S154L and V190A reside in CTL epitopes encompassing residues150-158 and 185-194.

UDPS also detects minority HBsAg immune/vaccine escape mutations (G145R, G130R, P120S and M133T) and HBsAg stop codons (known to increase HBV oncogenic potential) in 33.3% and 23.8% pts with an intra-patient prevalence ranging from 1.7% to 3.7% and from 1.5% to 2.2%, respectively.

Conclusions: HBV reactivation status is driven by a complex quasispecies with enhanced capability to evade immune response. This highlights the need of a careful monitoring and of establishing an adequate (high genetic barrier?) therapy in order to prevent HBV reactivation and consequent liver damage.

695 Isolated Hepatitis B Core Antibody Is Associated With Advanced Hepatic Fibrosis

Debika Bhattacharya[1], Chi-hong Tseng[1], Jan Tate[2, 3], Vincent Lo Re[4, 5], Cynthia Gibert[6, 7], Joseph K. Lim[2, 3], Maria Rodriguez-Barradas[8, 9], David Rimland[10, 11], Amy C. Justice[2, 3], Matthew B. Goetz[12, 13]

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Background: The relationship between isolated hepatitis B virus (HBV) core antibody (sole HBcAb) and liver disease in HIV+ patients is unclear. We determined if sole HBcAb was associated with advanced hepatic fibrosis in HIV+ persons

Methodology: We conducted a cross-sectional study among HIV+ patients in the Veterans Aging Cohort Study Virtual Cohort who had available laboratory data to determine chronic HCV status and 5 serological patterns of HBV antibodies: 1) sole HBcAb, 2) resolved HBV infection (HBcAb+/HBsAb+), 3) no evidence of HBV infection or vaccination (non-immune HBV), 4) HbsAb+ only, and 5) active HBV infection (HBsAg+). The main outcome was advanced hepatic fibrosis determined by FIB-4 >3.25 and APRI>2.0. Laboratory data to determine outcomes were obtained within +/- 1 year of the earliest time that complete serological data to define HBV and HCV serostatus were available. Logistic regression was used to determine adjusted odds ratios (ORs) of advanced fibrosis.

Results: Among 18,145 HIV+ patients (6,798 with and 11,347 without chronic HCV), sole HBcAb was more common in patients with chronic HCV than without (40% vs 13%; p<0.01). As shown in the table, compared with patients who were non-immune, HCV+ patients with sole HBcAb had a higher OR for advanced hepatic fibrosis by FIB-4 (OR 1.32, 1.09-1.60) but not APRI (OR 1.15, 0.92-1.44). In addition (data not shown), when compared to patients with resolved HBV or who were HBsAb+ only, patients with sole HBcAb had higher OR for advanced hepatic fibrosis by both FIB-4 (OR 1.34, 1.15-1.58 and 1.65, 1.20-2.28, respectively) and APRI (OR 1.40, 1.15-1.71 and 1.88, 1.25-2.84, respectively). No association between sole HBcAb status and advanced hepatic fibrosis was seen among HCV- patients. Patients with active HBV had a higher prevalence of advanced hepatic fibrosis than did patients with any other HBV serological pattern, regardless of HCV status.

Conclusions: HIV+/HCV+ persons with sole HBcAb have evidence of a higher prevalence of advanced hepatic fibrosis, as assessed by FIB-4 or APRI scores, than persons who are non-immune to HBV, who have resolved HBV, or who are HbsAb+ only. These findings suggest that persons with sole HBcAb may be at increased risk of clinical liver complications, and are consistent with prior studies showing an increased prevalence of occult HBV infection in such individuals.

Indicators of advanced hepatic fibrosis in patients with Sole HBcAb									
HBV Status	Non-immune	Sole HBcAb		Resolved HBV		HBsAb+ only		Active HBV	
		p		p		p		p	
N	1294	2707		2345		452		492	
Median Age	47	49	<0.001	48	<0.001	47	0.74	46	0.006
Median CD4	304	306	0.68	324	0.37	354	<0.001	240	<0.001
Median log VL	3.74	3.40	0.003	3.28	<0.001	3.68	0.23	3.57	0.68
FIB-4>3.25	18%	23%	<0.001	18%	0.70	13%	0.027	27%	<0.001
APRI>2.0	13%	14%	0.18	11%	0.20	8%	0.003	21%	<0.001
	OR* (95% CI)	OR (95% CI)		OR (95% CI)		OR (95% CI)		OR (95% CI)	
FIB-4>3.25	Reference	1.32 (1.09-1.60)		0.98 (0.80-1.21)		0.80 (0.56-1.13)		1.76 (1.32-2.35)	
APRI>2.0	Reference	1.15 (0.92-1.44)		0.82 (0.64-1.04)		0.61 (0.40-0.94)		1.69 (1.23-2.32)	
* adjusted for age, race/ethnicity, CD4 count, log VL, diabetes, body mass index, alcohol, drug use and smoking.									

696 Isolated Hepatitis B Core Antibody and Hepatic Fibrosis in HIV/HCV-Coinfected Women

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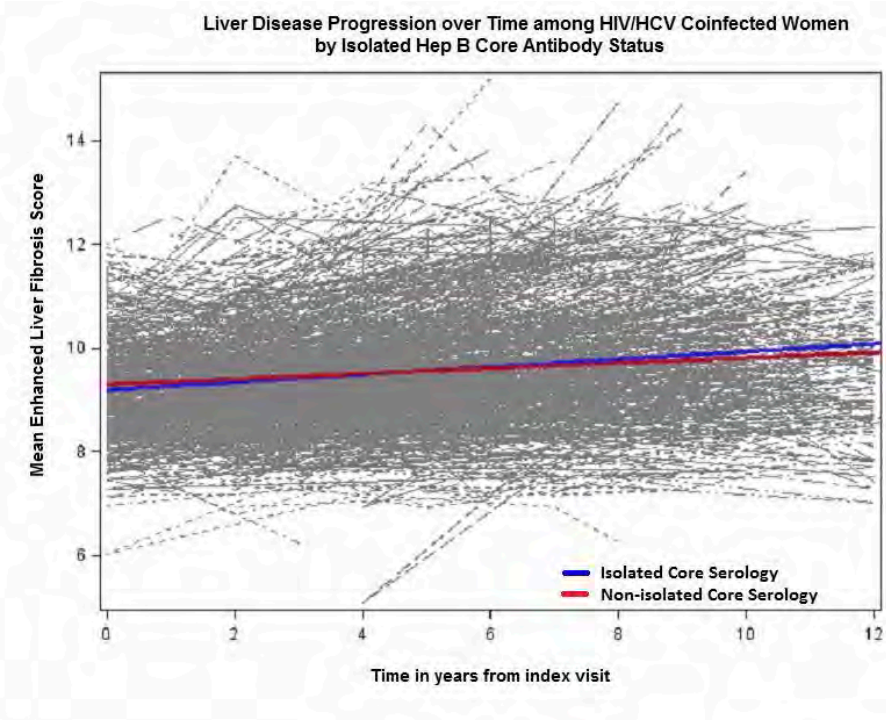
Background: Isolated hepatitis B (HB) core antibody positivity (anti- Hbc) is a common serologic finding in HIV and HCV infected persons. The clinical significance of isolated anti-HBc is uncertain; it may represent resolved HB infection with low anti-HBs, a false positive, the window period in acute HB or, as some have postulated, clinically significant occult active HB infection. We sought to determine if the trajectory of liver disease progression (LDP) in HIV/HCV co-infection is affected by isolated anti-HBc status.

Methodology: We performed a nested study of HIV/HCV-infected women participating in the Women's Interagency HIV Study (WIHS), a longitudinal observational study. HCV is defined by HCV RNA positivity. We performed enhanced liver fibrosis (ELF) markers on HIV/HCV infected women, comparing women with isolated anti-HBc to women with either negative HB serologies, anti-HBs alone, or both anti-HBs and anti-HBc. ELF, a serum marker that combines direct measures of extracellular matrix remodeling and fibrosis (tissue inhibitor of metalloproteinase-1, hyaluronic acid and propeptide type III collagen), was performed on stored serum q2 years for women with no or minimal fibrosis by APRI and FIB-4 at the baseline visit. We included women who had at least 3 ELF determinations and compared LDP in women with and without isolated anti-HBc using mixed effects linear regression models.

Results: 361 HIV/HCV infected women were studied, including 138 with isolated anti-HBc and 223 without. A median of 6 (IQR 5-7) biannual ELF values were available. At first ELF measurement, median age was 40, 62% of women were black, 21% Latina, 15% white, median CD4 count (CD4) was 359; there was no difference between the groups in terms of race, age, CD4, HIV RNA, HAART use or alcohol use. ELF increased over time from a median of 9.07 for women with isolated anti-HBc and 9.10 for those without to 9.81 and 9.78 respectively (Figure) with no difference in degree of change (p=0.170) by isolated anti-HBc status in the mixed effect model including age, race, history of injection drug use at the index visit, CD4, HAART use, and alcohol use. Factors independently associated with LDP were older age, lower CD4 and HAART non-use.

Conclusions: Isolated anti-HBc was not associated with accelerated liver disease progression over a median of 10 years among HIV/HCV co-infected women.



697 Effectiveness of Taiwan Nationwide HBV Vaccination in Persons at Risk for HIV Infection

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Background: The prevalence of chronic hepatitis B virus (HBV) infection was estimated 15% to 20% in the adults, regardless of HIV infection, who were born before universal neonatal hepatitis B virus (HBV) vaccination program was launched in 1986. The neonatal HBV vaccination program and catch-up vaccination program have significantly reduced acute and chronic HBV infection among persons born in the universal HBV vaccination era. However, the long-term effectiveness of the programs remains rarely investigated among the adults who were born in the universal vaccination era and engaged in high-risk sexual behavior.

Methodology: Between April 2006 and December 2012, we determined HBV serological markers (HBsAg, anti-HBs, and anti-HBc), anti-HCV and rapid plasma regain (RPR) titers among HIV-infected men who have sex with men (MSM) born during 1984-1985 (Group I) and those born in or after 1986 (Group II), and HIV-uninfected MSM (Group III) and heterosexuals (Group IV), both of whom were born in or after 1986 and sought anonymous voluntary counseling and testing for HIV infection. Prevalence of HBsAg positivity and incidence of HBV infection were estimated and multivariate analysis was performed to identify factors associated with HBsAg positivity.

Results: During the study period, 244 persons in Group I, 523 in Group II, 377 in Group III, and 217 in Group IV were included. Group I had a significantly higher prevalence of HBsAg (7.8%), anti-HBc (30.3%), anti-HCV (4.3%), and syphilis (RPR titers ≥4) (19.8%) than the other three groups (HBsAg: 3.7%/2.4%/3.2%; anti-HBc: 26.3%/19.6%/18.0%; anti-HCV: 3.5%/1.1%/1.4%; and syphilis: 21.2%/2.8%/0.5% for Groups II/III/IV, respectively). After adjustments for HIV seropositivity, birth year syphilis, and anti-HCV seropositivity in multivariable analysis, HBsAg seropositivity was significantly associated with syphilis (OR 2.990; 95% CI 1.502-5.953) and anti-HCV seropositivity (OR 3.402; 95% CI 1.091-10.614), but not birth year in or after 1986 (OR 0.421; 95% CI 0.208-0.854) (All P<0.05). In Group II with all negative HBV markers at baseline, the incidence rate of HBsAg seroconversion was 0.486 episodes per 100 person-years; and for those who received combination antiretroviral therapy containing tenofovir and/or lamivudine, none developed HBsAg seroconversion.

Conclusions: For the adults born after 1986 and engaged in high-risk sexual behaviors, universal neonatal HBV vaccination and catch-up vaccination programs offered long-term protection against HBsAg seropositivity and HBsAg seropositivity was associated with syphilis and anti-HCV seropositivity.

698 Hepatitis B Virus Mother-To-Child-Transmission Among HIV-Infected Pregnant Women in Kenya

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Background: Like HIV, hepatitis B virus (HBV) can be transmitted from mother to child. Our objective was to assess the prevalence of HBV co-infection and the HBV vertical transmission rate among HIV-infected mothers receiving lamivudine-containing triple-antiretroviral (ARV) regimens.

Methodology: The Kisumu Breastfeeding Study (2003-2009) was a prospective clinical trial of triple-ARV regimens to prevent mother to child HIV transmission (MTCT) in Kenyan women. Women received ARV regimens containing lamivudine from 34 weeks' gestation through six months of postpartum breastfeeding. Infant HBV vaccination starts at six weeks of life in Kenya. We retrospectively performed maternal HBV serology testing, including surface antigen (HBsAg), surface antibody (HBsAb), core antibody (HBcAb), and e antigen (HBeAg), in serum at enrollment (pre-ARV) and at six months postpartum. Maternal active HBV co-infection was defined as having detectable HBsAg. We tested infants of mothers with detectable HBsAg or an isolated HBcAb (HBsAg-/HBcAb+/HBsAb-) for HBcAb at two years of life. Infant HBV infection was defined as having detectable HBcAb.

Results: Among 439 HIV-infected women initiating lamivudine-containing ARVs, 25 (5.7%) had active HBV co-infection, including 9 (38%) women with detectable HBeAg. Among infants with available specimens, there were 0/17 HBV MTCT in infants of mothers with

Table: Clinical and laboratory features of HIV-infected mothers and their infants by HBV infection status

	HBV Infection N = 25	No HBV Infection N = 414	*P*-value*
Age (median; interquartile range (IQR)	22 (21–25)	24 (21–27)	0.10
CD4, initial [cells/mm^3] (median; IQR)	435 (152–815)	401 (279–546)	0.77
CD4, six months postpartum (median; IQR)	634 (433–864)	661 (464–856)	0.50
ALT, initial [U/mL] (median; IQR)	10 (8–15)	10 (7–13)	0.42
ALT, peak [U/mL] (median; range)	31 (13–101)	27 (1–824)	0.39
Severe Hepatotoxicity [ALT >200 U/mL] (n; %)	0	12 (3%)	1.00
Rash-Associated Hepatotoxicity [ALT >100 U/mL with rash] (n; %)	0	8 (2%)	1.00
Maternal Death (n; %)	0	9 (2%)	1.00
Infant ALT, birth [U/mL] (median; IQR)	15 (11–17)	14 (11–20)	0.57
Infant HIV Transmission (n; %)	1 (4%)	18 (4%)	1.00
Infant Death (n; %)	2 (8%)	41 (10%)	1.00
Serology Patterns (n; %)			
HBsAg+	25 (100%)	N/A	
HBsAg-/HBcAb-/HBsAb-	N/A	187 (45%)	
HBsAg-/HBcAb-/HBsAb+	N/A	21 (5%)	
HBsAg-/HBcAb+/HBsAb+	N/A	148 (36%)	
HBsAg-/HBcAb+/HBsAb-	N/A	58 14%)	

* Continuous variables tested with the Wilcoxon two-sample test; categorical variables tested by Fisher's exact test

active HBV (0%, 95% confidence interval [CI] = 0%-16%) and 0/46 HBV MTCT in infants of mothers with isolated HBcAb (0%, 95% CI = 0%-6%). HBV co-infected mothers did not significantly differ in CD4 count, alanine aminotransferase (ALT) levels, or rates of liver toxicity on ARVs compared with those without HBV co-infection (Table).

Conclusions: The prevalence of active HBV co-infection in this cohort of HIV-infected pregnant women (5.7%) was almost double the reported Kenyan prevalence (3%). Among HIV/HBV co-infected women receiving lamivudine containing triple-ARV regimens, there were no cases of HBV MTCT suggesting that vertical transmission of HBV is uncommon in this setting.

699 Vaccine Escape Mutants and Suboptimal Hepatitis B Virus Response in HIV HBV Coinfected Patients

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Background: Immune and antiviral-associated S gene mutations are associated with potential vaccine escape and are thus a major public health concern. The frequency of these mutations during antiretroviral therapy (ART) is unknown in ART-naïve HIV hepatitis B virus (HBV) coinfected patients with suboptimal HBV response, especially in sub Saharan Africa.

Methodology: 200 ART naïve, HIV-infected patients with positive hepatitis B surface antigen were selected from two randomized-control trials in Côte d'Ivoire: ANRS 1269, comparing treatment interruption strategies of lamivudine (LAM)-containing ART(n=103), and ANRS 12136, comparing early or differed initiation of tenofovir (TDF)/emtricitabine-containing ART (n=97). HBV DNA was quantified using an in-house assay (detection limit: <12 copies/mL) while preS/S regions of positive samples were sequenced. Patients with detectable HBV DNA at baseline were included in this analysis (LAM n=88, TDF n=51). Determinants for time to undetectable HBV DNA viral load were modeled using Cox proportional hazards model.

Results: Patients were mostly female (68%) with median 35 years of age (IQR: 30-40). At baseline, 39 (28.1%) patients were HBeAg positive and 37 (31.4%) had an ALT of >35 IU/mL. Patients harbored A (n=2) or E (n=97) HBV genotype. After a median 35.5 (IQR: 24.3-36.5) months of follow-up, higher rates of undetectable HBV DNA were observed in TDF vs LAM-treated patients (cumulative % at M36, 94.4% vs 76.1% respectively, HR=1.64, 95%CI: 1.01-2.66, p=0.046) and in patients with lower degrees of immunosuppression [compared to >500 CD4+ cells/mm3, HR (95%CI) at 350-500/mm3=1.07 (0.67-1.71); at 250-350/mm3=0.62 (0.34-1.11); at <250/mm3=0.41 (0.19-0.90)] after adjusting for baseline HBV DNA level, HBeAg status and percent of on-treatment follow-up time. In patients with available sequences at baseline (N=49), amino acid changes at positions recognized as immune and antiviral-associated S gene mutations were as follows: sP120A/L/T (n=3), s145 (n=0), sE164G/V (n=6) and s194 (n=0). Among patients with low detectable HBV DNA levels at the end of follow-up (<105 log10 copies/mL, LAM n=25, TDF n=5), incident amino acid changes were noted at positions: sI110L, sT126I, sA128D, sG130K, sM133L, sI213L, sF219G, and sF220C, but not at s120, s145, s164, or s195. Among patients with HBV DNA ≥105 log10 copies/mL at the end of follow-up (LAM n=8, TDF n=3), the only incident S gene mutations observed during follow-up were at both positions sE164D+sI195M in two LAM-treated patients (while also harboring rtV173L+rtL180M+rtM204V/I mutations) but not in any TDF-treated patient.

Conclusions: In HIV-HBV coinfected patients with low transaminases levels, immune and antiviral-associated S gene mutations are rare during suboptimal response.

700 Long-Term Benefit of Tenofovir On Hepatitis Delta

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Background: Hepatitis delta virus (HDV) infection produces the most severe form of chronic viral hepatitis. Treatment with peginterferon gives only limited benefit on delta hepatitis. Since HDV replication requires HBsAg and tenofovir is amongst the most potent anti-HBV agents and is widely used as part of HIV therapy, we explored whether prolonged tenofovir (TDF) exposure might be of benefit on hepatitis delta.

Methodology: All HIV-infected patients with hepatitis delta treated with TDF followed at an HIV clinic in Spain were retrospectively identified. Serum HBV/HDV-RNA was quantified using a commercial real-time PCR assay. Liver fibrosis was measured using elastometry (FibroScan). Significant liver fibrosis regression (sLFR) was defined as a 30% reduction in hepatic stiffness compared to baseline.

Results: A total of 19 HIV-infected patients with hepatitis delta were identified. HCV antibodies were present in 16 (84%), although HCV-RNA was detectable only in 3 (2%). Overall 79% were former intravenous drug users; 95% male; median age 48 years-old. HDV genotype 1 was present in all cases. HBV genotypes D and A were the most common (53% and 26%, respectively). Prior lamivudine exposure (median 59 months) before beginning TDF was recognized in 9 (47%), being the rest naïve for any anti-HBV agent.

After a median TDF exposure of 58 [34-93] months, all achieved undetectable HBV-DNA and 10 (53%) reached HDV-RNA <10 copies/mL. In the last group, the median time for the achievement of undetectable HDV-RNA was 54 [33-72] months. Of note, in the subset of HDV viremic patients at the end of follow-up there was also a median drop in HDV-RNA of 2.42 [1.27 - 3.09] log cop/mL.

sLFR was recognized in 6 (60%) out of 10 patients who achieved undetectable HDV-RNA and in none of 9 that remained viremic at the end of follow-up (p=0.02). Median liver enzymes slightly declined during the study period, but normalized in only 3. There were no significant changes in serum HBsAg levels during the study period, although HBsAg seroclearance occurred in 2 patients, who became negative for serum HDV-RNA.

Conclusions: Long-term exposure to TDF significantly reduces serum HDV-RNA besides completely suppress HBV-DNA in HIV-infected patients with hepatitis delta. This effect is accompanied by significant liver fibrosis regression.

Session P-N10 Poster Session
Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**
HEV

633 Chronic Hepatitis E Virus Infection Is Uncommon in HIV-Infected Patients

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Background: Background & Aims: The seroprevalence of the Hepatitis E virus (HEV) and its chronicity rate in the HIV-infected population has not been well established. Consequently, the magnitude of this emerging disease in this population cannot be established. The objective of our study was to evaluate the serological/virological HEV situation and factors associated with it in HIV-infected patients.

Methodology: Prospective study in Southern Spain that included HIV-infected patients who were followed up between September 2012 and May 2013. All patients included were tested for anti-HEV IgG/IgM. In those patients with confirmed anti-HEV IgG/IgM positivity, a RT-PCR was performed. In patients where HEV-RNA was amplified, a second RT-PCR was performed 6 months later to identify transient or chronic HEV infections. Additionally, we performed a RT-PCR in all patients with CD4+ cell counts that were lower than 200 cells/mL regardless of the anti-HEV IgG/IgM status. HEV seroprevalence and its associated factors were evaluated.

Results: Eight-hundred and ninety-four HIV infected patients were enrolled in the study. Of these patients, 399 (44.6%) were monoinfected with HIV; 462 (51.6%) were co-infected with HIV/HCV; 12 (1.3%) were co-infected with HIV/HBV; and 21 (2.3%) were coo-infected with HIV/HCV/HBV. In 88 patients, anti-HEV IgG/IgM (86 IgG+/IgM- and 2 IgG+/IgM+) were detected, and consequently, the overall HEV seroprevalence in our population was 9.8% (95% CI: 8.02%-11.9%). The anti-HEV IgG/IgM positive patients were older than those with serum that was anti-HEV IgG negative ($p < 0.001$). In the logistic multivariate analysis model, only age was associated with a positive anti-HEV IgG/IgM status (OR = 1.053; 95% CI: 1.017-1.091). When patients were sorted according to hepatitis virus co-infection, serum anti-HEV IgG/IgM was detected in 40 HIV monoinfected patients (10.03%; 95% CI: 7.3%-13.3%) and in 48 HIV/hepatotropic virus co-infected patients (9.7%; 95% CI: 7.3%-12.5%). However, no difference in the seroprevalence was found between the groups ($p = 0.866$). In five patients (0.5%; 95% CI: 0.2%-1.2%), RNA-HEV was detected, which indicated 5.7% (95% CI: 2.1%-12.1%) anti-HEV IgG/IgM-positive patients; however, none of those patients had detectable HEV-RNA six months later. None of the 98 anti-HEV IgG/IgM negative patients with a CD4+ cell count lower than 200 cells/mL had detectable HEV-RNA.

Conclusions: Our study found that despite HEV infection is frequent in HIV-infected patients, the detection of HEV-RNA in our study was low, and no development of chronic infection was found. Furthermore, in immunosuppressed patients with the absence of HEV-serum-marker positivity, HEV-RNA was not detected.

634 High Frequency of HEV Seropositivity in HIV-Infected Patients in Southern Spain

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Background: HEV has been reported to be a cause chronic liver disease with rapid progression to cirrhosis in HIV-infected patients. Anti-HEV seropositivity has been observed in 9% HIV carriers in Northern Spain. Likewise, rates of seropositivity of 2.6% and 4% have been reported in HIV-infected patients with unexplained transaminase elevation in Switzerland and France, respectively. However, the prevalence of HEV infection may dramatically vary from one region to another. Moreover, the rate of evolution to chronic hepatitis C and the relevance of HEV coinfection as a cause of unexplained liver disease in HIV-infected patients remain unclear. The purpose of this study was to analyze the prevalence of HEV seropositivity and of active HEV infection, as well as the factors associated thereof in HIV-infected patients in Southern Spain.

Methodology: 611 HIV-infected patients who consecutively attended a Unit of Infectious Diseases in Seville, Southern Spain, were tested for HEV serum antibodies by EIA (Wantai, Beijing, China). Positive samples were confirmed by immunoblot (Mikrogen, Munich, Germany); those that tested positive by both procedures were considered as seropositive and were also submitted to a PCR test (Mikrogen) for serum HEV RNA. The associations between HEV seropositivity and demographics, as well as data of liver disease were analyzed.

Results: 593 (97%) subjects were born in Spain. Median age was 43 years. 416 (68%) were anti-HCV positive. 105 (17.2%) were seropositive for HEV antibodies. HEV-RNA was detected only in one subject. The older the age, the higher the rate of seropositivity: <40 years, 8.2%; 40-49 years, 17.6%; >49 years, 31.3% (p=0.00001). Among anti-HCV negative patients, the frequencies of HEV seropositivity, according to liver enzyme abnormalities, were: AST >40 UI/L: 5/14 (36%), AST ≤40 UI/L: 28/181 (16%), p=0.073; ALT >100 UI/L: 2/4 (50%), ALT ≤100 UI/L: 32/191 (17%), p=0.141; GGT >50 UI/L: 12/46 (26%), GGT ≤50 UI/L 22/149 (15%), p=0.077.

Conclusions: The rate of exposure to HEV is high among HIV-infected patients from Southern Spain, and it increases with age, but chronic infection is very uncommon. This suggests that most cases of acute HEV infection in this setting are self-limited. However, a trend to an association exists between prior HEV exposure and data of liver disease not related with HCV. Further studies are required to establish if there is actually a causative relationship.

Session P-01 Poster Session
Tuesday March 4, 2014, 2:30 PM–4:00 PM Exhibit Hall B
Lymphoma/Liver/Gammopathy

701 Monoclonal Gammopathy and HIV-1 Infection: Evolution With Highly Active Antiretroviral Therapy

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Background: Monoclonal gammopathies (MG) associated with HIV infection are frequent but their significance and evolution are uncertain in this population with a high risk of lymphoproliferative disorder. Our aim was to describe the evolution of MG in HIV-infected subjects under highly active antiretroviral therapy (HAART).

Methodology: Retrospective study of HIV-1 infected adults, with a monoclonal spike identified by the serum protein electrophoresis confirmed by immunofixation, excluding subjects with concomitant or preceding hemopathy. Subjects were followed for at least 3 years if MG persisted or less if MG disappeared. Logistic regression models were used to identify factors associated with disappearance of monoclonal band.

Results: Seventy-one subjects were included: 65% were male, median age was 41 years, 46% had AIDS, median nadir CD4 count was 237/mm3, 41% had chronic hepatitis B or C infection. Eighteen subjects with preceding or concomitant hemopathy were excluded. After a median follow-up of 7.1 years (IQR 4.5-9.3), 71.8% showed spike disappearance. In multivariate analysis, MG disappearance was associated with HIV-virologic success (OR 6.67, CI95% [1.38;32.13], p 0.018), absence of active hepatitis C at end of follow-up (OR 11.16, CI95% [2.20;56.69], p 0.004) and age inferior to 40 years (OR 4.75, CI95% [1.00;22.55], p 0.050). One subject developed a myeloma after the diagnosis of an IgA kappa MG.

Conclusions: MG associated with HIV infection concerned a young population, and had a favorable evolution on HAART in most cases. The disappearance of monoclonal gammopathy was associated with HIV-virologic success, absence of active hepatitis C and younger age.

702 Predicting Survival of HIV-Infected Patients With Liver Cancer: The SHILCA Score and Staging Model

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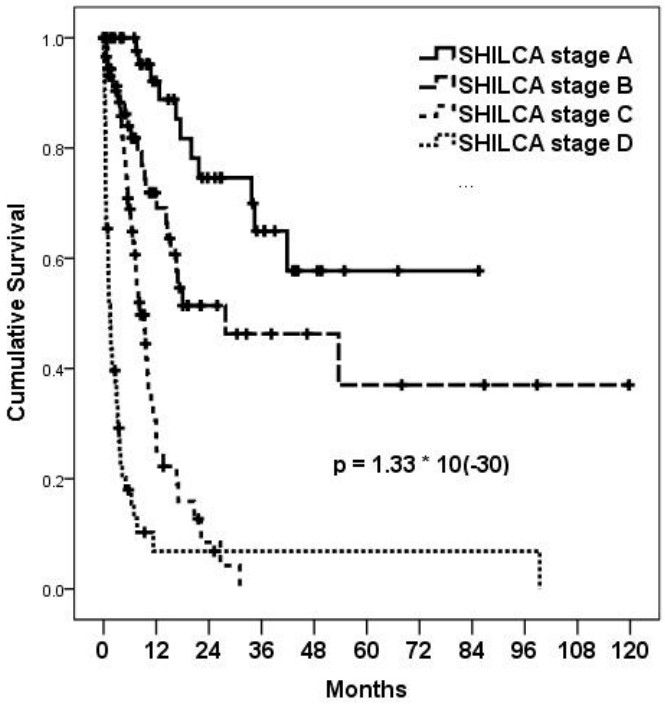
Background: Published staging and survival models of hepatocellular carcinoma (HCC), such as Barcelona-Clínic-Liver-Cancer (BCLC), Cancer-of-the-Liver-Italian-Program (CLIP), or Model-to-Estimate-Survival-in-Ambulatory-Patients-with-HCC (MESIAH) have been shown to predict survival in HIV-negative patients. They have not yet been validated in HIV-infected patients with HCC. Furthermore, HIV viral load as well as performance status have both been shown to independently predict survival of HCC in these patients. This study aimed at developing a model to predict survival of HCC in HIV-infected patients that incorporates these two variables.

Methodology: Using Cox proportional hazard analysis in 256 HIV-infected patients with HCC, a multivariable model identified all baseline variables that independently predicted survival. The SHILCA score was constructed by adding the value of each such variable multiplied by its beta of the Cox analysis. The SHILCA scores of the population were divided into 4 quartiles with increasing scores to define the 4 SHILCA stages A-B-C-D.

Results: Multi-variable Cox analysis identified the following 7 variables to independently predict survival: $\log_{10}$ HIV RNA, performance status, age, tumor size, metastases, albumin, and $\log_{10}$ alfa-fetoprotein. The SHILCA score had a median of 2.74 with a range of 0.71 - 5.89. Median survival was 12.0 months overall, and for SHILCA stage A undefined due to <50% deaths; stage B, 27.8 months, stage C, 8.2 months, and stage D, 1.5 months ($p=1.33*10^{-30}$, log rank). Actuarial survival at 1 year was stage A, 92%; stage B, 72%; stage C, 28%; and stage D, 7%. The SHILCA score (Cox chi-square, 137.2; C-statistic, 0.79) predicted survival better than MESIAH (Cox chi-square, 106.7; C-statistic, 0.76), CLIP (Cox chi-square, 92.7; C-statistic, 0.73), and BCLC (Cox chi-square, 43.4; C-statistic, 0.68).

Conclusions: The SHILCA score and staging model that includes HIV viral load, performance status and 5 other baseline variables, can predict survival of HCC in HIV-infected patients with a high degree of accuracy.



703 Different Immunologic and Virologic Contexts for HIV-Associated Lymphoma in the CNICS Cohort

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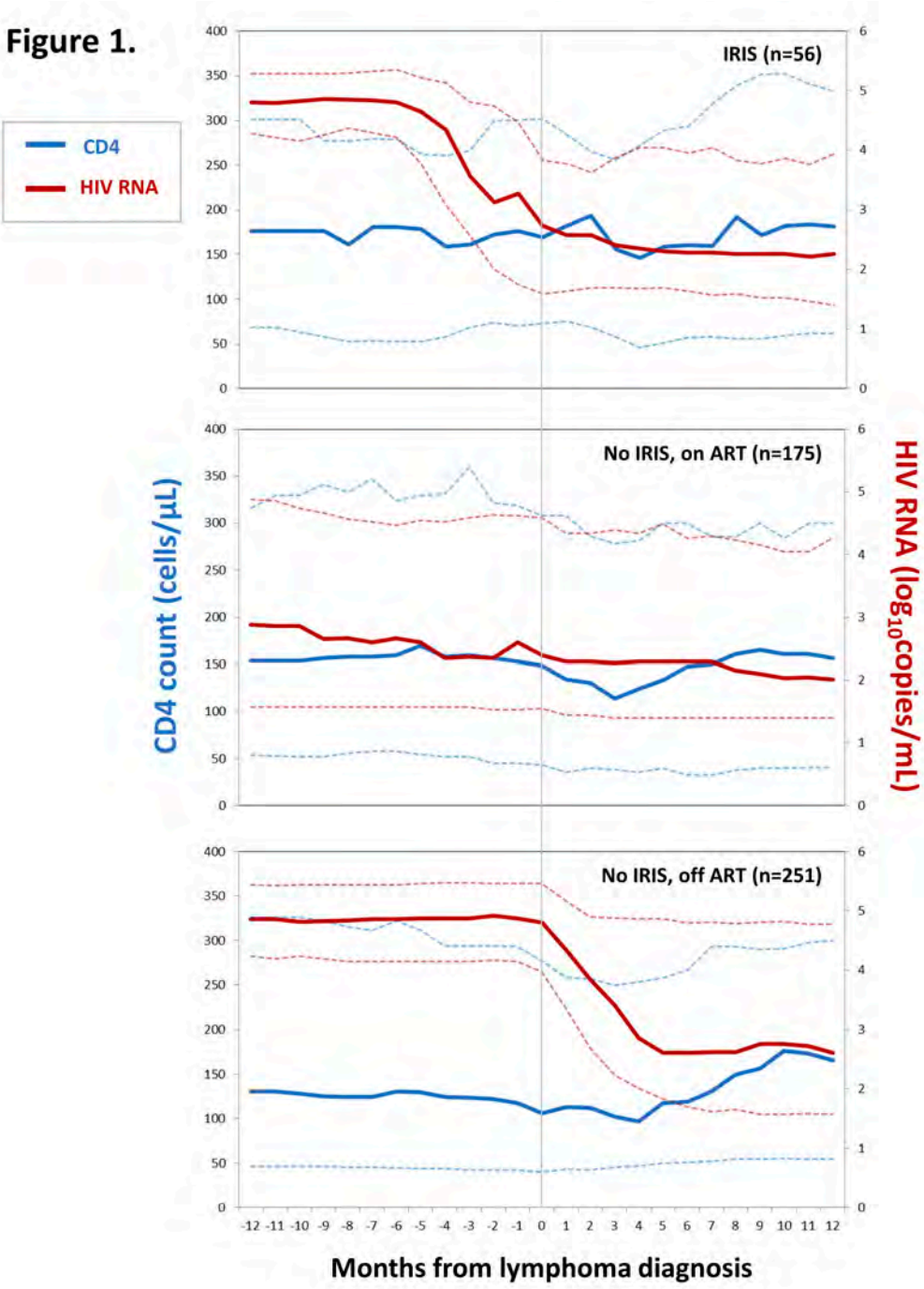
Background: Pathobiology of HIV-associated lymphoma may be changing in the era of effective antiretroviral therapy (ART). Lymphoma incidence is increased soon after ART, perhaps due to the immune reconstitution inflammatory syndrome (IRIS).

Methodology: In the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS), we characterized patients with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) between 1996 and 2011 as: (1) on ART ≤6 months with ≥0.5 log10copies/mL reduction in HIV RNA (unmasking lymphoma IRIS); (2) on ART without IRIS; or (3) off ART. CD4 and HIV RNA during the 12 months before and after lymphoma diagnosis, stratified by IRIS and ART status, were assessed using individual patient-level CD4 and HIV RNA curves. Summative curves were derived by plotting median and interquartile values at each monthly time point across all patients within each group.

Results: Of 24,203 HIV-infected individuals enrolled in CNICS, 482 (2%) were diagnosed with lymphoma between 1996 and 2011. Of these, 56 (12%) had unmasking lymphoma IRIS, 175 (36%) were on ART without IRIS, and 251 (52%) were off ART. Unmasking lymphoma IRIS cases were on ART for 2.2 months (IQR 0.9-3.5), and 48% had HIV RNA <400 copies/mL. On ART cases without IRIS were on ART for 20.3 months (IQR 7.5-42.9), and 58% had HIV RNA <400 copies/mL. Median CD4 and HIV RNA during the 12 months before and after lymphoma diagnosis are shown in Figure 1. During the 24-month window, there were 3439 CD4 measures for the entire study population [median 8 (IQR 5-10) per patient], and 3266 HIV RNA measures [median 7 (IQR 5-10) per patient]. IRIS cases demonstrated marked reductions in HIV RNA after ART in the months before lymphoma diagnosis, without significant CD4 increases. In the 12 months after lymphoma diagnosis, IRIS cases demonstrated modest CD4 increases. On ART cases without IRIS demonstrated modest CD4 increases and reductions in HIV RNA after lymphoma diagnosis. Off ART cases demonstrated robust CD4 increases and reductions in HIV RNA after lymphoma diagnosis, resulting from ART initiation within six months in 198 of 251 (79%) patients.

Conclusions: In the ART era, HIV-associated lymphoma develops in different immunologic and virologic contexts. The extent to which these differences influence histology, biology, and clinical outcomes remains unclear. Attenuated CD4 increases soon after ART initiation, despite HIV RNA suppression, might suggest developing lymphoma.

Figure 1.



Session P-02 Poster Session
Tuesday March 4, 2014, 2:30 PM–4:00 PM Exhibit Hall B
Cancer: Natural History and Epidemiology

704 Risk of Cancer Among HIV Patients Compared To the Background Population: Impact of Smoking and HIV

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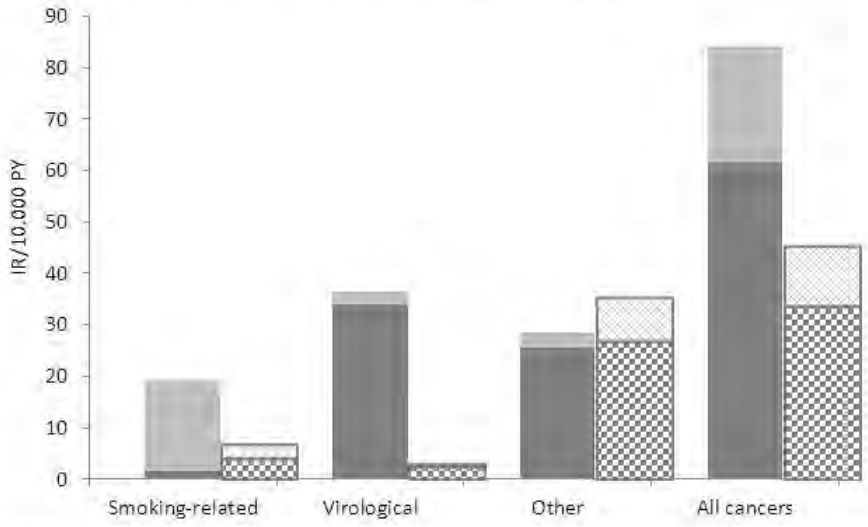
Background: The relative impact of immune deficiency and lifestyle related factors on risk of cancer in the HIV infected population is controversial. We aimed to estimate the population attributable fractions (PAFs) of cancer associated with smoking, immune deficiency and with being HIV-infected.

Methodology: In a Danish, nationwide, population-based cohort study, 1995-2011, incidences of cancer were compared between the HIV-infected population and a matched population-based cohort. Analyses were stratified on cancer category (smoking-related, virological or other), smoking status and nadir CD4/duration of CD4<200 cells/µL. We used Poisson regression to estimate incidence rate ratios (IRR). PAFs associated with HIV were calculated by comparing HIV-infected with HIV-uninfected non-smokers.

Results: A total of 3,503 HIV patients and 12,979 population controls were followed for 18,679 and 55,957 person-years. HIV patients were on antiretroviral therapy during 92% of the observation time. Median CD4 at study inclusion was 450 cells/µL (IQR 310-630). Smoking-related and virological cancers accounted for 23% and 43% of cancers in the HIV-infected population (Figure 1). The IRR (95% CI) of smoking-related, virological and other cancers among HIV patients compared to controls were 2.8 (1.6-4.9), 11.5 (6.5-20.5) and 1.0 (0.7-1.3), respectively. Among non-smoking HIV patients compared to non-smoking controls there was increased risk of virogical cancer (17.0 (6.02-47.9)), but the risk of non-virological cancers was not elevated (1.2 (0.7-2.1)).The PAFs associated with being HIV infected were 56% for all cancers and 94% for virological cancers. The PAF associated with smoking was 27% for all cancers and 91% for smoking-related cancers. The risk of lung cancer was increased among HIV patients with nadir CD4 <200 cells/µL (IRR (95%CI) 3.54 (1.00-12.59)), but was not associated with duration of CD4 <200 cells/µL (1.07 per year (0.87-1.32)). For non-virological cancers that are not strongly related to smoking the PAF associated with immune deficiency was 0%.

Conclusions: In a well-treated HIV infected population the risk of cancer is increased approximately two-fold compared to the background population. In absence of smoking the increase in risk is confined to virological cancers, whereas the risk of other cancers does not differ between HIV infected and uninfected individuals and does not seem to be associated with immune deficiency.

Figure 1. Incidence of cancers in HIV infected individuals compared to the background population: Impact of HIV and smoking



The bars show the total incidence rates of cancers in the HIV infected population and the background population cohort (dotted). The light colour indicates the incidence rate of cancer associated with smoking. The difference between the dark full and the dark dotted bars indicate the incidence of cancer associated with being HIV infected.
Cancer categories: Smoking-related: lung, head and neck, oesophagus and bladder cancer. Virological: lymphoma, Kaposi sarcoma, hepatocellular carcinoma, cervical, anal and penile cancer. Other: all other cancers, excluding non-melanoma skin cancer. The incidence of cancer associated with smoking is calculated as total incidence x PAF associated with smoking.

705 Cancer Stage at Diagnosis in HIV-Infected Individuals and Transplant Recipients

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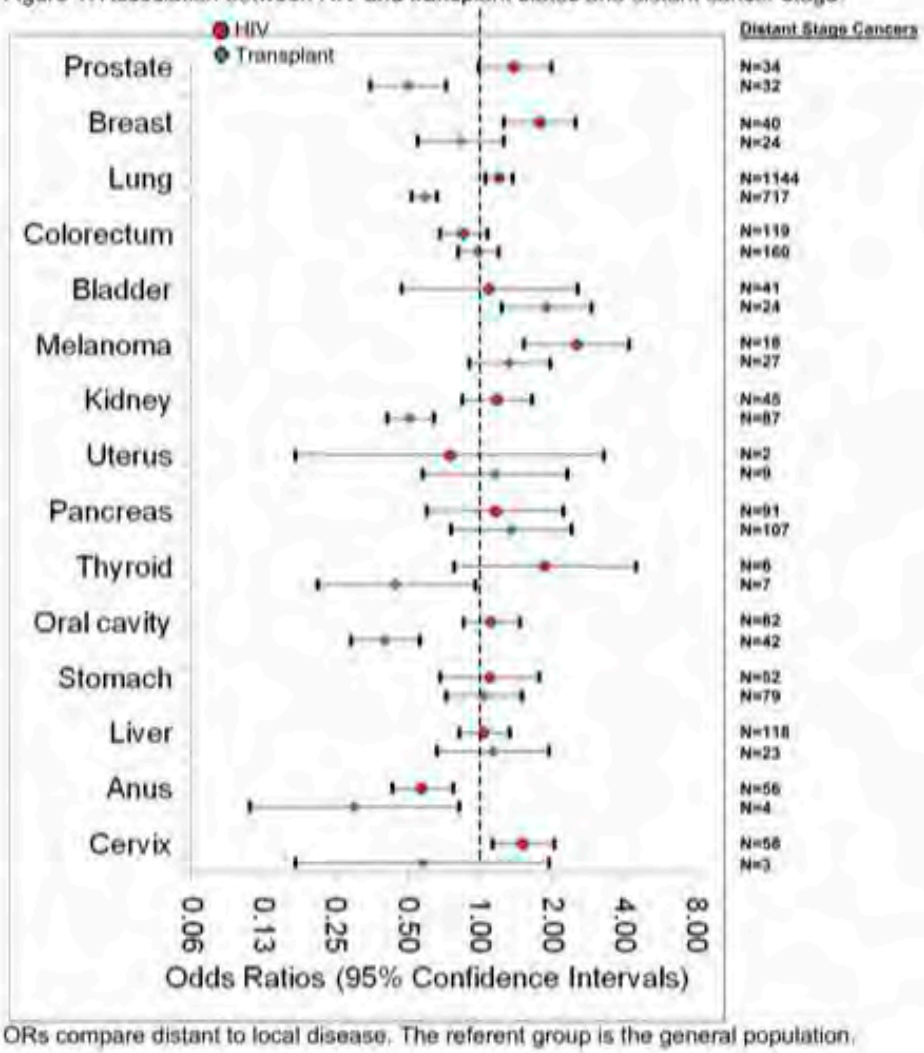
Background: Cancer risk is elevated with HIV infection; however, it is unknown whether immune suppression results in more aggressive, advanced stage cancers. As both tumor biology and delayed utilization of health care may lead to late stage of diagnosis among HIV-infected individuals, we compared cancer stage in HIV-infected individuals to solid organ transplant recipients, an immune suppressed population with more frequent utilization of care.

Methodology: We used data on all cases of 15 cancer sites occurring during 1996-2010 in two U.S. registry linkage studies: the HIV/AIDS Cancer Match (HACM) and the Transplant Cancer Match (TCM), which linked cancer registries to HIV and transplant registries, respectively. Cancer registries provided data on Surveillance, Epidemiology and End Results (SEER) summary stage at diagnosis. Odds ratios (ORs) for distant (vs. local) disease were estimated comparing HIV and transplant populations to the general population in separate logistic regression models, adjusted for age, sex, race, registry and calendar year.

Results: In the HACM Study, 9,362 of 4.7 million cancer cases occurred in HIV-infected individuals and in the TCM Study, 8,225 of 9.7 million cancer cases occurred in transplant recipients. Compared to cancer cases in the general population, HIV-infected individuals had more distant stage breast (OR=1.78), lung (OR=1.20), prostate (OR=1.39) and cervical cancers (OR=1.51), and melanoma (OR=2.53), and fewer cases of distant stage anal cancer (OR=0.57) (Figure 1). In contrast, compared to the general population, transplant recipients had fewer distant stage prostate (OR=0.50) and lung (OR=0.59) cancers, and no difference in stage of cervical cancer (OR=0.58) or melanoma (OR=1.33). Similar to HIV-infected individuals, transplant recipients had fewer distant stage anal cancers (OR=0.30).

Figure 1. Association between HIV and transplant status and distant cancer stage.



ORs compare distant to local disease. The referent group is the general population.

Conclusions: Prostate, lung, breast, and cervical cancers and melanomas diagnosed in HIV-infected individuals were more likely to be distant stage than in the general population. In contrast among transplant recipients, none of these cancer sites was more likely to be distant stage relative to the general population. This suggests that the increased stage observed in people with HIV is likely driven by delayed diagnosis due to under-utilization of care, particularly for screen-detectable cancers, and is unlikely to be due to immune suppression increasing cancer progression.

706 Cancer Incidence in a Nationwide HIV/AIDS Patient Cohort in Taiwan in 1998-2009

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Background: While there is sufficient information on the incidence, burden and spectrum of cancers associated with HIV in US, Europe and Australia, relatively sparse data is available from other world regions. Taiwan with a population of about 23.4 million has an HIV prevalence of approximately, 0.09%. The aims of this study were to investigate cancer incidence and survival among HIV/AIDS patients in Taiwan and compare their incidence to that of the general population and also to compare the HIV cancer spectrum in Taiwan with other world regions.

Methodology: An HIV/AIDS cohort was established using Taiwan's National Health Insurance Research Database (NHIRD). Standardized incidence rates (SIRs) were obtained using a control cohort database consisting of 1.8 million people from the general population. In the HIV/AIDS cohort, the start date for the calculation of person-years was the date of HIV diagnosis, and the end date was December 31, 2009. Kaplan-Meier and log rank tests were used for survival analysis.

Results: From 1998 to 2009, a total of 831 male and 127 female HIV/AIDS patients were diagnosed with cancer among 13,804 male and 1,619 female HIV/AIDS patients (59,772 person-years for males and 7,733 person-years for females). Non-Hodgkin lymphoma (n=193; SIR=6.04) was the most common AIDS Defining Cancer (ADC) in males; while cervical cancer was the most common ADC in females (n=49; person-years; SIR=10.15). Kaposi's sarcoma was also relatively common in male HIV/AIDS patients (n=187; SIR=1921.84). Common sites of Non-ADCs included the oral cavity (SIR=7.44), nasopharynx (SIR=6.52), colon (SIR=6.36), anus or anal canal (SIR=11.18), and liver (SIR=2.91). Survival after cancer diagnosis was longer in women than in men.

Conclusions: This is the first population-based cohort study investigating cancer incidence and survival in HIV/AIDS patients in South East Asia. Our study highlights the utility of insurance databases in linkage studies to address epidemiological questions of concurrent co-morbidities. In contrast to reports from other Asian regions, such as India, KS is frequently diagnosed in HIV infected individuals in Taiwan, as well as cancer and NHL the two other ADCs. Our results also identify a spectrum of Non-AIDS defining cancers, including oral, nasopharyngeal, anal, and liver cancer, for which risks are elevated and that are attributable to HIV and other infections.

707 Excess Burden of Cancer Among HIV-Infected Persons in the United States

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Background: Nearly 1 million people in the U.S. have diagnosed HIV infection and therefore increased cancer risk, but total cancer burden in the U.S. HIV population has not been quantified. We estimated the total number of incident cancers, and the number in excess of expected, among HIV-infected persons in the U.S. during 2010.

Methodology: To estimate cancer rates among HIV-infected persons, we applied Poisson models to linked HIV and cancer registry data from 6 states in the HIV/AIDS Cancer Match Study. We used data from the Surveillance, Epidemiology, and End Results (SEER) program for general population (expected) cancer rates. We applied these rates to CDC estimates of people living with diagnosed HIV infection, stratified by age, sex, race/ethnicity, HIV risk group, and AIDS-relative time, to calculate total and excess (i.e., total - expected) cancer cases in 2010.

Results: An estimated 7,764 cancers occurred among HIV-infected people, 3,915 (50.4%) in excess of expected. The most common cancer was non-Hodgkin lymphoma (N=1,645, 87.7% excess; Table 1), and nearly all cases were excess for Kaposi sarcoma (N=912, 99.8% excess), anal cancer (N=764, 97.4% excess), and Hodgkin lymphoma (N=317, 90.9% excess). Fewer than expected cases occurred for colorectal cancer (N=357, 5.8% deficit), prostate cancer (N=574, 40.7% deficit), and female breast cancer (N=177, 41.6% deficit). Most cancers occurred among males (N=6,237; 51.5% excess), specifically men who have sex with men (N=4,545; 55.9% excess). By age, the largest excess was among ages 40-49 (N=1,610), though the largest proportional excess was among ages 15-29 (92.7%). There was no excess among the oldest group (age ≥70). While most cancers occurred among non-Hispanic blacks (N=3,293) and whites (N=2,870), a larger proportional excess was among Hispanics (64.4%).

Conclusions: HIV infection in the U.S. is associated with a substantial excess burden of cancer, which largely occurs among men and individuals under 50. Despite major improvements in HIV treatment, approximately half of almost 8,000 cancer cases among HIV-infected persons in 2010 were excess cases.

Table 1: Estimated total and excess cancer cases among HIV-infected persons in the U.S. in 2010

Cancer site	Total (N)	Expected (N)	Excess or deficit (N)	Excess or deficit (%)
Non-Hodgkin lymphoma	1645	203	1443	87.7
Kaposi sarcoma	912	2	910	99.8
Lung	837	401	435	52.0
Anus	764	20	745	97.4
Prostate	574	969	-394	-40.7
Liver	389	106	282	72.7
Colorectum	357	379	-22	-5.8
Hodgkin lymphoma	317	29	289	90.9
Female breast	177	303	-126	-41.6
Miscellaneous	1792	1438	353	19.7

The percentage excess is calculated as excess/total; the percentage deficit is calculated as deficit/expected. Numbers may not sum exactly due to rounding.

Session P-04 Poster Session
Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**
Kaposi Sarcoma, PEL, and KSHV

708 The Effect of Protease Inhibitor Use On Kaposi Sarcoma Incidence in a cART-Experienced Cohort

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Background: The incidence of Kaposi Sarcoma (KS) has markedly decreased in countries with widespread availability of combined antiretroviral therapy (cART). Protease Inhibitors, and nelfinavir mesylate, in particular, have been shown to confer broad antineoplastic and antiviral activity in in vitro and pre-clinical in vivo studies. It has been hypothesized that protease inhibitors confer a specific reduction in KS risk independent of cART-related immune reconstitution, compared to non-nucleoside reverse transcriptase inhibitors (NNRTI). However, no large confirmatory clinical studies have been conducted.

Methodology: We performed a retrospective cohort study utilizing data from the Veterans Affairs HIV Clinical Case Registry (VA-CCR) from 1985-2010 of all male veterans who had ever received cART. KS cases were identified using ICD-9 codes. We excluded individuals without identifiable CD4 or viral load measurement, and <90 days of follow-up. Prevalent KS cases, defined as those occurring prior to or within 90 days of cART initiation, were excluded. Data for each cART class, defined as: PIs, excluding Nelfinavir (PI), Nelfinavir (NFV), and (NNRTIs) were used to calculate time-updated ratios of the time on each class of cART divided by the total time on cART treatment ("percent of time" on cART). Separate multivariable Poisson regression models adjusted for demographic, immunologic, and time-varying HIV viral load covariates were performed for each cART class "percent of time" variable.

Results: A total of 25,529 HIV+ male Veterans who had ever received cART were identified in the cohort, with 544 incident cases of KS. The overall KS incidence in the cohort was 339.7 (312.4-369.5) /105 person-years (py). The incidence of KS decreased from 458.4 (405.5-518.7) /105 py for those diagnosed in the pre-cART era (pre 1996) to 165.1 (127.4-214.1)/105 py in the late cART era (2002-2010). In multivariable models (table 1), percent of time on PI was associated with a 4% decreased risk of KS per 10% increase in PI use (IRR 0.96, p-value 0.001). However, NFV was associated with a 4% increased risk of KS per 10% increase in NFV use (IRR 1.04, p-value 0.02), and NNRTIs were associated with a small decreased risk of KS, but was not significant (IRR 0.98, p-value 0.11).

Conclusions: In this cohort of HIV+ male Veterans who had ever received cART, PI utilization was associated with a decreased risk of KS. PI utilization may independently decrease KS risk beyond the effects of PIs on immune reconstitution.

The Effect of cART Drug Class Use on Kaposi Sarcoma Incidence in a cART-Experienced Cohort

	Crude IRR (95% CI)	p-value	Adjusted IRRb (95% CI)	p-value
CART use (per 10% change in use)[a]				
% PI - excluding nelfinavir	0.98 (0.96-1.01)	0.31	0.96 (0.93-0.98)	0.001
% Nelfinavir	1.04 (1.01-1.06)	0.01	1.04 (1.01-1.07)	0.02
% NNRTI	0.94 (0.92-0.97)	<0.0001	0.98 (0.95-1.01)	0.11

[a] Percent use represents the percentage of total CART time spent on each class of medication
[b] Each Model was adjusted for: Follow-up time, Age at diagnosis, Race Ethnicity, Era of HIV diagnosis, Use of IV drugs, Deyo Comorbidity Score, Nadir CD4 count at time of cART initiation, Most recent CD4 count at time , and percent undetectable HIV viral load at event/censor

709 Guidelines On Kaposi's Sarcoma Treatment: Results From Two Cochrane Systematic Reviews

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Background: Kaposi's sarcoma (KS) is the most frequently observed HIV-associated malignancy in resource-poor settings. Widespread use of antiretroviral therapy (ART) has reduced KS incidence, but KS incidence remains high in countries where HIV is prevalent, and is still associated with poor survival. The World Health Organization (WHO) does not have guidelines for KS treatment. To that end, we performed two systematic Cochrane reviews of KS treatment in adults, for mild/moderate and severe disease, to aid WHO guideline development.

Methodology: Two systematic Cochrane reviews were undertaken using standard Cochrane HIV/AIDS Review Group search criteria. Randomized controlled trials (RCTs) and observational studies were included, excluding case reports. Adults were divided into two separate reviews a) mild/moderate disease, as defined by ACTG stage T0 disease and b) severe KS, as defined by stage T1 disease. Primary outcomes were mortality and clinical response; secondary outcomes included time to response, KS IRIS, adverse events, and quality of life.

Results: A total of 3,615 relevant abstracts were reviewed. Ultimately, 5 studies (3 RCTs, 2 cohorts) were included in treatment for mild/moderate KS, and 9 studies (6 RCTs, 3 cohorts) were included for severe KS. For adults with mild/moderate KS, there was no survival advantage to using a PI-based ART regimen as compared to a non-PI based regimen. Comparing chemotherapy plus ART to ART alone for mild/moderate KS, there were no studies designed

or powered to address outcomes. The 2 RCTs and 2 cohorts that included a small number of patients with mild/moderate disease found no difference in survival or treatment response comparing ART plus any type of chemotherapy to ART alone. For adults with severe KS, comparing ABV (bleomycin, vincristine, doxorubicin) plus ART to ART alone, no mortality benefit was observed, but overall clinical response (risk ratio 1.78; 95% CI 1.16 to 2.72) and reduced disease progression (RR 0.1; 95%CI 0.01 to 0.75) favored ABV plus ART. Comparing liposomal anthracyclines plus ART to ART alone, clinical response favored liposomal anthracyclines but was not statistically significant (of note two large RCTs had to be excluded due to a mixture of KS stages).

Conclusions: For adults with severe KS, chemotherapy in addition to ART as compared to ART alone provides a clinical response benefit and prevents progression of disease. For adults with mild/moderate KS, since no study was designed or powered to address this question, we are lacking definitive evidence of whether there is a survival or clinical response advantage of adding chemotherapy to ART. These Cochrane reviews will inform guidelines on KS treatment, through forthcoming WHO Guidelines on Skin and Oral Conditions in HIV positive Adults and Children.

710 Randomized Trial of Protease Inhibitor-Based Antiretroviral Therapy for Kaposi Sarcoma in Africa

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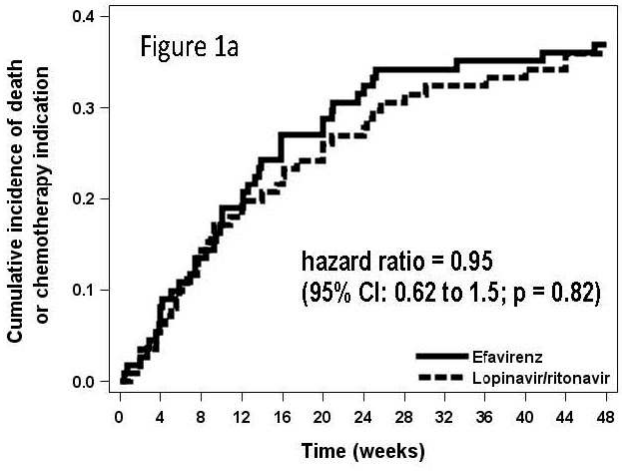
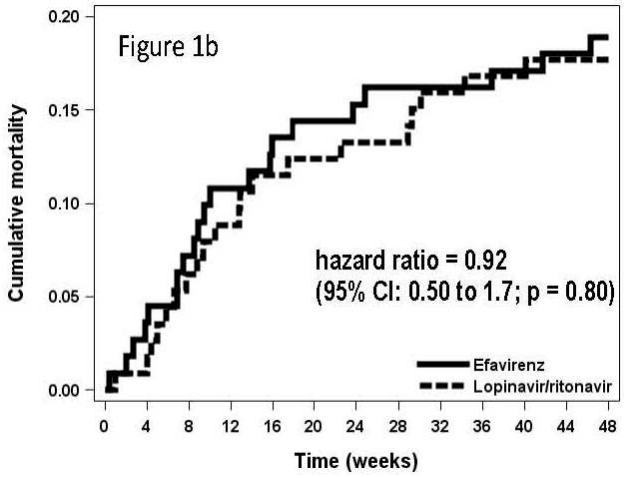
Background: Combination antiretroviral therapy (ART) -- including protease inhibitor (PI)-containing regimens -- has long been known to decrease lesion burden in some patients with Kaposi sarcoma (KS), but exactly which ART component/mechanism is responsible is unknown. Among the potential explanations, PIs have been speculated to have direct anti-KS effects in humans based on their anti-angiogenesis effects *in vitro*. We investigated the hypothesis that PI-based ART is clinically superior to PI-sparing ART for the treatment of KS in sub-Saharan Africa, a region where initial ART choice is critical given scarcity of chemotherapy.

Methodology: We enrolled ART-naïve HIV-infected adults with KS in Uganda who had no urgent indications for chemotherapy/radiotherapy. Subjects were randomized to either PI-based (lopinavir/ritonavir plus emtricitabine/tenofovir) or non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART (efavirenz plus emtricitabine/tenofovir) and observed every 4 weeks for 48 weeks for an indication for chemotherapy and overall survival. Chemotherapy was given free for those who developed an indication post-randomization.

Results: Among 224 subjects randomized (113 PI/111 NNRTI) in this completed trial, 44% were women and median pre-treatment values were: 34 years old, 119 CD4+ T-cells/mm^3 and 222,323 copies plasma HIV RNA/ml. Extent of KS was heterogeneous: 7.1% had oral lesions only, 24% had ≥ 50 skin lesions, and 71% were T1. ART was well tolerated with only 7.1% in the PI arm and 8.1% in the NNRTI arm discontinuing their original drug class. There was no loss to follow-up from the perspective of vital status, and only 3 alive subjects were unavailable for clinical assessment at 48 weeks. A total of 36% of subjects experienced the primary composite outcome (indication for chemotherapy or death) by 48 weeks, but we found no evidence in intent-to-treat analysis for a difference between treatment groups (Fig. 1a). Likewise, for mortality alone, 18% of subjects died by 48 weeks, but we found no treatment differences (Fig. 1b).

Conclusions: Despite biological plausibility, we found no evidence that PI-containing ART was superior to NNRTI-based ART in terms of survival or need for chemotherapy amongst patients with KS who did not initially have urgent chemotherapy indications. The high incidence of subsequent indications for chemotherapy and/or death indicates that ART alone for all comers with KS in Africa is suboptimal and additional interventions are needed.





711 Kaposi Sarcoma in the Era of Combination Antiretroviral Therapy

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Background: Combined antiretroviral therapy (cART) has reduced the risk of developing Kaposi Sarcoma (KS), however, the residual burden of disease remains unclear. We analyzed the data of a large prospective European multi-cohort project, the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) to examine risk factors at enrolment and KS incidence over 15 years of cART availability.

Methodology: We included HIV-infected patients aged >16 years who enrolled in a COHERE cohort after 1.1.1996. We defined cART as a regimen of at least 3 drugs from at least 2 drug classes. Incidence of KS was estimated for patients on cART and not on cART. We calculated incidence rates and ran Cox regression models adjusted for calendar period, age, exposure group, CD4 cell counts, HIV viral load and CDC stage at enrolment (model 1), and origin (model 2). cART was treated as a time-dependent variable. KS cases diagnosed within 30 days after cART start were classified as not on cART.

Results: We included 156,667 patients from 24 cohorts (median age 35 years, 73% male, median CD4 cell count at enrolment 338 cells/µL). 25,564 patients never started any antiretroviral therapy; 23,342 patients started mono- or dual-therapy, which was followed by cART in 17,703 patients; and 107,761 patients started cART being treatment naïve. During 877,920 person-years (pys) 2,090 patients developed KS. The incidence was 393/100,000 pys (95% CI 366-421) among patients not receiving cART and 123/100,000 pys (95% CI 115-133) among patients on cART for more than 6 months (HR 0.21, 95% CI 0.18-0.25; model 1). In the first 6 months of cART, the incidence was 976/100,000 pys (95% CI 89-1070). The risk of developing KS was higher among patients aged > 50 years, among men, men who have sex with men, and patients with low CD4 counts and high HIV viral loads at enrolment (Table 1). However, there was no evidence for an effect of CDC stage at enrolment on the risk of developing KS. KS incidence decreased over calendar years. Model 2 confirms these results and indicates a higher risk for patients of African origin.

Conclusions: In the era of cART the incidence of KS remains high during the first months on cART, possibly because of IRIS. Male patients, particularly men who have sex with men, patients of African origin or aged above 50 years are important risk groups. Patients enrolling into the cohort with uncontrolled HIV viral replication and advanced immunosuppression are also at increased risk of developing KS.

Table 1: Multivariate Cox-regression of the risk of Kaposi sarcoma (KS) in the COHERE collaboration

		Model 1 (1422 KS/103,411 patients)			Model 2 (763 KS/56,837 patients)		
		HR	(95% CI)	p-value	HR	(95% CI)	p-value
Treatment	No treatment	1.00		<0.0001	1.00		<0.0001
	Mono/dual therapy	0.54	(0.41-0.7)		0.64	(0.45-0.91)	
	cART (30-180 days)	1.32	(1.13-1.54)		1.52	(1.23-1.87)	
	cART (>180 days)	0.21	(0.18-0.25)		0.24	(0.19-0.31)	
Year of enrolment	1996-2000	1.37	(1.16-1.62)	0.001	1.25	(1-1.56)	0.13
	2001-2005	1.20	(1.02-1.4)		1.18	(0.96-1.43)	
	2006-2011	1.00			1.00		
Exposure group	Homo/bisexual men	3.05	(2.66-3.5)	<0.0001	3.74	(3.07-4.55)	<0.0001
	Other men	1.00			1.00		
	Women	0.57	(0.46-0.71)		0.51	(0.39-0.67)	
Age (years)*	16-30	1.00		<0.0001	1.00		0.009
	30-40	1.12	(0.97-1.29)		1.14	(0.94-1.38)	
	40-50	1.23	(1.05-1.45)		1.11	(0.89-1.39)	
	>50	1.65	(1.37-1.98)		1.54	(1.2-1.98)	
CD4 count (cells/µl)*	<49	2.68	(2.19-3.28)	<0.0001	2.46	(1.87-3.23)	<0.0001
	50-99	1.99	(1.58-2.51)		1.66	(1.2-2.29)	
	100-199	1.41	(1.15-1.73)		1.12	(0.84-1.49)	
	200-349	1.19	(1-1.4)		1.05	(0.83-1.31)	
	350-499	1.00			1.00		
	500-599	0.91	(0.74-1.12)		0.83	(0.62-1.11)	
	>600	0.77	(0.64-0.92)		0.84	(0.66-1.07)	
HIV RNA (copies/mL)*	>=100000	3.21	(2.04-5.05)	<0.0001	3.56	(1.88-6.76)	<0.0001
	10'000-99'999	2.15	(1.37-3.38)		2.52	(1.34-4.76)	
	501-9999	1.18	(0.74-1.87)		1.15	(0.59-2.23)	
	>=500	1.00			1.00		
CDC stage*	A/B	0.96	(0.81-1.12)	0.58	0.93	(0.75-1.14)	0.48
	C	1.00			1.00		
Origin	European				1.00		<0.0001
	African				2.62	(2.08-3.3)	
	Other				1.23	(0.98-1.53)	

* Values assessed at the time of enrolment
cART: Combination antiretroviral therapy

712 Vitamin D Insufficiency in AIDS-Associated Kaposi Sarcoma in Zimbabwe

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Background: Low 25-hydroxyvitamin D (25[OH]D) has been associated with progression of some malignancies. The activated form of vitamin D may slow tumor growth in vitro, and topical vitamin D may slow cutaneous KS in persons with localized KS. We hypothesized a high prevalence of 25(OH)D deficiency among persons with AIDS-KS in Zimbabwe, and that baseline 25(OH)D would be associated with AIDS-KS progression.

Methodology: 90 antiretroviral naive participants were enrolled in a prospective study of antiretroviral therapy for treatment of AIDS-KS in Harare, Zimbabwe. Co-formulated abacavir, lamivudine, and zidovudine was initiated in all subjects. Chemotherapy or radiation was provided at the discretion of the provider. Subjects were followed for 96 weeks. 25(OH)D was measured from stored plasma samples at study entry and dichotomized as insufficient (<75 nmol/L) or adequate (≥75 nmol/L). Relationship between 25(OH)D and HIV or AIDS-KS clinical response was described by Spearman correlation coefficient for continuous variables and odds ratios and 95% confidence intervals (CI) for dichotomous variables.

Results: Samples were available from 85 participants. Median 25(OH)D was 73 (56-89) nmol/L; 45 (53%) had insufficient levels. 25(OH)D insufficiency was associated with higher baseline plasma HIV-1 RNA (4.7 [4.3-5.0] versus 4.5 [3.9-4.9] log10 copies/mL; p=0.04), and baseline 25(OH)D correlated with log change in plasma HIV-1 RNA (r=0.34, p=0.009). No correlation was detected between baseline 25(OH)D and change in CD4+ count (r=0.05, p=0.64), plasma herpeshuman virus (HHV)-8 DNA (r=0.06, p=0.60), or peripheral blood mononuclear cell HHV-8 DNA (r=-0.12, p=0.26). Similarly, baseline and change in CD4+ count, plasma or peripheral blood mononuclear cell HHV-8 viral load were not significantly different between subjects with adequate or insufficient 25(OH)D (all p≥0.4). Adequate 25(OH) D was not significantly associated with KS clinical response (OR 0.6; CI 0.2, 1.9; p=0.40), KS-IRIS occurrence (0.4; 0.2, 1.9; p=0.40), chemotherapy initiation (1.2; 0.5, 2.8; p=0.68), radiation initiation (0.6; 0.2, 1.5; p=0.24), or death (0.5; 0.1, 1.9; p=0.30). Odds ratios and significance remained unchanged after adjustment for baseline HIV-1 viral load and CD4 count.

Conclusions: Vitamin D insufficiency was common among Zimbabweans with AIDS-KS. Although we detected a relationship between 25(OH)D levels and plasma HIV-1 RNA responses, baseline 25(OH)D was not associated with other virological, immunological or clinical outcomes during treatment of AIDS-KS. This study does not support a role for vitamin D supplementation in AIDS-KS treatment.

713 Primary Effusion Lymphoma and HIV Infection: 51 Patients From a Single Institution

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Background: Primary Effusion Lymphoma (PEL) is a rare B-cell non-Hodgkin lymphoma (NHL) that is almost exclusively observed in HIV-infected patients (pts). It accounts for approximately 4% of all HIV-NHL, with a stable incidence in combined antiretroviral therapy (cART) era. Lymphoma cells are always infected with HHV-8 and in most cases coinfected with EBV. In its classic presentation PEL is characterized by body cavity effusions with or without mass lesions. A variant with extracavitory localisation has more recently been described. We report a large single institution series of 51 pts with PEL in the cART era.

Methodology: All consecutive HIV-infected pts with a diagnosis of PEL since 1996 were included in the study. The main objective was to describe the characteristics and the outcome of pts with classic and extracavitary variant. Survival was estimated using Kaplan-Meier method, and was tested using the log-rank test.

Results: 51 pts were included between Jan 1996 and May 2013; 47 male (92%), median age 45 years. At PEL diagnosis, the median duration of HIV infection was 8 years (IQR, 1.4-15.6), 33 pts had prior AIDS and 35 pts received cART for a median of 40 months. The median CD4 cell count was 204 x 106/L (IQR, 90-370), and 25 pts (49%) had undetectable HIV-RNA. An other HHV-8-associated disease was observed in 30 pts (25 Kaposi sarcoma, 17 multicentric Castleman disease). 34 pts presented classic variant and 17 extracavitary variant. No major difference was observed between the 2 groups in terms of demographic, HIV and lymphoma characteristics. In classic PEL, pleural, peritoneal and pericardial involvement were present in 27, 17 and 12 pts, respectively. Extracavitary PEL was exclusively nodal in 6 patients and involved various organs in the others : GI tract (4), spleen (3), CNS (3), BM (2), liver (2), skin (2), testis, bone, sinus and muscle (1 each). 33 tumors were coinfected with EBV.

All but 2 pts received chemotherapy, including high dose methotrexate in 13 pts. Complete remission was achieved in 28 pts (56%), without difference between the classic and the extracavitary groups (62% vs 41%). After a median follow-up of 10 years, 34 pts have died (29 with lymphoma), providing a median overall survival (OS) of 10.2 months, without difference between the 2 variant groups (P=0.78). The 5-year Overall Survival rate was 42% [95%CI, 27-55].

Conclusions: Based on a large single institution series of 51 PEL, characteristics of classic and extracavitary variants seems to be very close. Despite cART use, control of HIV infection, and treatment with intensive chemotherapy, similar to that used in HIV-uninfected pts, the prognosis remains poor with a median survival below 1 year. However some pts have long-term survival, and the 5-year OS of 42% compares favorably with earlier series.

714 Indoleamine 2, 3-Dioxygenase (IDO) Activity as a Determinant of Kaposi Sarcoma in Africa

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Background: Other than human herpesvirus 8 (HHV-8) and CD4+ T cell lymphopenia, the mechanisms responsible for Kaposi's sarcoma (KS) are poorly understood. This is the case both in resource rich areas and in resource poor hyperendemic areas such as sub-Saharan Africa. Additional mechanisms must exist in Africa given the relatively low frequency of KS in HIV infected patients despite the high prevalence of both HHV-8 infection and low CD4+ T cell count. One recently explored pathway of HIV pathogenesis involves induction of the enzyme indoleamine 2,3 dioxygenase (IDO) in dendritic cells, which catabolizes tryptophan into kynurenine and several other immunologically active metabolites that suppress T cell proliferation. We investigated whether IDO has a role in KS etiology.

Methodology: 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) clinical trial. Controls without KS were derived from the Uganda Rural AIDS Treatment Outcomes (UARTO) cohort, a consecutive sample of HIV infected adults starting antiretroviral therapy (ART) in southwestern Uganda. All biological tests were performed on pre-ART samples. IDO activity was assessed by the ratio of plasma kynurenine to tryptophan levels (K:T) measured by liquid chromatography tandem mass spectrometry.

Results: We studied 631 subjects: 222 KS cases and 409 non KS controls (Table). Cases had a wide spectrum of mucocutaneous KS ranging from oral lesions only to widespread cutaneous dissemination. In multivariable regression, KS was independently associated with K:T but in a non-linear manner. There was no effect of K:T on KS amongst those in the lower three quartiles, but subjects with the highest quartile of K:T (i.e., highest values) had a 59% reduction in the odds of KS (Table). The relationship between K:T and KS was present at all levels of CD4+ T cell count (p = 0.44 for interaction). KS was also independently associated with lower CD4+ T cell counts, higher plasma HIV RNA levels and men.

Conclusions: Higher IDO activity as evidenced by higher plasma K:T, was protective against the occurrence of KS. This relationship is independent of both plasma HIV RNA level and CD4+ T cell count. The findings are consistent with the hypothesis that lymphocyte proliferation is necessary for the development of KS, which is compatible with the inflammatory nature of KS lesions.

	Participant characteristics		Multivariable logistic regression for KS	
	KS (n=222)	No KS (n=409)	Odds Ratio (95% CI)	*p* value
Sex				
Men	56%	32%	Ref	
Women	44%	68%	0.41 (0.28-0.61)	<0.001
Age in years	34 (28-40)[a]	35 (29-40)	0.79 (0.62-1.01)	0.059
CD4+ T cell count/mm^3				
<50	35%	16%	Ref	
51-100	11%	18%	0.30 (0.16-0.55)	<0.001
101-200	23%	41%	0.33 (0.21-0.54)	<0.001
201-350	18%	21%	0.54 (0.31-0.94)	0.029
>350	13%	3%	2.60 (1.15-5.87)	0.021
HIV RNA, copies/ml				
≤10, 000	2%	10%	Ref	
10,001-50,000	9%	18%	2.61 (0.84-8.08)	0.096
50,001-100,000	13%	18%	4.07 (1.34-12.34)	0.013
100,001-500,000	59%	33%	9.64 (3.35-27.74)	<0.001
>500,000	17%	21%	5.55 (1.80-17.07)	0.003
Kynurenine:Tryptophan (K:T) ratio, by quartile				
0.034-0.089 (lowest)	27%	24%	Ref	
0.090-0.120	28%	23%	1.02 (0.61-1.72)	0.93
0.121-0.179	29%	23%	0.86 (0.51-1.45)	0.58
0.180-1.369 (highest)	16%	30%	0.41 (0.23-0.73)	0.002

[a] median (IQR)

Session P-05 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Cervical Cancer, HPV, and HPV Vaccine

715 Epidemiology and Dynamics of HPV Infection in Romanian Women Infected With HIV in Early Childhood

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Background: Human Papilloma Virus (HPV) is the most common sexually transmitted virus worldwide and the most common cause of cervical cancer. Romania, where cervical cancer screening is not standard of care, has the highest rate of cervical cancer in Europe. Here we evaluate the prevalence and dynamics of HPV infection in a cohort of Romanian women in their early 20s who were parenterally infected with HIV during early childhood.

Methodology: 65 young women with chronic HIV infection and 25 age-matched controls were evaluated for the presence of cervical HPV infection and for cytologic abnormalities. HPV typing was performed using the Linear Array HPV Genotyping Test (Roche). Individuals were screened for other sexually transmitted infections, and HIV data was obtained from patients' charts. Risk factors for HPV infection and socio-demographic information were also obtained. 42 subjects were seen at two or more time-points. Statistical comparisons using standard approaches were made between the HIV infected (HIV+) and uninfected (HIV-) groups at baseline, and between HIV+ individuals with and without HPV infection.

Results: Although the HIV- and HIV+ groups were fairly similar, HIV- individuals had more years of schooling, were less likely to be on social support, and were more likely to use barrier contraception ($p<0.056$). 43% (28/65) of HIV+ and 32% (8/25) of HIV- subjects were infected with HPV, and 21/65 and 6/25 had high risk subtypes respectively. There was no significant difference between HIV+ (14) and HIV- (5) subjects in terms of having HPV infection with more than one strain (p=NS). Using our longitudinal data, we found an incidence rate of 0.69 HPV acquisition events per subject per year, and a rate of 0.52 for high risk subtypes. In individuals sampled more than once, those having maintaining or acquiring a new subtype in follow up were more likely to have a lower nadir CD4 count ($p=0.043$) and a lower current CD4 count ($p=0.010$). In the HIV+ group, of 13 individuals with abnormal cytology at baseline, nine (69.2%) progressed or remained stable while only four regressed.

Conclusions: We describe here HPV infection in a unique group of young women infected with HIV during early childhood, acquiring HPV in the setting of long-term HIV infection. Although HPV prevalence was only slightly higher among the HIV+ group, possibly due to differences barrier contraception use, the decreased ability of HIV infected young women to mount new immune responses predisposed them to HPV progression and Pap smear abnormalities. Given the high rate of HPV acquisition, and progression of abnormal cytology in this cohort, HPV vaccination even at this stage may be useful.

716 Baseline Data of a Phase 3 Trial of the Quadrivalent HPV Vaccine in HIV+ Males and Females: ACTG 5298

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Background: Human papillomavirus (HPV) is the main cause of anogenital and oropharyngeal squamous cell cancer. The prophylactic quadrivalent HPV vaccine (qHPV 6, 11, 16, 18) is indicated for males and females aged 9-26 years. A5298 is an ongoing randomized placebo controlled phase 3 study of the qHPV vaccine to prevent anal HPV infection.

Methodology: Entry Criteria: HIV+ females and males who have sex with males; $\geq$ 27 years old; no history of anogenital or oral cancer; ACTG sites with certified high resolution anoscopy (HRA) providers. Two baseline anal and oral specimens for HPV genotyping by polymerase chain reaction were collected. Anal cytology and HRA with or without biopsies were performed. Half of the females were required to have anal high grade squamous intraepithelial lesions (HSIL) at screening. The chi-square test was used to assess the association between HPV infection and HSIL status at baseline with no adjustment for co-infections. All statistical tests were performed at the 0.05 level without adjustment for multiple comparisons.

Results: 575 participants (ppts) were enrolled (82% male and 18% female). Median age was 47 years. Race/ethnicity was 45% White, 31% Black and 21% Hispanic. Plasma HIV RNA was <50 copies/mL in 84% and median CD4 count was 606 T cells/μL. Any abnormal anal cytology was detected in 61%. High-grade SIL was detected on biopsy in 33%. Anal HPV 6, 11, 16 and 18 was detected in 24%, 13%, 32%, and 18% of ppts respectively. The simultaneous prevalence of 0, 1, 2, 3, 4 qHPV vaccine types was 41%, 38%, 17%, 4%, and 1% respectively. The prevalence of types 31, 33, 45, 52 and 58 ranged from 12% to 24%. Types 16, 18, 31, 45, and 58 were significantly associated with detection of HSIL (p-values <.01). Types 11, 33, 52 were marginally associated with HSIL (p-values .05 to .1). Table 1. In males (n=343), oral infection with HPV 6, 11, 16 and 18 was present in 2%, 2%, 3%, and 2% of ppts respectively, with $\geq$ 1 quadrivalent HPV type detected in 27 (8%) ppts.

Conclusions: In this trial population with well controlled HIV infection, there was a high proportion of abnormal anal cytology, HSIL on anal biopsy, and anal HPV infection. However, less than one-quarter of ppts had more than one anal qHPV type detected, and could theoretically derive protection from the qHPV vaccine. The proportion of oral HPV in this population was low. The investigational nonavalent vaccine (qHPV + 31, 33, 45, 52, and 58) is in late stage clinical development and should offer even broader prevention of anal HSIL.

Table 1: Association of HPV types with HSIL									
HPV type	6	11	16	18	31	33	45	52	58
HSIL (n=163)	23%	17%	44%	26%	29%	21%	21%	28%	33%
No HSIL (n=358)	25%	12%	26%	14%	18%	14%	8%	21%	21%
P value	>0.5	0.08	<0.001	0.001	0.006	0.053	<0.001	0.064	0.004

717 Cervical Abnormalities in HIV-Infected South African Women With High Screening and Referral Rates

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Background: Access to antiretroviral therapy (ART) has improved in South Africa (SA), enabling HIV-infected women to live longer and healthier lives. However, they remain at increased risk of mortality from cervical cancer, the leading cause of cancer-related deaths. This study aims to advance our understanding of the prevalence of screening, cervical dysplasia, and histologic diagnoses from colposcopy and large loop excision of the transformation zone (LLETZ) in a high HIV prevalence region of SA.

Methodology: We performed a retrospective cohort study to determine the prevalence of cervical dysplasia and malignancy among HIV-infected women attending an urban ART clinic in KwaZulu-Natal (KZN), SA over a five-year period (2004-2009). A random sample of eligible women_defined as HIV-infected, >18 years old, and attending the clinic for > 3 months--enrolled in HIV-care was included from each study year. Data were abstracted from electronic records and paper charts, including date of birth, CD4+ count, viral load (VL), initial Pap smear results, colposcopy and LLETZ results. Per clinic guidelines, colposcopy/LLETZ was indicated for women with two consecutive LSIL's or a single HSIL Pap smear. We also tracked time to colposcopy among women with abnormal Pap smears.

Results: We reviewed charts of 462 women with median age 33.7 years (IQR 29.0-39.2 years), median baseline CD4 117.5 (IQR 55-177), median baseline VL 49 (IQR 24-61). 432 (93.3%) had at least one evaluable Pap smear over the study period and 330 (76%) had two or more Pap smears (median=3, IQR 2-4). At baseline, 237 (54.9%) women had an abnormal Pap smear (see Table). 103 women were referred for colposcopy, of whom 89/103 (86.4%) had documentation of completed colposcopy within a median of 39 days (IQR 20-119 days) of referral yielding 57/89 (64.0%) evaluable samples of which 21.1%, 28.1%, 26.3%, and 1.8% had cervical intraepithelial neoplasia (CIN) I, CIN 2, CIN 3, and invasive cervical cancer, respectively.

Conclusions: Among a sample of HIV-infected women in an urban clinic in KZN, SA where Pap smear coverage and rates of referral for colposcopy/LLETZ were very high, we observed a prevalence of >75% cervical dysplasia and malignancy among those referred. These findings support the importance of cervical screening upon entry into care, and suggest that all HIV-infected women with cytological abnormalities on Pap smear should undergo early evaluation with colposcopy to minimize loss to care and optimize chances for survival.

Pap smear results and Referrals for Colposcopy/LLETZ				
	Initial Pap Smear Result	Referred for Colposcopy/ LLETZ	Received Colposcopy/ LLETZ	Evaluable Colposcopy/ LLETZ
Normal	195 (45.1%)	n/a	n/a	n/a
Atypical Squamous Cells of Undetermined Significance (ASCUS)	62 (14.4%)	n/a	n/a	n/a
Low grade squamous intraepithelial lesions (LSIL)	125 (28.9%)	58/125 (46.4%)	47/58 (81.0%)	35/47 (74.4%)
High grade squamous intraepithelial lesions (HSIL)	125 (28.9%)	45/50 (90.0%)	42/45 (93.3%)	22/42 (52.3%)

Session P-06 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Anal Cancer and HPV

718 Prevalence of Anal Dysplasia in HIV-Infected Women From Johannesburg, South Africa

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Background: Cervical cancer caused by oncogenic Human Papillomavirus (HPV) infection is a common cause of morbidity and mortality in HIV-infected women in Sub-Saharan Africa. HPV infection also causes anal cancer, but the incidence of anal cancer in this population is unclear. In Sub-Saharan Africa, there are no known data available on the prevalence of anal HPV infection or dysplasia in HIV-infected individuals. These are the first epidemiological data on the prevalence of anal HPV infection and dysplasia in HIV-infected women from South Africa.

Methodology: Prospective cohort study of HIV-infected women age 25-65. Participants were recruited from an HIV clinic in Johannesburg, South Africa. Anal swabs were taken for conventional glass-slide cytology and oncogenic HPV testing (Digene HC2). All women with abnormal anal cytology and 20% of women with normal cytology were seen for high resolution anoscopy (HRA) with biopsy of visible lesions. Biopsies were taken at the 6 and 12 positions on anus for women without visible lesions. Women had cervical cytology and HPV specimens obtained. We summarized the baseline characteristics of this cohort using descriptive statistics. Quality assurance of HRA was done through digital pictures and discussion with a specialist.

Results: A total of 88 women have been enrolled. The anal cytology results were normal in 9/88 (10%); 61/88 (69%) had low grade squamous intraepithelial lesions (SIL), and 16/88 (20%) had high grade SIL. 84% of women had an abnormal cervical cytology defined as low grade lesions and above. Anal biopsies results are available for 48 women: 23 (48%) had negative histology, 9 (19%) had atypia, 11 (23%) had low-grade lesions anal intraepithelial neoplasia (AIN) and 5 (10%) had High Grade AIN. 45% of women had high risk HPV detected on anal swabs, and 36% had high risk HPV on cervical swabs. Anal high risk HPV was found in 34% of women with LSIL on anal cytology and 75% of women with HSIL anal cytology.

Conclusions: We have found significant burden of anal HPV infection and abnormal anal cytology. High grade (SIL) on anal cytology was found in 20% of our women which is 2-4X higher than reports from cohorts of men who have sex with men. The observed prevalence of high grade AIN was lower given the cytology reports, and correlation may improve with more provider experience. Further studies should evaluate with rate of anal cancer in HIV-infected women in sub-Saharan Africa. HPV vaccination programs and anal cancer screening should be considered.

719 Mucosal and Systemic Immune Responses in HIV/HPV Co-Infected Males

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Background: We investigated anal inflammation, systemic T cell phenotype activation, and HPV-specific immunity in HIV HPV coinfected patients (pts) with and without HPV driven dysplasia and the association with HPV disease progression or clearance at anal site.

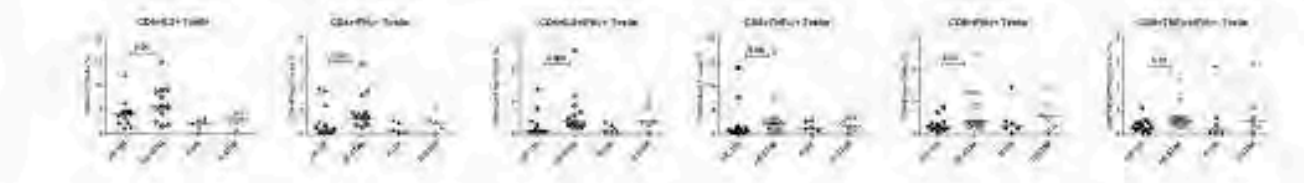
Methodology: We enrolled HIV+ men who underwent anorectal swabs for HPV-PCR detection/genotyping (High Risk HR) and cytologic abnormalities (Bethesda 2001: Low and High Grade Squamous Intraepithelial Lesions, L-HSIL). A subgroup was re-examined at a 18 months follow-up (FU) visit. The following parameters were measured at baseline (BL) and associated with anorectal cytology at FU: TNFα/IFNγ mRNA at anal site by RT-PCR; CD4/CD8 T cell activation (CD25, CD25/HLADRII, CD45R0, CD38/CD45R0), maturation (CCR7/CD45RA) and cytokine production (IL2, IFNγ, TNFα, granzyme, perforine) following HPV (type 16) specific stimulation were measured by flow cytometry on PBMCs. Mann-Whitney and χ-square test were used.

Table: Differences in immune parameters at baseline between SIL and No SIL patients

	CD4+ T-cell phenotype					HPV specific CD4+ T-cell responses		
	CD4+CD25+	CD4+CD25+HLADRII+	Naive CD4+CCR7+CD45RA+	Central Memory CD4+CCR7+CD45RA-	Effector Memory CD4+CCR7-CD45RA-	CD4+IL2+	CD4+IFNγ+	CD4+IL2+ IFNγ
No SIL								
SIL								
	CD8+ T-cell phenotype							
	CD8+CD25+	CD8+CD25+HLADRII	CD8+CD45RO+	CD8+CD38+CD45RO+	Naive CD8+CCR7+CD45RA+	Central Memory CD8+CCR7+CD45RA-	Effector Memory CD8+CCR7-CD45RA-	Terminally Differentiated CD8+CCR7-CD45RA+
No SIL								
SIL								
	HPV specific CD8+ T-cell responses						**Mucosal Cytokines**	
	CD8+IFNγ+	CD8+ IL2+	CD8+ TNFα+ IFNγ+	CD8+Granzyme+	CD8+Perforin+	CD8+Granzyme+Perforin+	TNFα+	IFNγ+	IL-2
No SIL									
SIL									

Note: Data are presented as median (IQR); no differences statistically significant were found between the two groups, using Mann-Whitney U test. IQR: interquartile range. SIL: squamous intraepithelial lesions.

Figure: Peripheral CD4+ and CD8+ HPV specific responses (UN=unstimulated, STIM= stimulated) according to mucosal damage (R=regressor, nR= non regressor) in HIV/HPV infected patients



Results: 40 pts were studied. 27 pts had SIL (26 LSIL) at BL while 13 had normal cytology. No differences were found in immune parameters between the two groups (Fig). 29/40 pts underwent a FU visit. 21/29 were diagnosed HR HPV and LSIL at BL. At FU, 13/21 displayed persistence of LSIL (non-regressors, nR), 6/21 normalised cytology (regressors, R), 2/21 had inadequate results. At BL, R pts displayed higher naïve CCR7+CD45RA+CD4+ T cells (6.45% IQR 1.9-7.6 vs 1.8% IQR 0.4-3.4, p=.05) and significantly higher activated CD45R0+CD8+(19.45% IQR 8.1-22.2 vs 7.2% IQR 3.7-15.7, p=.02) and CD38+CD45R0+CD8+ (10.8% IQR 7.6-17.6 vs 3.9% IQR 2.05-12.5, p=.03) compared to nRs. Interestingly, nRs were characterized by a significant increase in CD4/CD8 single-positive (CD4+IL2+, CD4+IFNγ+, CD8+TNFα+, CD8+IFNγ+), and double-positive (CD4+IL2+IFNγ+, CD8+TNFα+IFNγ+) cells upon HPV-specific stimulus (Fig), whereas no effect of HPV stimulation was displayed by R pts. At mucosal level, R pts tended to show higher anal TNFα (2.92% IQR 0.8-6.6 vs 0.53% IQR 0.19-2.8, p=.03) and IFNγ transcripts (2.81% IQR 1.2-9.1 vs 0.57% IQR 0.2-1.8, p=.08) compared to nR pts.

Conclusions: In HIV/HPV pts, clinical regression of HPV-related anal SIL seems to correlate with heightened local inflammation, systemic T cell activation and expansion of naïve lymphonode homing CCR7+ cells. These findings suggest efficacious immunity at the site of injury, that is not seen in patients with persistent dysplasia despite ex vivo reactivity to an HPV specific trigger.

720 Natural History of HIV-Related Anal Dysplasia: A Multi-State Modeling Analysis

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Background: The natural history of anal intraepithelial neoplasia (AIN) in the absence of treatment is incompletely understood. High grade AIN (HGAIN) is believed to be the precursor lesion for progression to invasive anal cancer (IAC), but rates of progression and regression of HGAIN are not known with precision. The aim of this study was to estimate progression and regression rates of HGAIN in the absence of treatment in a cohort of HIV-infected adults using multistate modeling.

Methodology: Retrospective cohort analysis of HIV-infected patients under care at UCSD Owen Clinic between 2003_2012. Inclusion criteria for multistate analysis: (1) confirmed HIV infection; (2) at least 2 anal cytology (Pap) results if no diagnosis of IAC OR at least 1 cytology result if subsequently diagnosed with IAC. Patients diagnosed with IAC within 180 days of the 1st anal cytology were excluded from multistate analysis. Cytology results were censored after the 1st treatment for AIN and if they were measured ≤ 180 before IAC diagnosis. Cytology transition probabilities (corrected for misclassification based on cytology sensitivity & specificity) for 3 states (<HGAIN, HGAIN, IAC) were estimated using the *msm* package implemented in R.

Results: During the study period, 2804 patients underwent ≥ 2 Paps (or 1 Pap + diagnosis of IAC) (median [range]: 3 [1-18]). Median [IQR] followup was 3.9 [1.9-6.9] years. Baseline characteristics: 89% male, 38% non-white, 75% on ART, 49% viral load <400 c/ml; median [IQR]: age 40[34-46], cd4 384 [217-572]. Of the 41 patients subsequently diagnosed with IAC, 23 were diagnosed > 180 days after the 1st cytology result and were included in the multistate model. Confirmatory biopsy results were available for 22/23 (96%). The distribution of person-time followup by selected covariates was: (1) on antiretroviral therapy (88%); (2) HIV viral load ≤ 400 (71%); (3) smoking (30%). The table presents estimated 2-year HGAIN progression and regression probabilities.

Estimated 2-year Transition Probabilities for Progression and Regression from HGAIN Adjusted for Cytology Misclassification Assumptions

Model	SE/SP[1]	2-year Transition Probability [95% C.I.[3]]	
		HGAIN → < HGAIN	HGAIN → IAC[2]
1	0.66 / 0.90	0.27 [0.21 - 0.33]	0.022 [0.014 - 0.033]
2	0.89 / 0.96	0.62 [0.58 - 0.66]	0.015 [0.001 - 0.022]
3	0.74 / 1.0	0.61 [0.58 - 0.65]	0.009 [0.006 - 0.014]
4	0.47 / 1.0	0.32 [0.28 - 0.36]	0.009 [0.006 - 0.013]

1. SE: sensitivity; SP: specificity [reference standard: HRA-directed biopsy] (from Mathews et al. PLoS One 2010; 5 (8):e12284)

2. HGAIN: high grade anal intraepithelial neoplasia. IAC: invasive anal cancer

3. 95% confidence interval

Conclusions: HGAIN regression within 2 years was estimated to vary between 27 - 62% (depending on assumptions regarding cytology accuracy), while progression to IAC was rare (1-2.2%). Initial observation without HGAIN treatment may be a reasonable option, assuming regular followup is assured.

721 Antiretroviral Therapy as Protector Factor of Anal Dysplasia in HIV-Infected MSM

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Background: Studies show higher incidences of anal carcinoma and faster progression in HIV-infected MSM patients. Chronic infection with oncogenic HPV is associated with the development of anal dysplasia. Antiretroviral therapy (ARV) has been shown to decrease the incidence of cervical carcinoma in woman living with HIV; however, so far in the majority of publications ARV has not proven beneficial effect in the appearance of anal dysplastic lesions, except in the Swiss cohort. **Objectives:**1-Analyze the role of ARVs in the prevalence of high-grade anal intrepithelial neoplasia (HGAIN) and/or anal cancer in our cohort of HIV positive MSM.2-Examine the prevalence of anal dysplastic lesions and HPV genotypes in our cohort.3- Evaluate the risk factors associated with the appearance of HGAIN and/or anal cancer.

Methodology: A cross-sectional study of an HIV-positive MSM cohort.Epidemiological (condylomatosis, sexual habits, use of condom, smoking, alcohol consumption, Other infections, etc), clinical (months since HIV diagnosis, HIV stage according to CDC criteria, ART, virological failure), and analytical (Cd4,

Viral load (VL), Cd4 nadir) data were collected. Two anal mucosa samples were taken and sent for HR-HPV PCR testing and cytology. Anoscopy was then performed for histological samples. The Bethesda cytological system and Richardt's histological classification were used.

Results: 140 patients were enrolled, with an average age of 37 years, Cd4 nadir 356.3 cel/uL; 77.1% were treated with ARV, currently Cd4 652.9 cel/uL, and Viral load 3.83 log; 6% had virological failure. Of 140 anoscopy procedures performed, 35.7% were normal, 47.1% were AIN1, 14.3% AIN 2/3, and 8.6% carcinoma in situ. 74.2% had high-risk (HR) HPV genotypes, 59.7% low-risk (LR) genotypes and 46.8% both. Logistic regression highlighted ARV as a protective factor against ≥ AIN2 lesions (OR: 0.214; 95%CI: 95%: 0.054-0.84). Anal/genital condylomas (OR: 4.26; 95%CI: 1.27-14.3), and HPV68 genotype (OR: 10.6; 95%CI: 1.23-91.47) were identified as risk factors.

Conclusions: In our cohort of HIV patients MSM, the antiretroviral therapy has a protective effect against the development of dysplastic anal lesions. 1/6 patients from our cohort has HGAIN, 1/11 has Carcimoma in situ, and 3/4 of them are infected with HR-HPV genotypes. The finding of anal or genital warts, and HPV-68 genotype in anal mucosa are two predictors of HGAIN and/or carcinoma in our cohort of HIV-MSM. This result requires further testing for confirmation of the finding.

722 HPV16-Specific T-Cell Responses and Spontaneous Regression of Anal Intraepithelial Neoplasia

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Background: 85% of anal cancers are attributable to persistent human papillomavirus type 16 (HPV16) infection. The anal cancer precursor, high grade anal intraepithelial neoplasia (AIN), is common (prevalence >30%) in MSM. High grade disease frequently regresses spontaneously. We hypothesized that T cell immune responses may contribute to its regression.

Methodology: We measured systemic T cell responses to HPV16 oncogenic proteins E6 and E7 (synthesized as overlapping peptides) in a substudy of the Study of the Prevention of ANal Cancer (SPANC). This is a natural history study of anal HPV and AIN in MSM aged ≥35 years, in which anal Papanicolaou smears and high resolution anoscopy (with biopsy of visually abnormal lesions) are performed at five visits over three years. At one visit, peripheral blood was taken for a novel assay for CD4 antigen-specific T cells based on CD25/CD134 co-expression after 44 hours culture, and an intracellular cytokine stain (ICS) assay for interferon-γ (IFNγ) and interleukin-2 (IL2) from CD4 and CD8 antigen-specific T cells. For both assays and each participant, negative and positive (staphylococcal enterotoxin B, cytomegalovirus lysate ± CEF peptides) controls were used. A positive response was defined as stimulation index ≥2 and an absolute cell count ≥20 for CD25/CD134 assay (or ≥15 for ICS assay) after subtracting background. Absolute T cell counts were measured with TruCount® tubes. High grade disease was HSIL on cytology and/or AIN2/3 on histology. We tested for associations using Pearson chi2 tests.

Results: See table for descriptive results. In cross-sectional analyses, 32.3% of HIV+ men had CD8 T cell responses (IFNγ and/or IL2) to E6 vs. 14.6% of HIV-negative men (p = 0.027). 23.5% of men with high grade disease had IFNγ CD8 T cell responses to E7 vs. 9.6% of men without (p = 0.028). Using longitudinal cytology / histology data from the main study, 26 men had high grade disease at study entry a mean 1 year prior, of which 6 experienced spontaneous regression by the time these assays were performed. Five (83%) of these 6 regressors had CD4 T cell responses to E6 on the CD25/CD134 assay vs. 35% of non-regressors (p = 0.037). ICS responses (CD4 or CD8) did not associate with regression.

Conclusions: Systemic HPV16-E6 and E7-specific T cell responses were detected in a substantial proportion of MSM. E7-specific CD8 T cell responses were more likely in those with high grade disease. E6-specific CD4 T cell responses were associated with recent high grade AIN regression.

Descriptive Results		
N Age (years, mean [SD]) HIV+ (N [%])	134 50.8 [9.3] 31 [23.1]	
High grade disease (N [%]) - Diagnosed on cytology (HSIL) - Diagnosed on histology (AIN2 or 3) Concurrent anal HPV16 detected (n=129)	51 [38.1] 22 [16.4] 47 [35.1] 37 [28.7]	
	CD4	CD8
Absolute T cell count (cells/μL, mean [SD]) - HIV-negative - HIV+	766 [271] 822 [254] 584 [250]	556 [337] 465 [198] 859 [496]
HPV16-E6-specific T cell positive responses (N [%]) - CD25/CD134 assay - ICS assay (IFNγ and/or IL2)	80 [59.7] 68 [50.8] 24 [17.9]	--- --- 25 [18.7]
HPV16-E7-specific T cell positive responses (N [%]) - CD25/CD134 assay - ICS assay (IFNγ and/or IL2)	40 [29.9] 32 [23.9] 16 [11.9]	--- --- 25 [18.7]

Session P-P1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Heart Failure, Cardiac Steatosis, and HIV

723 Elevated NT-proBNP Levels Predict Mortality in HIV-Infected Women

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Background: Cardiovascular and pulmonary diseases are common comorbidities in HIV-infected individuals. Elevated N-terminal-pro-brain natriuretic peptide (NT-pro-BNP) is a marker of cardiac ventricular strain and systolic dysfunction and has been previously been shown to be associated with co-morbidities in HIV. We aimed to determine if elevated NT-pro-BNP was associated with greater mortality in HIV-infected individuals.

Methodology: NT-pro-BNP was measured from stored serum samples from a random sample of half the HIV-infected and matched on age (1:2) HIV-uninfected participants in the Women's Interagency HIV Study at two time periods: early anti-retroviral therapy (ART) (10/11/94 to 7/17/97) and late ART (4/1/08 to 10/7/08). The proportion of participants with NT-pro-BNP levels >75th percentile were compared by HIV status at each time point. Cox proportional hazards models were used to determine if an elevated NT-pro-BNP was associated with mortality independent of other covariates (age, race, body mass index, smoking status, alcohol use, illicit drug use, hepatitis C serostatus, hypertension, renal function, hemoglobin, history of AIDS, antiretroviral use, CD4 count, and viral load).

Results: There were 387 HIV-uninfected and 936 HIV-infected and 448 HIV-uninfected and 1082 HIV-infected in the early and late ART periods, respectively. HIV infection was not associated with a NT-pro-BNP level in the early period, but HIV-infected persons were more likely to have a NT-pro-BNP level in the highest quartile in the late period (26.6% vs. 21.2%, unadjusted p=0.03). In HIV-infected participants, NT-pro-BNP>75th percentile was independently associated with worse survival in the 5 years subsequent to the date the sample was drawn in both the early (HR 1. 8, 95% CI 1.3-2.4, p<0.001) and late (HR 2.8, 95% CI 1.4-5.5, p=0.002) periods. The NT-pro-BNP level was not associated with mortality in HIV-uninfected women in the early period, and in the late period, there were too few deaths in the HIV-uninfected group to assess an association.

Conclusions: We have identified NT-pro-BNP as a novel independent predictor of mortality in HIV-infected women. As NT-pro-BNP is often associated with cardiopulmonary dysfunction, these findings suggest that these conditions may contribute to adverse outcomes in this population.

724 Cardiac Steatosis Increased in HIV: Related To Gender, Visceral Fat and ARV Exposure

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Background: Cardiac steatosis is identified in diabetes and is associated with impaired myocardial function. Abnormal visceral and intramuscular lipid deposition has been observed in HIV and therefore we determined intramyocardial lipid using magnetic resonance spectroscopy (MRS) in a cohort of HIV-infected adults compared to healthy volunteers to assess cardiac steatosis.

Methodology: We conducted a prospective cross-sectional study of 95 HIV-infected adults (mean age 48.6) and 30 age/sex/race-matched controls (mean age 46.2). Known cardiovascular disease was exclusionary. We measured intramyocardial lipid by MRS of the intraventricular septum, visceral fat volume by MRI, and we measured serum lipids, glucose, insulin, CD4 T-cell count, HIV viral load, and biomarkers of inflammation. Clinical history and past antiretroviral exposure was characterized for all subjects.

Results: Intramyocardial lipid content was significantly increased in HIV+ subjects compared to control subjects (1.45 ± 1.22 vs. 1.05 ± 1.00%, p=0.04). Overall, intramyocardial lipid was positively associated with age (r=0.22, p=0.01), glucose (r=0.21, p=0.02), triglyceride levels (r=0.19, p=0.04), and visceral abdominal fat (r=0.37, p<0.001), but there was no relationship with CD4 T-cell count, HIV viral burden, CRP, D-dimer or pro-BNP levels. In a multivariate model which included age, sex, smoking, glucose, triglycerides and visceral fat, HIV status remained a significant independent predictor of intramyocardial lipid (p=0.03) as did visceral fat volume (p=0.001) and female sex (p=0.02). Among those with HIV, years of ARV exposure was positively correlated with intramyocardial lipid (r=0.27, p=0.007), but there were no increases related to NNRTI or PI exposure specifically. However, visceral fat volume was also correlated with ARV years (r=0.31, p=0.004). In a regression model of HIV+ subjects which included age, sex, years of ARVs, visceral fat, glucose and triglycerides, female sex (p=0.02) and visceral fat (p=0.02) were significantly associated with intramyocardial lipid but not years of ARV exposure.

Conclusions: Cardiac steatosis, which is associated with impaired myocardial function, is increased in person with HIV. We showed a 38% increase in myocardial lipid content in HIV-infected adults compared to healthy controls. Our data suggest women may be particularly vulnerable to cardiac steatosis. Further, increased intramyocardial lipid was observed in association with metabolic parameters such as elevated triglycerides, as well as ARV exposure. Increases in visceral adiposity which occur with ARV exposure may drive some of the observed increases in myocardial lipid and convey an increased risk of myocardial dysfunction in HIV.

725 ST2 and GDF-15 Are Associated With Structural Heart Disease and Mortality in HIV

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Background: HIV-infected individuals have a high rate of cardiovascular disease, and traditional factors do not fully identify at-risk patients. We studied whether biomarkers of inflammation, cardiac stress and renal function are associated with structural heart disease and overall mortality in ambulatory HIV patients.

Methodology: Serum biomarkers (ST2, NT-proBNP, GDF-15, Cystatin C, IL-6, D-Dimer, ultrasensitive Troponin I, hsCRP) and echocardiograms were assessed in 332 HIV patients and 50 controls in 2004-2011. We defined systolic dysfunction as ejection fraction <50%, and diastolic dysfunction as ≥ stage 1 . Mortality data was obtained through the National Death Index.

Results: HIV patients were a median age of 49 years, 80% male, 34% hypertensive, 59% dyslipidemic, and 35% smokers. Sixty eight percent were treated with undetectable viral loads. Compared to controls, HIV patients had higher levels of all biomarkers except IL-6 ($p<0.05$ for all). Among HIV patients, 45% had diastolic dysfunction (DD); only ST2 was associated with DD in fully-adjusted analysis (RR=1.43 per doubling, 95%CI 1.06-1.92, p=0.019). Systolic dysfunction was rare in this cohort and showed no association with the candidate biomarkers. Thirty-three deaths occurred among HIV subjects over a median 5.8 years. In fully-adjusted analysis, only ST2 (HR 1.89, 95%CI 1.04-3.44, p=0.036) and GDF-15 (HR 1.35, 95%CI 1.02-1.79, p=0.038) were individually associated with mortality. Using ROC analyses, thresholds > 40 ng/ml for ST2 and 1665 pg/ml for GDF-15 were each predictive of mortality. This association was strengthened when both thresholds were surpassed (see figure).

Conclusions: Among HIV patients, ST2 and GDF-15 were associated with mortality risk. ST2 was also associated with diastolic dysfunction. ST2 and GDF-15 may be useful biomarkers of CV risk and overall mortality in HIV.

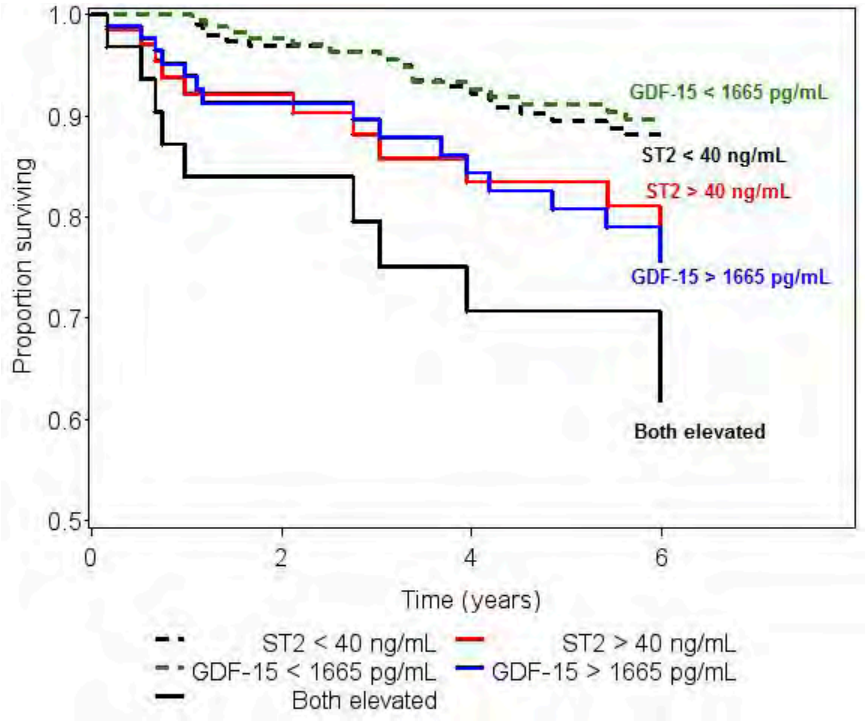

Figure 1. **Associations of Elevated ST2 and GDF-15 with Mortality in HIV-Infected Individuals**

726 Depression and HIV Are Risk Factors for Incident Heart Failure Among Veterans

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Background: HIV infection is associated with an increased risk of heart failure (HF). Depression, a common comorbidity among HIV infected (HIV+) and uninfected (HIV$^-$) people, is also associated with HF. The high prevalence of clinical depression among HIV$^+$ adults is concerning due to increased risk of HF among HIV+ people. This study examined the association between depression and HF in a large cohort of HIV+ and HIV$^-$ Veterans.

Methodology: We analyzed data on 81,427 Veterans (33% HIV+) without prevalent cardiovascular disease (CVD) from the Veterans Aging Cohort Study - Virtual Cohort (VACS VC), a prospective study of HIV$^+$ and their age-, sex-, race/ethnicity- and clinical site-matched HIV$^-$ Veterans. Veterans were followed from their first clinical encounter on or after 4/1/2003 until a HF event, death, or their last follow-up date (12/31/2009). Using baseline diagnoses of Major Depressive Disorder (MDD; ICD-9 codes 296.2x & 296.3x), participants were categorized into 4 groups: HIV$^-$ without depression (referent), HIV$^-$ with depression; HIV$^+$ without depression; and HIV$^+$ with depression. HF was determined using VA and Medicare ICD-9 codes (428.xx, 429.3, 402.01, 402.11, 402.91, 425.xx). Cox proportional hazards regression was used to model the association between depression, HIV-infection, and incident HF, adjusting for demographics, serum lipids, smoking, blood pressure, diabetes, renal disease, obesity, hepatitis C, atrial fibrillation, and atrial flutter, and substance use. Secondary analysis restricted the assessment to include only HIV$^+$ patients, adjusting the same covariates plus HIV-specific risk factors.

Results: During a median of 5.9 years of follow-up, there were 2666 HF events (38% HIV+). HF rates per 1000 person-years and risks adjusting for covariates are presented in Table 1 by HIV status and MDD diagnosis. Compared to Veterans without either condition, those with only MDD, with only HIV, or with both HIV and MDD were at higher risk for incident HF (Table 1). Among HIV+ Veterans, MDD remained a significant risk factor for HF after adjusting for covariates in Table 1 and baseline ART regimen, CD4 count, and viral load (HR(95%): 1.30 (1.11 - 1.51)) and with recent (i.e., within 6 months of event) ART regimen, recent CD4 count, and recent viral load (HR(95%): 1.27 (1.09 - 1.48)).

Conclusions: Depression is associated with an increased risk for incident HF regardless of HIV status. Among those with HIV, depressed Veterans had higher rates of HF compared to those without depression.

Table 1. Rates and risks of incident HF by HIV status and depression diagnosis

HIV status	Depression diagnosis	No. of participants	No. of HF events	Rates of HF per 1000 p-y (95% CI)	Risk of HF hazard ratio (95% CI)*
HIV −	No depression	45 728	1 339	60.4 (57.3 - 63.8)	1 [Reference]
HIV −	Depression	8 791	319	68.7 (61.6 - 76.7)	1.19 (1.05 - 1.35)
HIV +	No depression	21 850	774	75.6 (70.5 - 81.1)	1.28 (1.16 - 1.41)
HIV +	Depression	5 058	234	93.2 (92.0 - 106.0)	1.68 (1.45 - 1.95)

*All models for HF were adjusted for age, gender, race/ethnicity, hypertension, diabetes, dyslipidemia, smoking, atrial fibrillation, atrial flutter, hepatitis C infection, body mass index, renal disease, anemia, and substance use.
Abbreviations: CI, confidence interval; HF, heart failure; HIV, human immunodeficiency virus; p-y, person-years

Session P-P2 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Immune Activation, Immunodeficiency, and CVD

727 Impact of Low CD4 Count and HIV Persistence On Endothelial Function in Patients With Low Plasma RNA

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Background: Chronic inflammation contributes to increased cardiovascular (CV) risk among HIV-infected individuals with low plasma viral RNA levels. Hyperemic velocity (HV), a measure of microvascular function, is the stimulus for brachial artery flow-mediated vasodilation (FMD), a measure of macrovascular function. HV is more predictive of CV events than FMD in the general population. The contribution of HIV persistence and traditional CV risk factors to microvascular and macrovascular dysfunction has not previously been evaluated.

Methodology: We studied 71 HIV-infected individuals. Endothelial function was assessed using FMD. HV was measured as peak velocity-time integral (VTI) of the first complete velocity envelope after cuff release. D-dimer, hs-CRP, IL-6, sCD14, sCD163, and TNF-α were also measured. HIV persistence was determined using ultrasensitive plasma HIV RNA (lower limit of detection <0.3 copies/ mL, single copy assay), total proviral DNA in PBMCs (copies/ million CD4+ T-cells), and cell-associated RNA in PBMCs using TMA assay (signal/cutoff per million CD4+ T-cells). Multivariate Poisson regression was used to determine predictors of HV and FMD.

Results: Most participants were male (96%) with a median age of 51 years. Approximately 30% had traditional CV risk factors. Based on conventional assays, 72% were treated and suppressed while 28% were untreated elite controllers. The median CD4+ T-cell count was 554 (IQR 314-741). The median plasma RNA using single copy assay was 0.8 copies/mL; 63% had <0.3 copies/mL plasma RNA. The median cell-associated RNA level was 5.6 (IQR 3.8-6.8) and the median proviral DNA level was 1.75 (IQR 1.1-2.5) log10 S/Co per million CD4+ T-cells, respectively. The median HV was 85 cm (IQR 57.8 -100.7) and the median FMD was 4.8% (IQR 2.9-5.7). Worsened HV was independently associated with lower CD4+ T-cell count (RR 1.04 per 100 CD4+ T-cells, p<.001). In contrast, lower eGFR (RR 1.72, p=0.002), smoking (RR 1.25, p=0.039), and higher cell-associated RNA (RR 0.95, p=0.045) were associated with impaired FMD after adjustment for age and gender. Inflammatory and coagulation markers were not significantly associated with FMD or HV. Among treated and suppressed individuals only, lower eGFR and smoking remained significantly associated with impaired FMD while the association with cell-associated RNA weakened.

Conclusions: Among HIV-infected subjects with low plasma RNA levels, a low CD4+ T-cell count was associated with impaired HV, while traditional risk factors and cell-associated HIV RNA levels were associated with worsened FMD. Our findings suggest that HIV may preferentially affect the microvasculature leading to endothelial dysfunction. Therapies targeted at further reduction of HIV persistence may also decrease CV risk.

728 Carotid Distensibility and Immune Activation in HIV-Infected Patients Without Coronary Calcium

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Background: Coronary artery calcification (CAC) scoring significantly improves cardiovascular risk stratification; however, CAC is a late finding of atherosclerotic vascular disease. Increased vascular stiffness (i.e. decreased distensibility) may be an early marker of vascular disease in HIV-infected patients on antiretroviral therapy (ART) prior to the development of vascular calcification. The relationship of chronic systemic immune dysregulation to these early vascular changes in HIV is poorly understood.

Methodology: High-resolution carotid ultrasound was used to examine common carotid artery intima-media thickness (CCA-IMT) and distensibility among 147 HIV-infected patients on ART. CAC scoring was performed with computed tomography. T-tests and Spearman correlations were used to examine the relationships between carotid distensibility and biomarkers of inflammation and immune activation among those with and without detectable CAC.

Results: Median (interquartile range) age was 46 (40-53) years; 78% were male and 68% African American. Median CD4 count was 613(425, 853) cells/μl and 10-year Framingham risk score was 3(1-7)%. Ninety-three subjects (63%) had zero CAC, but 29 (31%) of those with zero CAC had carotid atherosclerosis by ultrasound (CCA-IMT>1mm or discreet carotid plaque). Median carotid distensibility was higher among those without CAC [26(19-33) vs. 23(19-26) 10-6*Newtons-1*m2, p=0.045, CAC=0 vs. CAC>0, respectively); however, 13 subjects (9% of total population) without any CAC or carotid atherosclerosis had carotid distensibility below the 25th percentile. Distensibility was negatively correlated with CD4+ CD38+HLA-DR+, CD14dimCD16+ (patrolling) monocytes, and IL-6 concentrations among those with CAC=0, but not among those with CAC>0 (see Table). Among subjects with CAC=0, distensibility was significantly or marginally significantly correlated with CCA-IMT (r 0.339, p <0.001) and two measures of endothelial function (r 0.192, p=0.066 for flow-mediated brachial artery dilation; and r 0.374, p<0.001 for hyperemic velocity-time integral).

Table: Circulating biomarkers of inflammation and immune activation are more strongly correlated with carotid distensibility among subjects without coronary calcification (CAC=0) compared to those with calcified coronary disease (CAC >0).

	Spearman Correlation Coefficient	
	CAC=0	CAC>0
CD8 38+DR+ T-cells (%)	*	*
CD4 38+DR+ T-cells (%)	-0.342	*
CD8 PD1+38+DR+ T-cells (%)	*	*
CD4 PD1+38+DR+ T-cells (%)	-0.300	*
CD14+CD16+ monocytes (%)	*	*
CD14dimCD16+ monocytes (%)	-0.269	*
Soluble CD14 (ng/ml)	*	*
Soluble CD163 (ng/ml)	*	*
Soluble Vascular Cell Adhesion Molecule-1 (ng/ml)	*	-0.350
Interleukin-6 (pg/ml)	-0.220	*
Tumor Necrosis Factor-α Receptor-1 (pg/ml)	*	*
High-sensitivity C-reactive Protein (μg/ml)	*	*

* p>0.05

Conclusions: Among HIV-infected patients on ART who do not have coronary artery calcification, impaired carotid distensibility may be a sign of early vascular disease that is associated with immune activation and inflammation.

729 Microvascular Disease in Controllers Is Mediated by HIV DNA and Immune Dysfunction

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Background: HIV-infected individuals ("controllers") who are able to maintain low levels of plasma RNA in the absence of antiretroviral therapy (ART) have stable low-level viremia, elevated T cell activation, and a higher risk of cardiovascular disease (CVD). The mechanisms underlying this increased risk are unknown but may include low-level viral replication leading to chronic inflammation and subsequent endothelial dysfunction.

Methodology: We performed an open-label study to compare the impact of ART on endothelial function (as measured by flow-mediated vasodilation of the brachial artery [FMD]) and microvascular function (as measured by hyperemic velocity [HV]) in "elite" controllers (EC, n=4), viremic controllers (VC, n=11), and non-controllers (NC, n=5). Lower levels of FMD and HV have been shown to be predictors of future CVD. All subjects received 24-36 weeks of RGV+TDF/FTC. FMD and HV were measured at weeks 0, 4, 24, and 36. Linear mixed models were used to evaluate changes in FMD and HV.

Results: Baseline FMD levels were 6.9±2.0% (EC), 5.3±0.9 (VC), and 6.3±1.7% (NC) (p=0.18, overall test of difference). There were no statistically significant changes over time in FMD (p=0.24), and FMD did not differ significantly between groups (EC vs. NC, p=0.98; VC vs. NC, p=0.17). Baseline HV levels were 101.5±31cm (EC), 89.8±19.7cm (VC), and 67.3±24.2cm (NC) (p=0.14, overall test of difference). Overall, HV was 39.9 cm higher in EC vs.

NC (p=0.018) and somewhat higher in VC vs. NC (+20.0cm, p=0.13). Both proviral DNA and %CD8+PD1+ levels were significantly lower in EC patients compared to NC at weeks 0, 4, 24; models which controlled for these factors attenuated the differences in HV between EC and NC.

Conclusions: In this small pilot study, while 24 weeks of ART resulted in significant reductions in levels of ultrasensitive plasma RNA and T cell activation in HIV-infected controllers, this did not translate into improved macrovascular function (as measured by FMD). However, controllers as a group had better microvascular function (as measured by HV) compared to non-controllers; lower proviral DNA levels and lower markers of immune dysfunction in controllers appeared to mediate the differences in HV. Thus, HIV persistence and immune dysfunction may preferentially impact the microvasculature (rather than the macrovasculature), which may contribute to increased CVD risk. These findings should be replicated in future larger studies that also account for differences between the groups in traditional CVD risk factors.

730 Monocyte But Not Cellular Activation Is Associated With Coronary Atherosclerosis in the MACS

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Background: Immune activation is a proposed mechanism for increased cardiac risk in HIV infection. We hypothesize that virally suppressed HIV-infected patients have higher CD8+ T cell and monocyte activation than uninfected controls, and that these measures are associated with coronary atherosclerosis.

Methodology: Cross-sectional analyses of HIV-uninfected (n=71) and virally suppressed HIV-infected (n=95) men in Los Angeles, in the Multicenter AIDS Cohort Study (MACS). Non-contrast cardiac computed tomography (CT) for presence of coronary artery calcium (CAC) and CT angiograms for presence of calcified plaque (CP), mixed plaque (MP), non-calcified plaque (NCP) and total plaque (TP) were performed. CD8+ T cell activation (CD38+/HLADR+) was assessed by flow cytometry and soluble monocyte activation markers, sCD163 and sCD14 by ELISA. Associations between immune activation and presence of atherosclerosis were assessed with logistic regression, adjusting for age, ethnicity and cardiovascular risk factors.

Results: Characteristics, CT and immune marker findings are in Table. HIV-infected men were younger with significantly higher CD8+ T cell activation and plasma sCD14 and sCD163 levels than HIV-uninfected men. There was no evidence for a relationship between CD8+ T cell activation and presence of any type of plaque (P>0.05 for all) in either group. In HIV-uninfected both sCD163 and sCD14 were associated with presence of CAC, adjusted odds ratio [aOR] (95% confidence interval [CI]) 1.82 (1.04, 4.28) and 1.36 (1.01, 2.05), as well as CP, 2.53 (1.37, 6.42) and 1.67 (1.21, 2.67), respectively. For HIV-infected men, sCD14 was not associated with presence of atherosclerosis but sCD163 was for CP, MP and TP with aOR (95% CI) of 1.28 (1.01, 1.66), 1.45 (1.13, 1.91) and 1.56 (1.13, 2.32), respectively.

Conclusions: Virally suppressed HIV-infected men had significantly higher CD8+ T cell and monocyte activation than HIV-uninfected men. CD8+ T cell activation was not associated with coronary atherosclerosis in either group. In contrast, the monocyte activation markers sCD14 and sCD163 were associated with coronary calcium and calcified plaque in HIV-uninfected while sCD163 but not sCD14 were associated with presence of calcified, mixed and total plaque in HIV-infected. Further study is needed to define the mechanism behind increased immune activation in virally suppressed HIV-infected patients and the role monocyte activation plays in coronary atherosclerosis.

Characteristic	HIV-uninfected (n=71)	HIV-infected (n=95)
Age, mean years (SD)*	54 (7)	51 (7)
Race/ethnicity (%)*		
White	58	44
African American	25	20
Hispanic/other	17	36
CD4 count, median cells/uL (IQR)	N/A	
Current		667 (451, 804)
Nadir		277 (151, 399)
Time on antiretrovirals, median years (IQR)	N/A	10 (8, 12)
CD38+/HLADR+ CD8+ T cells, median percent (IQR)*	2.15 (1.30, 3.34)	3.51 (2.20, 6.24)
Soluble markers, median ng/mL (IQR)		
sCD14*	1251 (1049, 1433)	1532 (1322, 1774)
sCD163*	554 (387, 714)	667 (535, 865)
Computerized tomography findings (%)		
CAC+	52	48
CP+	45	35
NCP+	52	57
MCP+	39	35
TP+	80	75

SD, standard deviation; IQR, interquartile range; CAC, coronary artery calcium; CP, calcified plaque; NCP, non-calcified plaque; MCP, any mixed calcified plaque; TP, any plaque.
*p<0.05 (Kruskal-Wallis or Chi-square test for comparison between HIV-uninfected and infected)

Session P-P3 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Alcohol, Smoking, and Atherosclerosis

731 The J-Curve in HIV: Better Cardiovascular-Disease-Free Survival With Moderate Alcohol Intake

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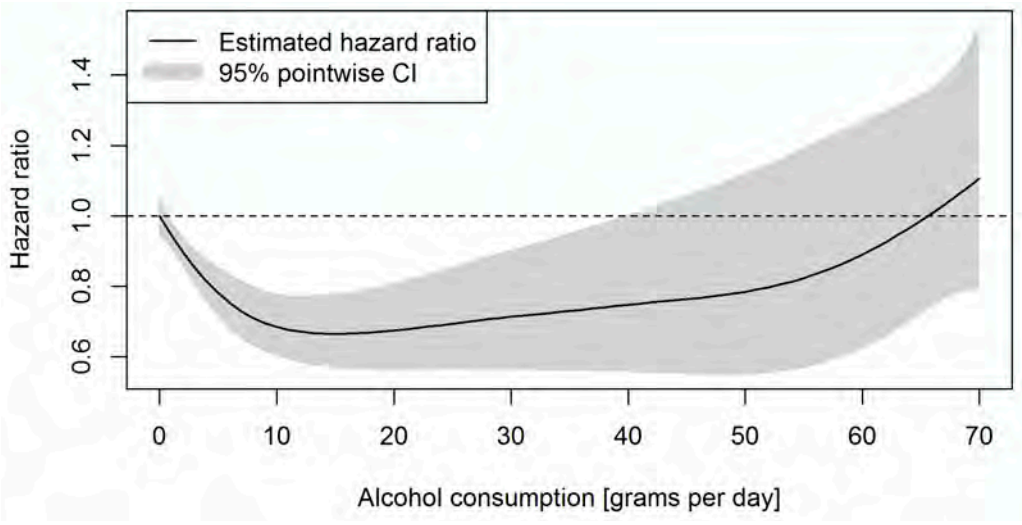
Background: In HIV-negative populations light to moderate alcohol consumption is associated with a lower cardiovascular morbidity and mortality than alcohol abstention. Whether the same holds true for HIV-infected individuals has not been evaluated in detail.

Methodology: All adult individuals enrolled in the Swiss HIV Cohort Study who started antiretroviral treatment and had follow-up (fup) time after August 2005 were included. Fup was characterized by alcohol abstention, low (1-9 g/d), moderate (10-29 g/d in females and 10-39g/d in men) and severe alcohol intake. Cox proportional hazards models were used to find an association between alcohol consumption and cardiovascular disease free survival (combined endpoint) as well as cardiovascular disease events (CADE) (myocardial infarction, coronary angioplasty, coronary artery by-pass grafting, carotid endarterectomy, procedures on other arteries, cerebral infarction and cerebral haemorrhage) and overall survival. Baseline and time-updated risk factors for CADE were included in the models.

Results: Among 10,547 individuals included, there were 464 events of CADE and 520 deaths during 52'000 years of fup. The incidence of CADE or death (whichever occurred first) was 1.8 events/100 person-years. Fup according to the alcohol consumption level was 53% abstention, 20% low, 23% moderate and 6% severe intake. As compared to abstention, low (Hazard Ratio (HR) 0.73 (95% Confidence Interval (95% CI) 0.60-0.88; p=0.001)) and moderate alcohol intake (HR 0.67 (0.56-0-80; p<0.001)) were associated with a lower incidence of the combined endpoint, whereas for severe intake no association was detected (HR 0.9 (0.70-1.14; p=0.40)). All classical cardiovascular risk-factors as well as low CD4 cell counts were significantly associated with a higher hazard of CADE or death. The figure shows a fitted curve of daily alcohol consumption level with the HR of the combined endpoint. A similar pattern was observed for overall survival. Alcohol consumption showed a monotonic inverse association with CADE incidence: HR 0.91 (95% CI 0.85-0.97, p= 0.01) per 10g increase of daily alcohol intake.



Conclusions: Compared to abstention, low and moderate alcohol intake is associated with a better CADE free survival in participants of the Swiss HIV Cohort Study on antiretroviral therapy.

732 Soluble CD14 and D-Dimer Are Associated With Smoking and Heavy Alcohol Use in HIV-Infected Adults

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Background: HIV-infected adults are at increased risk for cardiovascular disease (CVD) compared with uninfected adults. In the general population and among HIV-infected adults, biomarkers of monocyte activation (soluble CD14 [sCD14]) and altered coagulation (D-dimer) have been independently associated with increased risk for myocardial infarction, coronary heart disease, and all-cause mortality. We examined whether cigarette smoking and heavy alcohol use were associated with higher levels of these biomarkers in persons living with HIV to inform CVD prevention efforts among HIV-infected persons.

Methodology: The Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (the 'SUN' Study) was an observational prospective cohort study that enrolled 700 participants between 2004 and 2006 in four U.S. cities. Biomarkers of monocyte activation (sCD14) and altered coagulation (D-dimer) were analyzed in blood samples from study participants at baseline (n = 689). Each participant completed a baseline audio computer-assisted self-interview to assess behavioral risk factors. Regression analyses examined associations between current cigarette smoking, heavy alcohol use (defined as more than 5 alcohol drinks on at least one day in the past month), and biomarker levels.

Results: Of the 689 participants included in this analysis, 76% were male, 58% non-Hispanic white, 77% were taking antiretroviral therapy, and 73% had an undetectable HIV viral load (<400 copies/mL). Mean age was 41 years and median CD4 count was 438 cells/μL. Heavy alcohol use was reported by 29%, and 42% currently smoked tobacco. In regression analyses, controlling for age, race, current CD4, and viral load, current smoking compared to nonsmoking was associated with significantly elevated sCD14 (B= 135.57, 95%CI (84.95, 186.19), p=.000); whereas heavy alcohol use compared to nondrinking was associated with significantly lower D-dimer levels (B= -.059, 95%CI (-.102, -.016), p=.007).

Conclusions: In this contemporary HIV cohort, current cigarette smoking appears to be associated with elevated sCD14. By contrast, heavy alcohol use is associated with lower D-dimer levels. Smoking cessation should be encouraged by HIV care providers to improve cardiovascular and other all-cause mortality outcomes among HIV-infected persons. However, further research is needed to better understand whether alcohol use confers a protective effect.

733 Antiviral Therapy and Smoking Associated With Coronary Vessel Thickening in HIV-Infected Youth

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Background: Individuals infected with HIV early in life may be at higher risk for premature vasculopathy and cardiovascular disease. Whether this increased cardiovascular disease risk is associated with chronic HIV-infection or with long-term antiretroviral therapy has yet to be elucidated. The purpose of this study therefore was to assess subclinical coronary vessel wall thickening and plaque burden in patients infected with HIV early in life compared to healthy controls.

Methodology: This is a prospective cross-sectional study of 35 youth and young adults who acquired HIV in early life and 11 uninfected healthy controls, all free of active cardiovascular disease. Phase-sensitive dual inversion-recovery black-blood vessel wall imaging was utilized for MR imaging of the proximal right coronary artery (RCA) and CT angiography was performed for determination of coronary plaque burden.

Results: HIV-infected subjects (mean age 22; range 15-29 years; 54% male) had significantly increased proximal RCA thickness compared to uninfected controls (mean age 25; 22-29 years; 27% male). RCA thickness in HIV+ was 1.32±0.21 mm vs. 1.09±0.12 mm in controls (p=0.002). HIV status remained a significant predictor of RCA thickness (p=0.01), as did smoking pack years (p=0.004), in a multivariate regression adjusting for age, sex, and BMI. The difference in proximal RCA thickness also remained significant in a sub-analysis which excluded HIV+ subjects <20 y (p=0.002). Atherosclerotic plaque was present in the coronary vessels among 45% of controls, but only 19% of HIV-infected subjects (p=0.1) and plaque was not associated with proximal RCA thickness. There was no association between vessel wall thickness and levels of CRP, d-dimer, pro-BNP, or homocysteine for either study group. Among the HIV-infected subjects, duration of antiretroviral therapy corresponded to vessel wall thickness (r=0.38, p=0.02) and duration of stavudine was most closely correlated to RCA thickness (r=0.43, p<0.01). These associations remained significant after adjusting for age, BMI and smoking pack years, which also was consistently associated with RCA thickness.

Conclusions: This investigation provides evidence of vascular injury in individuals infected with HIV early in life compared to healthy volunteers, as shown by coronary vessel wall thickness. Among HIV-infected subjects, increased duration of antiretroviral therapy, in particular stavudine, and smoking pack years were strong indicators of proximal RCA thickening. However, coronary vessel wall thickening was independent of atherosclerotic plaque, indicating that vessel wall thickening related to antiretroviral therapy exposure occurs through a mechanism distinctive from traditional atherogenesis.

Session P-P4 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Risk Factors and Incidence: MI and Stroke

734 HIV Infection and the Risk of Cardiovascular Disease in Women

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Background: HIV infection is associated with increased risk of cardiovascular disease (CVD) in women. However, whether HIV is an independent predictor of CVD is unclear. We investigated this question in a cohort of HIV infected (HIV+) and uninfected (HIV-) women.

Methodology: We analyzed data on 2190 women participants (32% HIV+) free of CVD at baseline from the Veterans Aging Cohort Study who were followed from their first clinical encounter (on/after 04/01/2003) until a CVD event, death, or the last follow-up date (12/31/2009). The primary outcome was CVD [acute myocardial infarction (AMI), ischemic stroke, heart failure]. AMI events were defined using clinical data, ICD-9-CM codes and or death certificate data; ischemic stroke and heart failure were determined using ICD-9-CM codes. We used Cox proportional hazards models to assess the association of HIV and incident CVD, adjusting for age, race/ethnicity, lipids, smoking, blood pressure, diabetes, renal disease, obesity, hepatitis C, and substance use/abuse. Using the counting process technique for a time updated Cox proportional hazards model, we explored the risk for CVD among HIV+ women with HIV-RNA levels <500 copies/mL and those with CD4 cell count >200 cells/mm^3 .

Results: During a median follow-up time of 5.9 years, there were 86 CVD events (53%, HIV+): AMI: 24%; ischemic stroke: 20%; heart failure: 56%. Incident CVD/1000 person years was significantly higher among HIV+ (13.5, 95% CI 10.1, 18.1) than HIV- women (5.3, 95% CI 3.9, 7.2), p<0.001, despite the fact that the baseline Framingham risk score was 3 for both groups (p=0.28). After adjusting for all covariates, HIV+ women had an increased risk of CVD compared to HIV- (HR 3.12, 95% CI=1.89, 5.11). Median age at and time to CVD event for HIV+ vs. HIV- women was 49.3 vs. 52.0 years (P=0.05), respectively, and 5.85 vs 6.05 years (p<0.001). In time updated analyses, HIV+ women with HIV-1 RNA level ≥500 copies/mL (HR=3.23, 95% CI=1.61, 6.47) and <500 copies/mL (HR=3.27, 95% CI=1.82, 5.88) were both at greater risk of CVD compared to HIV- women. There was no difference in risk between the two HIV groups (p=0.97). Similar associations were found for HIV+ women with CD4 cell count <200 cells/mm^3 (HR=2.75, 95% CI=1.54, 4.92) and those with CD4 count ≥200 cells/mm^3 (HR= 5.63, 95% CI=2.71, 11.7) compared to HIV- women. However the risk of CVD was greater among those with CD4 cell counts ≥200 cells/mm^3 compared to those with CD4 cell counts <200 cells/mm^3 (p=0.047).

Conclusions: HIV is an independent predictor of CVD in women. These results have important policy and clinical implications given the growing number of HIV+ women and the fact that heart disease is the leading cause of death among women in the US. Research must explore the etiology and predictors of CVD in this high risk population of women.

735 Depression Predicts Incident Myocardial Infarction in HIV+ Veterans: Veterans Aging Cohort Study

Tasneem Khambaty[1], Jesse C. Stewart[1], Samir K. Gupta[2], Chung-Chou H. Chang.[3], Adeel A. Butt[3], Cynthia L. Gilbert[4], Hilary A. Tindle[3], Heidi Crane[5], Roger Bedimo[6], Matthew S. Freiberg[3], on behalf of the VACS project team

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Background: Incidence of acute myocardial infarction (AMI) is higher in HIV-infected patients than in uninfected patients. As depressive disorders are independent risk factors for AMI in the general population, and because depressive disorders are highly prevalent in those with HIV infection, we examined the relationships between these psychiatric conditions and incident AMI in a large sample of HIV-infected patients.

Methodology: Our sample included 27,362 HIV-infected men (mean (SD) age: 49 (10) years, 47% African American) from the Veterans Aging Cohort Study Virtual Cohort who were free of cardiovascular disease at baseline (1998-2003). Patients with a diagnosis of either major depressive disorder (MDD; ICD-9 codes 296.2 or 296.3) or dysthymic disorder (ICD-9 code 300.4) during the baseline period were identified as depression cases. Incident AMI was defined as discharge summary documentation and enzyme/ECG evidence of AMI (Veteran Affairs data), an inpatient ICD-9 code 410 (Medicare data), or AMI (ICD-10 code 121) as underlying cause of death (death certificate data) during the follow-up period. All patients were followed for a median of 5.9 years from their first clinic visit on or after April 1, 2003 to an AMI event, death, or the last follow-up date (December 31, 2009).

Results: 5,204 (19%) MDD cases and 2,480 (9%) dysthymic disorder cases were identified during baseline, and 363 (1.3%) incident AMI cases occurred during follow-up. Cox proportional hazards models, adjusted for demographics (age, race/ethnicity) and cardiovascular risk factors (hypercholesterolemia, hypertension, smoking, diabetes, body mass index) revealed that any depressive disorder (MDD or dysthymic disorder; HR=1.35, 95% CI: 1.07-1.70 p=.01) was a predictor of incident AMI, as were MDD (HR=1.30, 95% CI: 1.01-1.67 p=.03) and dysthymic disorder (HR=1.50, 95% CI: 1.11-2.03 p=.01) separately. After further adjustment for HIV-related factors (hepatitis C infection, renal disease, alcohol and cocaine abuse, hemoglobin level, CD4 cell count, HIV-1 RNA level, antiretroviral medications), any depressive disorder (HR=1.31, 95% CI: 1.03-1.67 p=.03) and dysthymic disorder (OR=1.47, 95% CI: 1.08-2.01, p=.01) remained predictive of incident AMI, while the HR for MDD (HR=1.28, 95% CI: 0.99-1.65, p=.06) fell just short of significance.

Conclusions: To our knowledge, this study is the first to examine depression as a predictor of AMI in HIV-infected patients. Like the general population, our results suggest that depressive disorders are independent risk factors for AMI in this population, and support further research to evaluate whether delivering evidence-based depression treatment may be a novel approach to managing the excess cardiovascular risk of HIV-infected patients with depression.

736 HIV Infection, Cardiovascular Risk Factor Profile, and Risk for Acute Myocardial Infarction

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Background: Optimal cardiac health is associated with low rates of cardiovascular disease (CVD) though its prevalence is low in the general population. HIV is also associated with acute myocardial infarction (AMI) but the prevalence of optimal cardiac health in this population is unknown. We compared the prevalence of optimal cardiac health by HIV status and assessed whether the association between HIV status and AMI persisted among those with optimal and non-optimal CVD risk factors (CVDRFs) as defined by prior work.

Methodology: We analyzed data on 81322 (33% HIV+) who were free of baseline CVD from the Veterans Aging Cohort Study Virtual Cohort, a prospective study of HIV+ and matched HIV- veterans in care. Veterans were followed from their first clinical encounter on or after 4/1/2003 until an AMI event, death or the last follow up date (12/31/2009). We used CVDRFs (total cholesterol, cholesterol lowering agents, blood pressure (BP), BP medication, smoking, diabetes) to create 6 CVDRF profiles: all CVDRFs optimal, 1+ non-optimal CVDRFs, 1+ elevated CVDRFs, and 1, 2, or 3+ major CVDRFs. Incident AMI

was defined using enzyme and EKG clinical data, an inpatient ICD-9 code 410 in Medicare data, and or death certificate data. We calculated AMI rates and estimated AMI risk using Cox proportional hazard models adjusted for demographics, hepatitis C, renal disease, obesity, and substance use.

Results: During a median of 5.9 years there were 858 AMI events (42% HIV+). The prevalence of optimal cardiac health was <2% for HIV+ and HIV- veterans. Optimal CVDRF profile was associated with lower adjusted AMI rates (Fig 1). Compared to HIV¬¬- veterans with the same CVDRF profile, HIV+ veterans had higher adjusted AMI rates, particularly among those with at least 1 major CVDRF present (Fig 1). Adjusted AMI rates among HIV+ veterans increased more with each additional major CVDRF compared to rate increases among HIV- veterans (Fig 1). Compared to HIV- veterans without major CVDRFs, HIV+ veterans without major CVDRFs had a 2-fold increased risk of AMI (HR: 2.0 95%CI: 1.0-3.9, p=0.044) even after covariate adjustment.

Conclusions: The prevalence of optimal cardiac health is low in the VACS VC. Increasing risk factor burden is associated with an increase in AMI rates. This increase is accelerated among HIV+ veterans. Among those without major CVDRFs, HIV+ veterans have twice the AMI risk compared to HIV- veterans. Preventing or reducing CVDRF burden may result in a substantial reduction in AMI risk among HIV+ people.

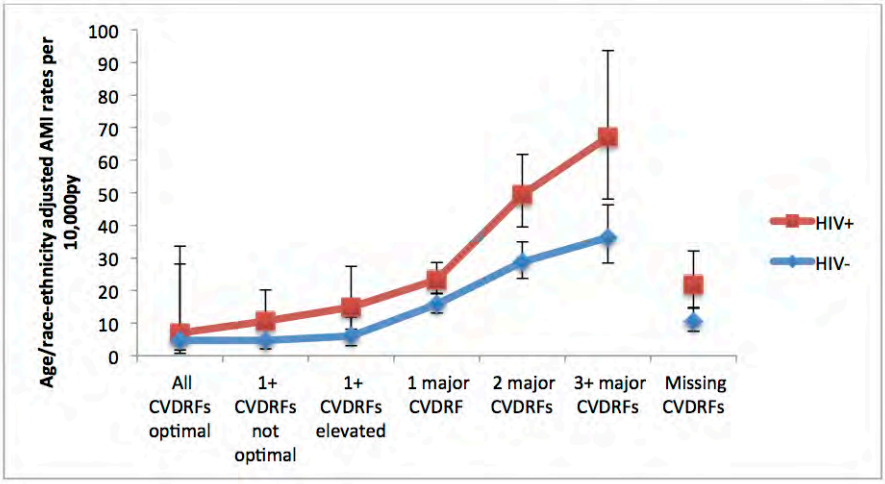

Figure 1: Age/race-ethnicity adjusted rates of acute myocardial infarction (AMI) by cardiovascular disease risk factor profile (CVDRF) stratified by HIV status

737 No Difference in Incidence of Myocardial Infarction for HIV+ and HIV- Individuals in Recent Years

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Background: With an aging HIV+ population, medical care has increasingly focused on non-AIDS complications such as myocardial infarctions (MI). Here, we compared MI incidence rates between HIV+ and HIV- individuals over time to determine if efforts to reduce MI risk have been successful.

Methodology: We conducted a cohort study from 1996-2011 of HIV+ and 10:1 demographically-matched HIV- Kaiser Permanente California health plan members. Rate ratios (RR) were obtained from Poisson regression models comparing MI incidence rates by HIV status stratified by calendar era (1996-99, 2000-03, 2004-07, 2008-09, 2010-11). Models adjusted for age, sex, race/ethnicity, census-based socioeconomic status, smoking, alcohol/drug abuse, overweight/obesity, diabetes, hypertension, and lipid-lowering therapy. For the most recent era (2010-11), we also compared Framingham risk scores and specific components of the Framingham risk score by HIV status.

Results: 24,768 HIV+ and 257,600 HIV- members contributed 122,032 and 1,522,574 person years, respectively. We observed 320 MIs among HIV+ subjects and 2,483 MIs among HIV- subjects. The crude and adjusted MI RRs for HIV status are shown in the Table. By 2010-2011, the MI incidence rates were similar among HIV+ and HIV- patients with a crude RR of 1.2 (95%CI: 0.7-1.6). In adjusted models, the RR for HIV status in 2010-11 was further reduced to 1.0 (95% CI: 0.7-1.4). In 2010-11, calculated Framingham risk scores were slightly lower in HIV+ patients (9.2% HIV+ and 9.6% HIV-; p<0.001), and fewer HIV patients had high total cholesterol (30.0 vs. 39.6%; P<0.001). However, HIV+ patients had a slightly higher prevalence of hypertension (28.5% vs. 26.2%; P<0.001), and were more likely to have ever smoked (49% vs. 35%; p<0.001) and have HDL<40 (39% vs. 26%; p<0.001).

Conclusions: The increased MI risk in HIV+ patients compared with HIV- patients was no longer observed in recent years. The exact reason for this is unclear, but likely a result of a combination of factors such as cardiovascular risk factor reduction, use of more lipid-friendly antiretrovirals, and reduced immunodeficiency.

Table. Crude and adjusted MI RRs (95% CI) for HIV status over time (HIV- ref)

	1996-99	2000-03	2004-07	2008-09	2010-11
Crude	2.0(1.5, 2.8)	2.0 (1.6, 2.5)	1.5 (1.2, 1.9)	1.5 (1.1, 2.0)	1.2 (0.9, 1.6)
Adjusted	1.8 (1.3, 2.6)	1.7 (1.4, 2.1)	1.3 (1.0, 1.6)	1.3 (0.9, 1.7)	1.0 (0.7, 1.4)

738 MACE Incidence Among HIV- and Non-HIV-Infected Patients in a Clinical Care Cohort

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Background: HIV-infected patients have an elevated risk of coronary heart disease, yet rates of major adverse cardiac events as frequently studied in large clinical trials in the general population remain incompletely characterized.

Methodology: Incidence rates of a composite cardiovascular endpoint were calculated using the Partners HealthCare System HIV longitudinal cohort. The cohort was derived from the Research Patient Data Registry, a clinical care data registry which includes comprehensive clinical information for over 4.5 million patients from the Partners HealthCare System, including Massachusetts General Hospital, Brigham and Women's Hospital, and their associated outpatient systems. Control patients were matched on the basis of demographic factors. The observation period was between 2000 and 2009, with all patients age 40 or greater at the start of observation. The composite CVD endpoint was ascertained as documentation of relevant ICD-9-CM or CPT codes for myocardial infarction, stroke, angina or coronary revascularization.

Results: The cohort consisted of 3,109 HIV-infected and 23,237 non-HIV-infected control patients followed for 4.8 years (14,942 person-years, PYs) for HIV-infected and 4.6 years (106,885 PYs) for non-HIV-infected patients. Rates of the composite endpoint were 20.8 events (95% confidence interval, CI 18.6-23.3) per 1000 PYs for the HIV-infected patients versus 15.1 (95% CI 14.4-15.9) per 1000 PYs for non-HIV-infected patients. Of the 332 events observed in the infected cohort, 165 (50%) were MI, 124 (37%) were stroke, 35 (11%) were angina and 8 (2%) were revascularization, translating into rates as shown in the Table. Incidence rate ratios (IRR) comparing HIV-infected to non-HIV-infected patients were 1.4 for the overall endpoint, 1.4 for myocardial infarction, 1.3 for stroke, 1.6 for angina, and 1.8 for revascularization.

Conclusions: In a clinical care cohort of HIV-infected and matched control patients, major adverse cardiac events including myocardial infarction, stroke, angina and coronary revascularization were more common among HIV-infected patients when compared as a composite endpoint or individually. The association of HIV with broader CVD endpoints and complications underscores the need for targeted interventions to prevent CVD, particularly in the setting of an aging HIV population.

MACE Incidence Rates			
	Incidence Rate HIV (95% CI)	Incidence Rate Non-HIV (95% CI)	Incidence Rate Ratio
Composite Endpoint	20.814 (18.625-23.261)	15.138 (14.418-15.894)	1.37 (1.214-1.553)
Myocardial Infarction	11.043 (9.480-12.863)	7.943 (7.426-8.500)	1.39 (1.170-1.644)
Stroke	8.299 (6.960-9.900)	6.175 (5.721-6.664)	1.34 (1.100-1.630)
Angina	2.342 (1.682-3.622)	1.431 (1.222-1.677)	1.64 (1.100-2.375)
Revascularization	0.535 (0.267-1.071)	0.299 (0.212-0.423)	1.79 (0.712-3.963)

739 Lower CD4 Count and Higher Viral Load Are Associated With Increased Risk of Myocardial Infarction

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Background: There is increasing evidence that cardiovascular disease (CVD) is more common among persons living with HIV (PLWH) than among HIV-negative individuals. However, most previous studies have been limited by small sample size, lack of well-defined clinical events, incomplete case ascertainment, and the use of composite endpoints. We examined which traditional CVD risk factors and HIV-specific factors predict myocardial infarction (MI) in PLWH.

Methodology: CNICS is a multi-center cohort comprised of 8 clinical sites contributing comprehensive clinical data on >27,000 HIV patients followed during routine care. We developed a state-of-the-art screening algorithm and central adjudication protocol for the validation of incident MIs. Among 18,115 eligible participants, we found 1360 individuals with potential incident MIs, of which 314 were confirmed as incident MIs. We used logistic regression to estimate risk of MI associated with baseline Framingham risk score (FRS) covariates (total and HDL cholesterol, systolic blood pressure (SBP), age, sex, diabetes, and smoking) and HIV factors (current CD4, HIV viral load, and transmission risk of injection drug use).

Results: In multivariate analysis the Framingham covariates smoking, age, total and HDL cholesterol, and SBP were significant predictors of incident MI. Diabetes and IDU were not significant. After adjusting for traditional CVD risk factors, each 300 cell/mm3 increase in current CD4 count was associated with a 25% decrease in the risk of MI, and higher HIV viral load was associated with a significant increase in MI risk. Median time between last measured CD4 count and end of follow-up due to event or administrative censoring was 84 days (IQR: 30-172 days).

Conclusions: While FRS covariates remain important, HIV-specific factors are also significantly associated with incident MI in PLWH. Higher prevalence of IDU among females likely confounds the effect of male sex. After adjusting for traditional CVD risk factors, the most recent CD4 count and HIV viral load prior to the event were independent predictors of MI incidence. Our findings highlight the importance of early and effective treatment for PLWH and provide additional evidence, based on a rigorously adjudicated clinical endpoint (MI), that immunodeficiency and active viral replication may be associated with the excess CVD risk in PLWH.

Traditional CVD and HIV-specific Risk Factors for MI	
Variable	Odds Ratio (95% CI)
Current CD4 (per 300 cell/mL)	0.75 (0.64, 0.88)
Current HIV RNA (log(copies/mL) +1)	1.10 (1.05, 1.16)
Smoker	3.08 (2.41, 3.95)
Age (decade)	1.65 (1.46, 1.86)
Total cholesterol (per 50 mg/dL)	1.22 (1.08, 1.37)
HDL cholesterol (per 20 mg/dL)	0.66 (0.55, 0.80)
Systolic Blood Pressure (per 20 mmHg)	1.22 (1.07, 1.41)
Male Sex	0.74 (0.56, 0.98)
Diabetes	1.30 (0.83, 2.05)
Injection Drug Use	1.19 (0.92, 1.54)

740 Long-Term Effects of Nitrite Inhalants On Cardiovascular and Renal Outcomes in the MACS Cohort

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Background: Drug abuse is strongly associated with risk behaviors linked to the HIV epidemic, and some forms of drug abuse are associated with more rapid disease progression and increased medical comorbidities. Stimulants, marijuana, and nitrite inhalants are recreational drugs frequently used in HIV-infected populations, but long-term effects of heavy use of these drugs on comorbidities and adverse outcomes with aging are not well characterized.

Methodology: Participants were 3366 HIV-negative and HIV-positive gay and bisexual men (68% Caucasian, 21% African American; median age 42 years at baseline visit, median 10 visits per subject) followed at semi-annual visits from 1996-2007 in the longitudinal Multicenter AIDS Cohort Study (MACS). Demographic, clinical, and behavioral variables from the MACS public dataset (p20 release) were translated from the data matrix to create a local SQL database. Substance abuse variables characterizing use of nitrite inhalants (poppers), cocaine, MDMA/MDA, uppers, marijuana, and heroin/opiates were harmonized and synthesized across study visits to classify within-subject trajectories of alcohol, smoking, and drug usage defined by maximum usage reported at 2 or more visits. Unadjusted analyses comparing frequency of cardiovascular diagnoses, eGFR<60 at 2 or more visits, malignancy outcomes, HCV and HBV status, and death outcomes across all study visits in groups classified by HIV status and drug use were performed using Fisher's exact test ($p<0.05$).

Results: In HIV-negative and HIV-positive subjects (n=1670 and 1589, respectively, 107 seroconverters; >30,000 person-visits), nitrite inhalants (53%), marijuana (44%), cocaine/crack (20%), uppers (10%), and MDMA/MDA (7%) were drugs used most commonly within the prior 6 months. Trajectory analysis showed most subjects had relatively consistent patterns of drug use over the study interval. Frequency of reported popper usage at all levels (daily, weekly, monthly, less than monthly, none) was similar among HIV-negative (3%, 18%, 10%, 19%, 51%) and HIV-positive subjects (3%, 22%, 13%, 19%, 44%). Unadjusted analysis of groups classified by HIV status and heavy (daily/weekly) or episodic (monthly or less) drug use revealed expected associations between cocaine or heroin use and HCV infection regardless of HIV status, and unexpected associations between heavy use of nitrite inhalants and increased frequency of cardiovascular, renal, and malignancy comorbidities in both HIV-negative ($p<0.001$, 0.02, and 0.004) and HIV-positive subjects ($p=0.04$, 0.048, <0.001), with median age for these outcomes > age 55.

Conclusions: These results suggest long-term adverse effects of heavy nitrite inhalant use on cardiovascular and renal comorbidities in HIV-negative and HIV-positive men.

741 HIV Infection and Immunodeficiency as Risk Factors for Ischemic Stroke

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Background: Large-scale epidemiologic data comparing ischemic stroke between HIV-positive and HIV-negative individuals are limited. We aimed to determine the association of HIV infection and immunodeficiency with ischemic stroke in a large cohort of HIV-positive and HIV-negative individuals with access to care.

Methodology: We conducted a cohort study of HIV-positive and demographically-matched HIV-negative members of Kaiser Permanente (KP) California during 1996-2011. Primary diagnoses of acute ischemic stroke were identified using ICD-9 codes 433.x1, 434 (excluding 434.x0), or 436; patients with a prior stroke within two years were excluded. We used Poisson regression to estimate rate ratios (RR) comparing stroke incidence rates between HIV-negative and HIV-positive subjects, both overall and stratified by recent CD4 cells/μL, recent HIV RNA copies/mL, and nadir CD4 cells/μL. Models were adjusted for age, sex, calendar year, race/ethnicity, socioeconomic status, smoking, alcohol/drug abuse, obesity, diabetes, hypertension, and lipid-lowering therapy. We also assessed risk factors for stroke in the HIV-positive subset.

Results: Among 24,768 HIV-positive and 257,600 HIV-negative subjects, the crude stroke incidence rate per 100,000 person-years was 125 for HIV-positive subjects and 74 for HIV-negative subjects, with an adjusted RR of 1.4 (95% confidence interval [CI]: 1.2-1.7). Compared with HIV-negative subjects, HIV-positive subjects with recent CD4 ≥500/μL or recent HIV RNA <500/mL were not at increased risk of stroke (Table). However, compared with HIV-negative subjects, stroke incidence was increased in HIV-positive subjects with recent CD4 <500/μL and recent HIV RNA ≥500/mL, with a weaker association for nadir CD4 <200/μL (Table). Among HIV-positive subjects, the only HIV-specific risk factor for stroke was recent CD4 <200/μL compared with ≥500/μL (RR 2.5, 95% CI: 1.3-4.6), whereas nadir CD4, recent viral load, and ever having used combination antiretroviral therapy were not independently associated with stroke.

Conclusions: Incidence of ischemic stroke in HIV-positive individuals with recent CD4 ≥500/μL was similar to that of HIV-negative individuals, while those with lower recent CD4 were at increased risk. The weaker results for nadir CD4 compared with recent CD4 suggest an acute effect of immunodeficiency on ischemic stroke incidence.

Table. Adjusted Risk of Ischemic Stroke Comparing HIV-positive with HIV-negative Subjects, 1996-2011

	RR (95% CI)		RR (95% CI)		RR (95% CI)
HIV-positive		HIV-positive		HIV-positive	
Recent CD4 <200	3.2 (2.3-4.4)	Recent HIV RNA ≥10,000	2.5 (1.8-3.5)	Nadir CD4 <200	1.6 (1.3-2.1)
Recent CD4 200-499	1.3 (1.0-1.7)	Recent HIV RNA 500-999	1.9 (1.3-2.9)	Nadir CD4 200-499	1.2 (0.9-1.5)
Recent CD4 ≥500	1.0 (0.8-1.4)	Recent HIV RNA <500	1.1 (0.9-1.4)	Nadir CD4 ≥500	1.4 (0.8-2.2)
HIV-negative (ref)	1	HIV-negative (ref)	1	HIV-negative (ref)	1
Overall *P*-value	<0.001		<0.001		0.16

Session P-P5 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Antiretroviral Therapy, Lipids, and CVD

742 Antiretroviral Therapy Is Associated With Significant Changes in Plasma Lipidome

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Background: Targeted measurement of over 400 plasma lipid species by mass spectrometry can sensitively identify changes in the plasma lipidome associated with the development of atherosclerosis and stratify patients into levels of future cardiovascular risk. Some of the HIV and ART-associated cardiovascular risk that persists despite correction for fasting lipids may be explained by changes in plasma lipidome. This study was performed to determine the change in lipidome associated with initiation of different antiretroviral regimens.

Methodology: Plasma lipid profiling (by liquid chromatography, electrospray isonisation-tandem mass spectrometry) was performed on 297 samples from the ALTAIR study which randomised ART-naïve HIV positive participants to one of three initial regiments, enofovir/emtricitabine with efavirenz (EFV), ritonavir-boosted atazanavir (ATZr) or zidovudine/abacavir (ZDV/ABC). Participants (n = 99) who remained on the randomised regimen with complete samples available at baseline, week 12 and 48 were included. 306 lipid species were detected in significant abundance for inclusion.

Results: Baseline characteristics and lipid profile (including lipid classes and species) were similar between the arms. Lower total and LDL cholesterol was seen with ZDV/ABC at week 48 compared with EFV or ATZ/r. In the EFV and ATZr arms there were significant changes in a number of lipid species from baseline to week 48 (27 and 49 respectively), some of which (4 and 6 respectively) have been previously identified to be associated with cardiovascular events in HIV.

There were no significant changes from baseline seen with ZDV/ABC. At week 48 significant differences in lipid species and classes by treatment regimen were detected; including increased trihexosylceramide (1.24 nM vs 1.0 nM, p <0.001), monohexosylceramide (9.81 nM vs 6.80 nM, p<0.001) and GM3 ganglioside (4.43 nM vs 3.20 nM, p<0.001) classes with EFV compared with ATZr. The same pattern of results was seen when comparing EFV with ZDV/ABC. The total and percent change in lipid species from baseline to week 48 was not statistically different between arms. Baseline HIV and metabolic characteristics did not predict changes in lipid species. Early change in HIV viral load was predictive of change in 24 lipid species and 1 class at 12 weeks; independent of treatment arm.

Conclusions: ART with EFV or ATVr induces significant changes in plasma lipidome which may be associated with future cardiovascular risk.

743 Rosuvastatin Lowers Cystatin C in HIV-Infected Subjects On Antioretroviral Therapy: SATURN-HIV

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Background: In chronic HIV-infection, both creatinine and cystatin C (CysC) based estimates of glomerular filtration rate (eGFRcr and eGFRcys) are less accurate than combined estimates (eGFRcr-cys) when compared to measured GFR; however, eGFRcys is a better predictor of mortality. This may be explained by non-GFR determinants of plasma cystatin C levels, particularly inflammation. Statins may improve CysC by decreasing inflammation.

Methodology: The Stopping Atherosclerosis and Treating Unhealthy Bone with Rosuvastatin in HIV (SATURN-HIV) trial randomized 147 patients on stable antiretroviral therapy (ART) with LDL-cholesterol <130mg/dL to 10 mg daily rosuvastatin or placebo. We analyzed relationships of baseline and 0-24 week changes in plasma CysC concentration with measures of cardiovascular risk and biomarkers of inflammation and immune activation using Spearman correlation analysis and multiple linear regression.

Results: Median (interquartile range) age was 46 (40-53) years; 78% were male, 68% African American, and 14% had hepatitis C. Tenofovir and protease inhibitors (PI) were used in 88% and 49% of subjects, respectively. Median eGFRcr was 100 (87-118) mL/min per 1.73 m2 and CysC was 0.83 (0.73-0.95) mg/L, without treatment group differences. Baseline CysC concentration correlated with carotid intima-media thickness (r 0.324, p<0.001), carotid distensibility (r 0.193, p=0.019), and coronary calcium score (r 0.170, p=0.040). Baseline CysC was associated with several markers of inflammation and immune activation and with use of PI, but not tenofovir (see Table). Soluble intercellular adhesion molecule-1 (sICAM-1) and tumor necrosis factor-α receptors I and II (TNF-RI/ II) were associated with CysC in a multivariable model independent of eGFRcr. After 24 weeks, mean CysC decreased significantly with statin therapy compared to placebo (-0.034mg/L vs. +0.010mg/L, p=0.008). Within the statin group, changes in CysC correlated with changes in sICAM-1 and TNF-RI (r 0.460, p<0.001 and r 0.372, p=0.002, respectively).

Conclusions: Rosuvastatin 10mg daily reduces plasma CysC in HIV-infected patients on ART. Baseline CysC concentrations are associated with cardiovascular risk, inflammation and immune activation. Reductions in CysC with statin therapy correlate with reductions in inflammatory biomarkers. The relationship between Cystatin C, cardiovascular disease, and mortality in HIV may partly be related to non-GFR factors such as inflammation.

Table: Relationship of demographics, HIV-specific parameters, and biomarkers of inflammation and immune activation to log-transformed baseline plasma cystatin C concentration.

	Univariable Analysis[†]		Multivariable Model[‡]	
	Estimate	p	Estimate	p
Demographics and Clinical Parameters				
Age (per decade)	0.0772	<0.001		
Caucasian Race	0.0889	0.028		
Male sex	0.0693	0.123		
Hepatitis B	0.1322	0.129		
Hepatitis C	0.0787	0.246		
Systolic BP (per 10mmHg)	0.0162	0.152	0.0206	0.018
Diastolic BP (per 10mmHg)	0.0224	0.245		
$eGFR_{cr}$ (per mL/min per 1.73 m^2)	-0.0057	<0.001	-0.0022	0.005
HIV-Specific Parameters				
Nadir CD4 (per 100cells/uL)	-0.0260	0.042		
HIV Duration (per year)	0.0060	0.024		
ART Duration (per year)	0.0064	0.093		
Protease Inhibitor use	0.0785	0.034	0.0715	0.009
Tenofovir use	0.0009	0.988		
Inflammation and Immune Activation[*]				
CD14+ CD16+ monocytes	0.0337	0.210		
Soluble CD163	0.1736	<0.001		
CD4+CD38+HLA-DR+ T-cells	0.0909	0.031		
CD8+ CD38+HLA-DR+ T-cells	0.0516	0.130		
Interleukin-6	0.1196	<0.001		
Soluble ICAM-1	0.0486	0.156	-0.058	0.041
Soluble VCAM-1	0.2158	<0.001		
Soluble TNF-α R1	0.3060	<0.001	0.2994	<0.001
Soluble TNF-α R2	0.2457	<0.001	0.2716	<0.001

[†] Only variables with p<0.25 in univariable analyses are shown (except for tenofovir use).
[‡] Multivariable model includes systolic BP, eGFRcr, PI use, ICAM, TNF-RI, and TNF-RII
[*] Cystatin C and all biomarkers of inflammation and immune activation were log-transformed prior to analyses
BP, blood pressure; $eGFR_{cr}$, 2009 Chronic Kidney Disease Epidemiology Collaboration equation for estimated glomerular filtration rate; ART, antiretroviral therapy; ICAM, intercellular adhesion molecule; VCAM, vascular cell adhesion molecule; TNF-α R1/2, tumor necrosis factor-α receptors 1 & 2.

744 Abacavir Induces Leukocyte Accumulation Through the Interaction of ATP and $P2X_7$ Receptors

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Background: The use of abacavir has been linked to cardiovascular disease. We have demonstrated (using a flow chamber system in vitro) that cyclic purine analogues (abacavir and didanosine) induce leukocyte-endothelial cell interactions through Mac-1/ICAM-1 interaction, and that this effect is not produced by pyrimidine analogues (lamivudine, zidovudine, emtricitabine) or the acyclic nucleotide tenofovir. However, the molecular mechanism underlying these interactions remains elusive. Given the chemical structure of abacavir, we have explored whether its proinflammatory effects are a result of the interference of its structure with the purine signalling pathway.

Methodology: Human umbilical vein endothelial cells (HUVEC) and polymorphonuclear leukocytes (PMN) were treated with abacavir (0.5-15 µmol/L) to determine: 1) intracellular ATP levels by a luciferase bioluminescence assay; and 2) expression of CD73 (the enzyme responsible for ATP degradation) by western blotting. To analyse the role of ATP and its receptors in the leukocyte accumulation induced by abacavir, HUVEC and PMN were pre-treated with antagonists of $P2X_7$ ATP receptors [oxATP (600 µmol/L) or BGG (5 µmol/L)] prior to abacavir (10 µmol/L, 4h) administration and leukocyte-endothelium interactions were then measured using a flow chamber system. Data are expressed as mean±SEM. Statistical analysis was performed with one-way ANOVA and a Newman-Keuls post-hoc test, with significance set at $^{**}p<0.01$ (vs. control), $n\geq3$.

Results: Clinical concentrations of abacavir (0.5-15 µmol/L, 4h) produced an increase in intracellular ATP levels on HUVEC (abacavir 10 µmol/L: 197.6±22.4** vs. 100% control) and PMN (abacavir 10 µmol/L: 158.1±15.4** vs. 100% control) and a decrease in CD73 expression on HUVEC (abacavir 10 µmol/L: 52.2±10.2** vs. 100% control) and PMN (abacavir 10 µmol/L: 18.7±14.7** vs. 100% control). Abacavir-induced leukocyte-endothelial cell interactions were absent following pre-treatment with $P2X_7$ receptor antagonists.

Conclusions: Our results suggest a structure-activity relationship in the effects of abacavir on leukocyte accumulation through the interaction of ATP with its $P2X_7$ receptors. This proinflammatory mechanism may be especially relevant for understanding the vascular damage observed in abacavir-treated patients.

745 LDL Particles and Lipoprotein-Phospholipase A2 in Naive HIV+ Patients Randomized To DRV/r vs ATV/r

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Background: Atadar study compared plasma lipids in HIV naïve patients randomized to Atazanavir/ritonavir (ATV/r) or darunavir/ritonavir (DRV/r) plus tenofovir/emtricitabine (NCT 01274780, 11th HIV Congress, Glasgow 2012, abstract O423). The aim of this substudy was to obtain a more profound knowledge of the proinflammatory properties of lipid changes by the analysis of LDL particles and lipoprotein-phospholipase A2 (Lp-PLA2) at week 48.

Methodology: Multicenter, randomized study. Fasting total cholesterol (TC), high density lipoprotein (HDL-c), and low density lipoprotein (LDL-c)-cholesterol, Apo A-I, Apo B, triglycerides (TG), LDL size (by gel electrophoresis) and Lp-PLA2 activity (by 2-thio-PAF) were measured at baseline and w 48. Comparisons between groups and within groups were performed by t-student and paired t test. Multivariate analysis was done by regression analysis. Variables are expressed as mean (SD).

Results: Eighty-six (ATZ/r n=45 and DRV/r n=41) patients were included: age 36.7 (8.7), 89% men, 51.1 % current smokers. No differences in demographic and lipid measurements were found at baseline: TC 150.7 (28.7), LDL-c 92.5 (26.1), HDL-c 36.7 (9.9), TG 112.7 (71.5) mg/dL, LDL size 270.6 A(2.95), total Lp-PLA2 22.3 umol/min-1xml (6.31), 34% (10.6) in HDL particles and 66 %(10.6) in LDL particles . At w 48 an increase in TC (+15.5 (41.8); p=0.03 and +14.9 (28.3);p=0.004 in ATZ/r and DRV/r) and HDL-c (+5.4 (8.8); p<0.001 and +3.5 (8.2);p=0.02 in ATZ/r and DRV/r) was observed, with LDL-c increasing only in DRV/r (+10.5 (27.5);p=0.035) and TG in ATZ/r (+39.4 (85.6); p=0.002). Only TG change was significantly different between arms, favoring DRV/r (p=0.02). No change was found in TC/HDL-c while Apo A-I/Apo B increased in ATZ/r (+0.16 (0.4); p=0.02). LDL particles size increased only in DRV/r (1.09 A(2.55); p=0.02; p (between arms)=0.006), associated with a shift to the less atherogenic LDL phenotype A (80% at baseline to 91.4% at w 48 in DRV/r and 73.3% at baseline to 69.2% at w 48 in ATZ/r arm, p (between arms at w 48)= 0.06). No changes in total Lp-PLA2 activity nor in the distribution in LDL or HDL particles were found at w 48; nevertheless a decrease in HDL-Lp-PLA2 activity was observed in both arms (- 0.72 (1.41); p<0.001 in ATZ/r and -0.96 (2.54); p=0.06 in DRV/r). In multivariate analysis, only TG change was related to LDL particle size change (b -0.138 (-0.19 to -0.086); p<0.001).

Conclusions: An improvement in the atherogenecity of LDL particles was found in DRV/r arm, related to a lower TG increase. No significant changes in total Lp-PLA2 were observed in any arm, although HDL-Lp-PLA2 decreased with both PI/r-based regimens.

746 Darunavir or Atazanavir vs Raltegravir Lipid Changes Are Unlinked To Ritonavir Exposure: ACTG 5257

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Background: Lipid profiles following antiretroviral therapy (ART) vary by regimen type and by ritonavir (RTV) exposure. Changes in fasting lipid profile (FLP) were assessed after ART initiation and correlated with plasma RTV trough concentrations (C24) in the A5257 study.

Methodology: ART-naïve individuals >age 18 years with HIV-1 RNA level>1000 copies/mL were eligible. Subjects were randomized 1:1:1 to ATV (atazanavir 300 mg daily (QD)+RTV 100 mg QD), RAL (raltegravir 400mg twice daily) or DRV (darunavir 800mg QD+RTV); all subjects received emtricitabine/tenofovir 200/300 mg QD. Subjects were followed until the last enrolled reached 96 weeks. FLP was measured at weeks 0, 24, 48, 96, and 144, and steady state RTV C24 (24±2 hours post dose) was measured once for a subset of subjects on RTV tablet. Mean changes in FLP over time from baseline were plotted with 95% confidence intervals (CI), differences between ART regimens were estimated with 97.5% CI and compared using pairwise Student's T-tests. Associations between RTV C24 and changes in FLP at 48 weeks were evaluated via Spearman correlations.

Results: A total of 1809 subjects were enrolled; 34% non-Hispanic white, 42% non-Hispanic black, 22% Hispanic. 24% were women. Subjects with confirmed baseline fasting samples were included in the analyses (n=1797). Baseline overall median HDL-cholesterol (HDL-C) 38 mg/dL, calculated LDL-cholesterol (LDL-C) 92 mg/dL, and triglycerides (TG) 103 mg/dL. LDL-C and TG levels increased with DRV and ATV but not with RAL from baseline to week 144 (Fig 1a-b). While these 2 lipid parameters were not different between DRV and ATV, each protease inhibitor (PI) arm had greater increases in these parameters compared with the RAL arm (all p≤0.001). HDL-C increased modestly with no differences between arms (all p>0.05) [Fig 1 c]. As-treated and sensitivity analyses excluding subjects on lipid-lowering agents did not change results. RTV C24 was quantified in a subset (109 on ATV and 119 on DRV) with median values of 69 ng/mL and 74 ng/mL in the ATV and DRV arms, respectively (p=0.9). No significant correlation existed between RTV C24 and changes in any of the lipid parameters (p>0.1) (Fig 1d).

Conclusions: The RAL arm produced the most favorable lipid profile. RTV C24 was not different between the 2 PI arms and had no relationship with the modest but similar increases in lipids observed with either the ATV or the DRV arm. The long-term clinical significance of the lipid changes noted in the PI arms relative to the RAL arm are unknown.

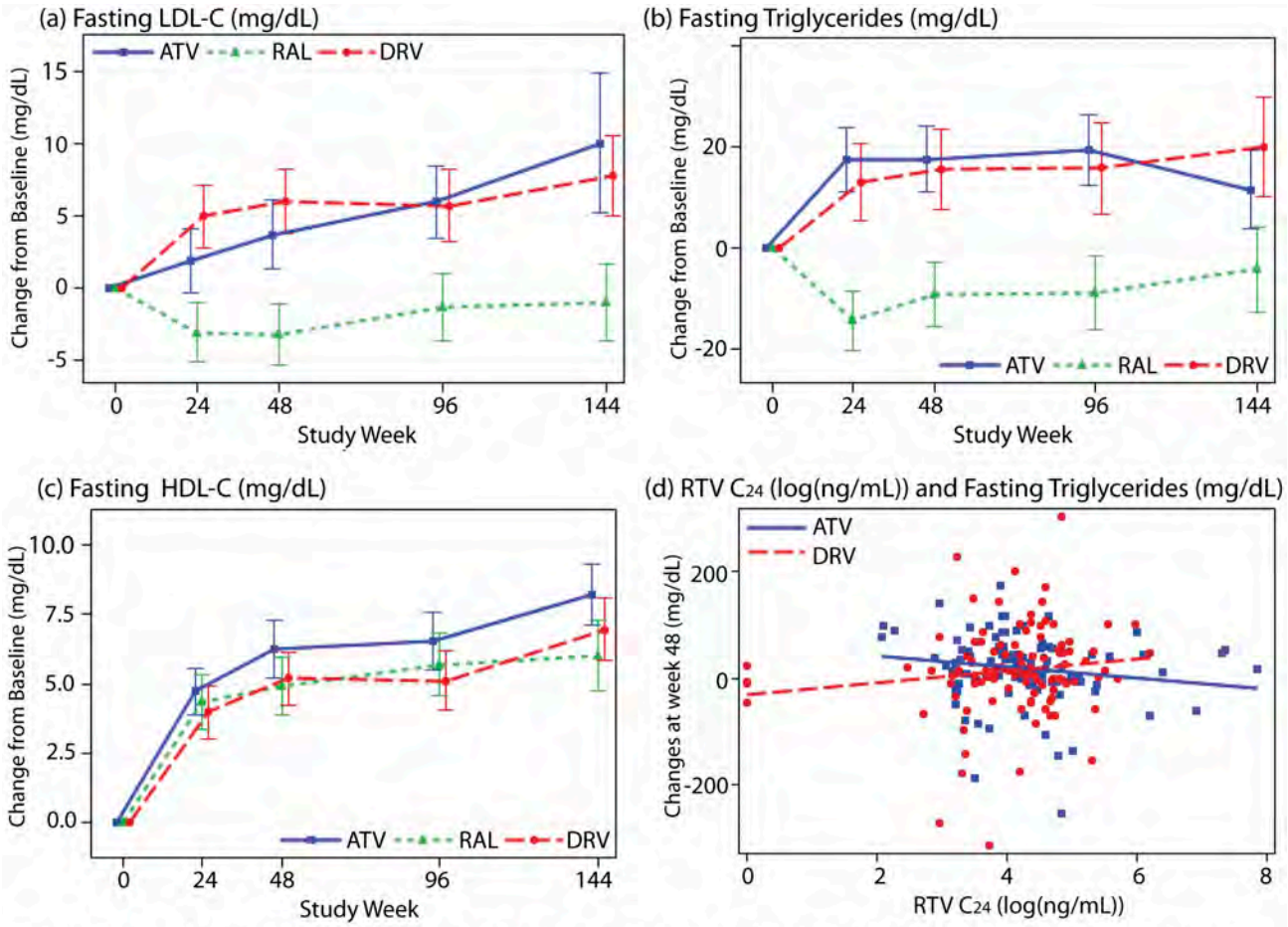

Figure 1: Panels a-c: Mean of Changes from Baseline in Fasting Lipid Profile (mg/dL) over Time; panel d: C_{24} (log(ng/mL)) and Fasting Triglycerides: Change from Baseline to Week 48

747LB Is There Continued Evidence for an Association Between Abacavir and Myocardial Infarction Risk?

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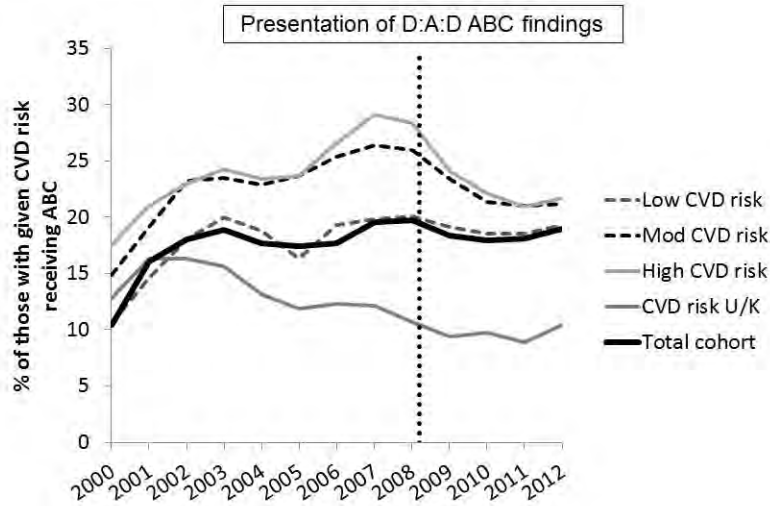
Background: In March 2008, the D:A:D study published results showing an increased risk of myocardial infarction (MI) in those on abacavir (ABC). We describe changes in use of ABC since publication, and reinvestigate this association with subsequent follow-up.

Methodology: D:A:D participants were followed from study entry until the first of: MI, death, 1st Feb 2013 or end of follow up. Associations between 10-year Framingham cardiovascular disease (CVD) risk (low [<10%], moderate [10-20%], high [>20%] or unknown [U/K]) and likelihood of initiating or discontinuing ABC were assessed with multivariable logistic/Poisson regression. Poisson regression also assessed the association between current ABC use (with 6-month lag to allow for recent discontinuation) and MI risk, adjusting for use of other ART drugs and confounders. Analyses were performed separately pre- and post-March 2008.

Results: Use of ABC increased from 10% in 2000 to 20% in 2008, before stabilising at 18-19% (Figure). Increases in use pre-March 2008, and subsequent decreases, were greatest in those at moderate and high CVD risk. Post-March 2008, those on ABC at moderate/high CVD risk were more likely to discontinue ABC than those at low/unknown CVD risk, regardless of VL (≤1000 cps/ml: relative rate (RR) 1.49 [95% CI 1.34-1.65]; >1000 cps/ml: 1.23 [1.02-1.48]); no such associations were seen pre-March 2008. There was some evidence that ART-naïve people at moderate/high CVD risk post-March 2008 were less likely to initiate ABC than those at low/unknown CVD risk (odds ratio 0.74 [0.48-1.13]). By 1st Feb 2013, 941 MI events occurred in 367,559 person years (PYRS) (rate 0.26 [0.24-0.27]/100 PYRS). Rate of MI was 0.47 [0.42-0.52] for current ABC use and 0.21 [0.19-0.22] otherwise. Current ABC use was associated with a 98% increase in MI rate (RR 1.98 [1.72-2.29]), with no difference in the pre- (1.97 [1.68-2.33]; 672 events, 210,250 PYRS) or post- (1.97 [1.43-2.72]; 269 events, 157,309 PYRS) March 2008 periods (interaction p=0.74). Results were unchanged after further adjusting for factors potentially on the causal pathway (pre-March 2008: 1.88 [1.55-2.28]; post-March 2008: 2.03[1.46-2.84]), including renal function, dyslipidaemia and hypertension.

Figure: Use of ABC in D:A:D cohort over time



Conclusions: Despite channelling of ABC away from those at higher CVD risk since 2008, we continue to observe an association between ABC use and MI risk. Whilst confounding cannot be ruled out in any cohort study, this argues against channelling bias as an explanation for our findings

748 Lipidomic Profiling in HIV: Implications for Risk-Prediction Models

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Background: HIV positive patients are at increased risk for coronary artery disease (CAD) with both HIV and antiretroviral associated dyslipidaemia contributing. Targeted analysis of over 400 plasma lipid species by mass spectrometry can sensitively identify changes in the plasma lipidome associated with the development of atherosclerosis.

Methodology: In a retrospective case-control study we profiled the plasma lipidome (268 lipid species included) of 113 subjects. Cases (n=23) were HIV positive individuals who had a blood sample available in the 12 months prior to the diagnosis of CAD. They were age and sex matched 1:2 with HIV positive individuals without a diagnosis of CAD (n=45, HIV+ controls) and with healthy HIV negative volunteers (n=45, Healthy controls). Risk prediction models incorporating the plasma lipidome were compared with established cardiovascular risk scores.

Results: 104 (92%) were male with a median age of 52.2 years (IQR 40.9-61.4). HIV patients (combined cases and HIV+ controls) were more likely to smoke (31 [45.5%] v's 3 [6.7%], p <0.001), had higher median hsCRP (2.78 [IQR 1.97 - 6.67] v's 0.64 [IQR 0.36 - 1.48], p<0.001) and triglyceride levels (1.77 [IQR 1.47-2.76] v's 1.00 [0.7-1.76], p <0.001) and lower high density lipoprotein cholesterol (0.95 [IQR 0.78 - 1.13] v's 1.50 [IQR 1.1 - 1.7], p <0.001) than healthy controls. 23 (100%) of cases and 40 (88.9%) of HIV+ controls were currently receiving antiretroviral therapy. 83 lipid species and 7 lipid classes were identified that were significantly associated with HIV infection. A further 74 species and 8 classes where significantly associated with future CAD event. 15 species (predominantly in the triacylglycerol and diacylglycerol classes) were elevated in HIV infection and further elevated in HIV subjects who went on to have a CAD event. Risk prediction models incorporating lipid species outperformed (AUC=0.78 (0.775,0.785)) all other tested risk scores (including the Framingham, Reynolds and the Data Collection on Adverse Events of Anti-HIV drugs [D:A:D] risk equations) in the identification of HIV positive subjects who went on to develop CAD.

Conclusions: Treatment-experienced HIV positive patients demonstrate significant differences in plasma lipidome when compared with healthy HIV negative controls. There is a potential application for improved cardiovascular risk screening of HIV positive patients in the clinical setting by including lipid species in risk prediction models.

749LB Effect of Switch From Abacavir To Tenofovir DF On Platelet Function Markers: A SWIFT Trial Substudy

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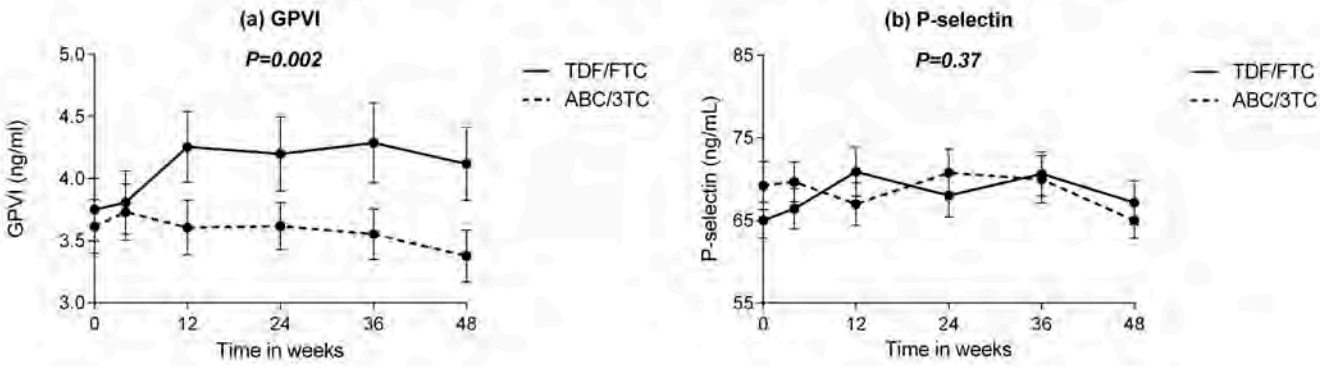
Background: Current and recent use of the nucleoside reverse transcriptase inhibitor, abacavir (ABC) has been associated with increased risk of myocardial infarction, with both endothelial dysfunction and altered platelet reactivity with ABC use implicated.

Methodology: Changes in markers of platelet function were examined in a sub-study of the SWIFT trial, a prospective, randomised, 48-week trial of virally suppressed, protease-inhibitor-treated, HIV-1 positive subjects randomised to switch abacavir/ lamivudine (ABC/3TC) to tenofovir disoproxil fumarate/ emtricitabine (TDF/FTC) or remain on ABC/3TC. Soluble glycoprotein VI (sGPVI), a marker of collagen-mediated platelet activation and soluble P-selectin (sP-sel), involved in platelet-leucocyte interactions, were measured by enzyme-linked immunosorbent assays (Meso Scale Discovery, Rockville, MD) in stored plasma samples collected at weeks 0, 4, 12, 24, 36 and 48. Changes in platelet markers over time were assessed using mixed effect models. Data are mean [SD] unless specified.

Results: Of 312 patients (age 46 [9.3] years, 85% male, 65% Caucasian), 156 switched to TDF/FTC. Groups were well matched for baseline demographic and laboratory data including CD4+ T-cell count (TDF/TFC versus ABC/3TC, 548 [257], 582 [287] /µl respectively), platelet count (244 [58], 253 [72] x103/µl), total cholesterol (5.4 [1.2], 5.3 [1.0] mmol/L), LDL (3.1 [1.0], 3.1 [0.8] mmol/L) and HDL (1.29 [0.38], 1.31 [0.42] mmol/L) cholesterol and history of dyslipidaemia or hypertension. There were no between-group differences in baseline sGPVI (mean (SEM) 3.75 [0.25] ng/ml versus 3.61 [0.22] ng/ml, p=0.68) or sP-sel (65.0 [2.2] ng/ml versus 69.2 [2.9], p=0.25) and no between-group differences in change in sP-sel from baseline to 48 weeks (p=0.37, figure 1b). However, relative to the ABC/3TC group, sGPVI increased to week 48 in those who switched to TDF/FTC (effect size +0.012 (95%CI 0.0041, 0.02), between group p=0.002, figure 1a). This effect persisted when corrected for age, ethnicity, history of dyslipidaemia or hypertension, baseline CD4+ T-cell and platelet count and change from baseline to week 48 in creatinine, LDL, HDL, CD4+ T-cell and platelet count.

Conclusions: The observed increases in sGPVI point to changes in intrinsic platelet function with a switch away from ABC/3TC to TDF/FTC. Further mechanistic research is required to determine the relevance of these changes on overall platelet reactivity and cardiovascular disease.

Figure 1. Change in markers of platelet function over time



Session P-P6 Poster Session
Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall B**

Statins and ARV Effects in HIV

750 Rosuvastatin Lowers Oxidative LDL in HIV-Infected Persons On Antiretroviral Therapy: SATURN-HIV

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Background: Circulating oxidative low density lipoprotein (oxLDL), a known risk marker for cardiovascular disease (CVD), has not been well studied in HIV. Also, in HIV-uninfected populations, statins reduce oxLDL, but their effect in HIV is unknown. We report the first comprehensive study of oxLDL in HIV assessing its relationship to immune activation and CVD risk, and changes in oxLDL with rosuvastatin.

Methodology: We randomized 147 patients on stable antiretroviral therapy with LDL ≤130mg/dl to rosuvastatin 10 mg daily or placebo. Baseline and 0-24 week changes in oxLDL and oxLDL:LDL ratio were compared between groups. Spearman correlation was used to explore relationships between baseline oxLDL and oxLDL:LDL with inflammation/immune activation markers and CVD risk measures. Linear regression was used to determine predictors of 0-24 week change in oxLDL and oxLDL:LDL in the rosuvastatin group.

Results: Overall, 78% were men, 68% African American, 63% current smokers. 49% were on a protease inhibitor. Baseline median (Q1-Q3) age was 46 (40-53) years, BMI 27 (23-30) kg/m^2, CD4$^+$ count 613 (425-853) cells/mm^3 and 79% had HIV-1 RNA ≤50 copies/ml. Baseline LDL was 97 (77-113) mg/dl, oxLDL 45 (37-56) U/l and oxLDL:LDL 18 (15-23) U/mmol without differences between groups. The table shows correlates of oxLDL and oxLDL:LDL at baseline. OxLDL was significantly correlated with HOMA-IR (ρ=+0.17; p=0.038), hyperemic velocity (measure of microvascular health) (ρ=-0.16; p=0.051) and carotid distensibility (measure of vascular stiffness) (ρ=-0.17; p=0.047), but not with brachial artery flow mediated dilation, carotid intima media thickness or coronary artery calcification. After 24 weeks oxLDL decreased significantly within the rosuvastatin group (p<0.0001) and vs placebo (-6.64 vs +1.02 U/l; p<0.01); whereas oxLDL:LDL increased with rosuvastatin (p<0.01) and vs placebo (+3.25 vs -0.5 U/mmol; p=0.02). CD4$^+$ count (β=-3.58x10^{-4}; p=0.047), cystatin C (β=-0.75; p=0.003), change in LDL (β=0.01; p=0.025) and change in HDL (β=-0.02; p=0.011) were independently associated with change in oxLDL in the rosuvastatin group, but not change in any inflammation or immune activation markers.

Conclusions: In HIV, oxLDL levels are associated with several inflammation markers as well as insulin resistance, microvascular health and vascular stiffness. Rosuvastatin decreased oxLDL over 24 weeks, but this was not associated with changes in inflammation or immune activation.

Spearman Correlation Analysis- Baseline OxLDL and OxLDL:LDL with Inflammation/Immune Activation

Baseline	Oxidative LDL (U/l)		Oxidative LDL:LDL (mmol/l)	
	Coefficient	P	Coefficient	P
LDL (mg/dl)	0.52	<0.001	-0.3	<0.001
HDL (mg/dl)	-0.24	0.004	-0.22	0.008
eGRFcr (ml/min per 1.73 m^2)	-0.17	0.04	-0.22	0.009
Cystatin C (mg/l)	0.19	0.026	0.33	<0.001
IL-6 (pg/ml)		NS	0.18	0.027
hsCRP (**µg/ml)**	0.19	0.02		NS
sICAM-1 (ng/ml)	0.17	0.030		NS
IP-10 (pg/ml)		NS	0.18	0.031
sCD163 (ng/ml)		NS	0.17	0.039

eGFRcr, 2009 Chronic Kidney Disease Epidemiology Collaboration equation for estimated glomerular filtration rate; IL-6, interleukin-6; hsCRP, high sensitivity C-reactive protein; sICAM-1, soluble intercellular adhesion molecule-1; IP-10, interferon-γ-inducible protein-10; sCD163, soluble CD163

751LB After 52 Weeks, Pitavastatin Is Superior To Pravastatin for LDL-C Lowering in Patients With HIV

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Background: Based on current guidelines for patients with HIV and dyslipidemia, statins with the lowest potential for drug-drug interactions (DDIs) with antiretroviral therapy (ART) are recommended. Pitavastatin (PTA) has a reduced potential for cytochrome P450-mediated DDIs and in the phase 4 trial INTREPID, PTA 4 mg demonstrated superior LDL-C reduction vs pravastatin (PRA) 40 mg in adult, HIV subjects after 12 weeks. The objective was to evaluate the safety and secondary efficacy endpoints of PTA 4 mg vs PRA 40 mg following the INTREPID 40-week safety extension (Week 52).

Methodology: INTREPID was a 12-week, phase 4, randomized (1:1), double-blind, double-dummy, active-controlled, parallelgroup superiority study followed by a 40-week safety extension. Eligible patients (250 planned for enrollment for ~ 90% power to detect difference in LDL-C) were on stable ART with a HIV-1 RNA <200 copies/mL, CD4 count >200 cells/µL, and an elevated fasting serum LDL-C (≥130 mg/dL and ≤220 mg/dL) and TG (≤400 mg/dL). Least squares means, SEs, and CIs are from an ANCOVA model with percent change in LDL-C to Week 52 as the dependent variable and treatment as the independent variable, adjusting for site and randomized viral hepatitis B or C infection status. Safety assessments included AEs, clinical/laboratory tests, HIV-1 RNA load, CD4 count, and virologic failure.

Results: 252 patients were randomized (126/group): mean age ~ 50 years, BMI ~ 28 kg/m2, male ~86%, Caucasian ~80%, and negative for hepatitis B or C infection (90.5%). After 52 weeks, LDL-C reduction was statistically superior for PTA (-30%) vs PRA (-21%) with a treatment difference of -8.4% (p = 0.0007)(Table). Increases in HDL-C and decreases in TG were not significantly different between PTA and PRA. Subjects experiencing TEAEs through Week 52 were similar between PTA (85 subjects; 67.5%) and PRA (88 subjects; 69.8%). The frequency of TEAEs leading to study discontinuation was similar between PTA (4.8%) and PRA (4.0%). HIV-1 RNA viral load mean change was 0.03 copies/mL (mean 6.5%) in the PTA group and 0.07 copies/mL (mean 9.2%) in the PRA group. No deaths and no notable changes in CD4 count or AST/ALT for either treatment. Virologic failure occurred in 4 (3.2%) PTA subjects and in 6 (4.8%) PRA subjects.

Conclusion: Pitavastatin 4 mg demonstrated sustained safety and was superior to pravastatin 40 mg in LDL-C reduction after 52 weeks of therapy in HIV-infected adults with dyslipidemia.

	Pitavastatin 4 mg			Pravastatin 40 mg		
	Hepatitis B/C Present (n = 11)	Hepatitis B/C Absent (n = 110)	All Subjects (N = 121)	Hepatitis B/C Present (n = 13)	Hepatitis B/C Absent (n = 113)	All Subjects (N = 126)
Baseline LDL-C						
n	11	110	121	13	113	126
Mean (SD)	145.8 (23.90)	156.0 (26.04)	155.1 (25.93)	143.2 (24.82)	155.9 (23.56)	154.6 (23.91)
Week 52 LDL-C						
n	7	89	96	11	79	90
Mean (SD)	120.4 (12.25)	107.9 (24.30)	108.9 (24.12)	116.2 (31.74)	123.0 (25.82)	122.2 (26.50)
Week 52 Mean %Change from Baseline[a] LDL-C						
n	7	89	96	11	79	90
Mean (SD)	–17.1 (16.73)	–30.7 (17.17)	–29.7 (17.42)	–20.3 (20.49)	–20.5 (14.70)	–20.5 (15.38)

Treatment Difference in Adjusted Mean Percent Change in LDL-C at Week 52		
Least squares mean (SE)	95% CI	*P* value
–8.35 (2.42)	(–13.13, –3.56)	0.0007

752 Endothelial Progenitor Cells Increase in Older HIV-Infected Patients Receiving Telmisartan

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University of California Los Angeles, Los Angeles, CA, United States

Background: Bone marrow-derived endothelial progenitor cell (EPC) production reflects endothelial regenerative capacity. EPC production is partially mediated by angiotensin II, decreases with age, and correlates with measures of vascular function and cardiovascular disease (CVD; Hill, 2003; Schmidt-Lucke, 2010). Endothelial dysfunction and decreased EPC numbers have been documented in HIV-infected patients (Teofili 2010; da Silva 2011). Telmisartan is an angiotensin receptor blocker that increases EPC production in HIV-uninfected persons (Pelliccia, 2010); therefore, we assessed its effects on EPC number and type in older HIV-infected patients.

Methodology: HIV-infected persons >50 years of age with plasma HIV-1 RNA <50 copies/mL on stable ART and ≥1 CVD risk factor were recruited and received open label telmisartan 80mg daily for twelve weeks. In this exploratory analysis, EPCs were quantitated via flow cytometry using fresh blood. Using CD34 and CD133 as markers of "early" EPC maturity and KDR as a marker for endothelial lineage commitment, EPCs were defined as viable CD3-/CD33-/CD19- cells that were also CD133+/KDR+, CD34+/KDR+, CD34+/CD133+, or CD34+/KDR+/CD133+.

	Median # per 10^5 PBMC (IQR)			Median Within-Person Change (IQR)			
Total Absolute EPC	**Week 0**	**Week 6**	**Week 12*†**	**6 Weeks**	***p***	**12 Weeks*†**	***p***
$Glycophorin^-/CD133^+/KDR^+$	8.0 (2.7, 112.4)	82.8 (11.3, 188.2)	89.2 (17.6, 159.9)	9.8 (1.0, 119.4)	***0.02***	14.6 (-2.3, 133.4)	*0.13*
$CD34^+/CD133^+$	33.3 (13.4, 85.5)	67.2 (31.6, 121.8)	87.6 (31.2, 128.5)	11.4 (-1.3, 25.4)	***0.06***	50.1 (6.0, 70.9)	***0.009***
$CD34^+/KDR^+$	1.8 (0.8, 49.6)	39.5 (2.0, 85.2)	45.9 (4.1, 77.6)	2.3 (-1.4, 50.4)	***0.09***	5.6 (-0.3, 59.3)	***0.04***
$CD34^+/CD133^+/KDR^+$	0.9 (0.3, 48.0)	38.5 (1.6, 83.9)	44.1 (3.0, 74.6)	1.6 (0.0, 50.4)	***0.04***	4.5 (0.1, 64.0)	***0.02***
$CD34^+$ EPC Subset	**% of CD34+ EPC (IQR)**			**Median Within-Person Change (IQR)**			
$CD133^+$	34.9 (32.5, 46.4)	37.6 (31.7, 43.1)	36.4 (25.3, 41.7)	-0.4 (-2.7, 6.3)	*0.93*	-0.1 (-13.6, 14.1)	*0.98*
KDR^+	5.9 (1.7, 17.4)	14.8 (2.6, 26.0)	14.5 (4.9, 20.8)	2.7 (-0.2, 11.2)	*0.12*	-0.2 (-6.1, 6.9)	*0.71*
$CD133^+/KDR^+$	4.2 (0.4, 15.2)	14.4 (2.4, 25.4)	14.1 (3.1, 19.8)	2.6 (-0.1, 12.9)	***0.07***	0.4 (-6.0, 13.0)	*0.59*

*One subject excluded for increasing statin dose between weeks 6 and 12
†12 subjects off drug
IQR=Interquartile range

Results: Seventeen subjects (65% non-Caucasian, 88% male, median age 60 years, Framingham risk score 10%, BMI 27 kg/m2, blood CD4+ T cell count 625 cells/mm3) enrolled and completed all evaluations. Frequencies of ART classes used in this group included: 71% PI, 29% NNRTI, 29% integrase inhibitor, 65% TDF, 29% ABC. Cardiovascular risk factor prevalence in this group included: 82% hyperlipidemia, 65% hypertension, 18% current tobacco use, 12% diabetes mellitus. After twelve weeks, absolute numbers of all EPC subtypes increased significantly (see table), including CD34+/133+/KDR+ EPCs, which are rare in circulation but highly specific for EPC lineage. In a subset analysis of CD34+ EPCs, maturity markers remained stable, but endothelial commitment increased.

Conclusions: Telmisartan increased endothelial regenerative potential (EPC number and type) in older HIV-infected patients on ART. The magnitude of EPC increase (specifically CD34+/KDR+ cells) was greater than previously reported amongst HIV-uninfected persons with coronary artery disease (Endtmann, 2011), however the exact clinical significance of this is unknown. Larger, randomized studies are needed to confirm this finding and define telmisartan's role as an agent for endothelial preservation in HIV-infected patients.

Session P-Q1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Biomarkers and Non-AIDS Events

753 Incidence of CD4/CD8 Ratio Normalization and Its Role in the Onset of Non-AIDS-Related Events

Cristina Mussini[1], Patrizia Lorenzini[2], Alessandro Cozzi-Lepri[3], Giuseppe Lapadula[4], Giulia Marchetti[5], Emanuele Nicastri[2], Antonella Cingolani[6], Miriam Lichtner[7], Andrea Antinori[2], Antonella d'Arminio Monforte[5], for the Icona Foundation Study Group

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Background: Immune-reconstitution after therapy (cART) is often either quantitatively or qualitatively incomplete. Aim of the study was to evaluate in the Icona cohort patients (pts) the probability of reaching a CD4/CD8 ratio >=1 after starting cART and its possible protective role against the onset of non-AIDS related events (nADE) or death for any cause.

Methodology: Pts were included if started cART, reached undetectable viral load (VL) (<=80 copies/mL) (time 0 of the analysis) and had a CD4/CD8 ratio at undetectability 1. nADE were: cardiovascular events, stroke, non-AIDS defining cancers. Multivariable Poisson regression model was used to analyze factors independently associated with normalization and with clinical progression.

Results: 3,236 pts were included, 76.4% males, mean age 39 years, 88.3% Italians, 18.3% CDC stage C. At starting cART, mean CD4 was: 223 cells/uL (range 101-317) and mean CD4/CD8 ratio was 0.39 (range 0.26-0.55). 717 pts (22.2%) were HCV co-infected and 178 (5.5%) HBV. Median CD4 count at time 0 was 378 cells/uL (range 249-518). Over 7,305 PYFU, 458 pts reached a CD4/CD8 ratio >1 [IR=6.3 per 100 PYFU (95%CI 5.7-6.9)]. Probability of normalization was 30%, 95%CI 26%-35% by 15 years using KM method. At multivariable analysis, factors associated with a higher chance of achieving normalization were: a higher CD4/CD8 ratio before starting cART (RR: 1.72 for 0.10 higher, 95%CI 1.62-1.83; p=0.000) and having started cART more recently (RR: 1.03 per more recent year, 95%CI 1.01-1.06; p=0.007). In contrast, older pts (RR: 0.87 per 10 year older, 95%CI 0.78-0.97; p=0.016), homosexual contacts (RR: 0.74 vs. heterosexuals; 95%CI 0.57-0.96; p=0.022), those with a nadir CD4 value below 200 (RR: 0.73 vs. >200, 95%CI: 0.57-0.95; p=0.017), HBV co-infected (RR 0.58 vs. HIV mono-infected, 95%CI: 0.35-0.99; p=0.045) and those treated with AZT/3TC (RR 0.70 95%CI 0.48-1.00 p=0.051) or ddI/d4T (RR 0.31 95%CI 0.11-0.87 p=0.027) using tdf+ftc as reference were less likely to achieve normalization. CD4/CD8 was associated with the risk of developing nADE or death independently of current CD4 count (Table 1).

Conclusions: A minority of pts who start cART reaches a CD4/CD8 ratio >1. Younger patients, those with a higher CD4/CD8 ratio at time of viral suppression and those starting cART more recently and with higher CD4 count have higher possibilities to achieve normalization. The CD4/CD8 ratio was predictive of clinical progression independently from CD4 cell count.

Factors associated to clinical progression or death			
	ARR*	>95% CI	p
Current CD4 (per 100 cell/mmc higher)	0.94	0.89–0.99	0.013
Current CD4/CD8 T-cell ratio			
>0.45	1.00		
0.30-0.45	0.99	0.73– 1.34	0.934
<0.30	1.64	1.20– 2.24	0.002
*Adjusted for gender, mode of HIV transmission, white race, and the following variables measured at baseline: age, HCV coinfection, CDC C stage and log10 HIV-RNA. No colinearity problems were found (mean VIF=1.13).			

754 Longitudinal Changes in Free Testosterone Among Older HIV-Infected and HIV-Uninfected Men

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Background: In the general population, aging is associated with lower testosterone levels and a decrease in the diurnal variation of testosterone secretion. Although cross-sectional studies have shown lower than expected testosterone levels in HIV-infected men, it is unclear whether age-related longitudinal changes in serum testosterone differ by HIV serostatus.

Methodology: We identified HIV-infected men from the Multicenter AIDS Cohort Study (MACS), age ≥ 45 years at initiation of highly active antiretroviral therapy (HAART), who had ≥ one serum sample available prior to HAART-initiation (i.e. the baseline visit) and ≥ 2 serum samples in the 10 years following HAART-initiation. They were matched to HIV-uninfected men by age, race, MACS site and calendar time of pre and post-HAART samples. Men who received exogenous hormones of any kind and/or had free testosterone concentrations (FT) >150 ng/dL, suggestive of unreported testosterone use, were excluded. Linear mixed effects regression was used to determine whether log FT and its rate of change over the study interval differed by HIV serostatus. Log FT values were back-transformed for reporting.

Results: Data were available from 182 HIV-infected and 267 HIV-uninfected men. The median age at baseline was 48.8 years (Interquartile range (IQR); 45.8, 53.4). The median number of FT measurements per participant was 4 (IQR; 3, 5) drawn over a median of 6 years (IQR; 2.9, 9.5). Of the 1737 samples analyzed, 65% were drawn in the morning. After adjustment for age, race, BMI, hepatitis C status, smoking, the presence of diabetes mellitus and MACS site, median baseline FT levels were significantly lower among HIV-infected men than HIV-uninfected men in morning samples (67 ng/dL [95% Confidence Interval (CI):65-71] v. 72 ng/dL [95% CI: 69-74], respectively; p=0.037), but not in afternoon/evening samples (65 ng/dL [95% CI:62-69] v. 65 ng/dL [95% CI: 62-67], respectively; p= 0.728). However, the annual rate of FT decline after adjustment for time of day of the sample draw and other covariates did not differ significantly by HIV serostatus: -1.1% for HIV- infected men (95% CI: -0.4% , -1.8%) v. -1.0% for HIV-uninfected men (95% CI: -0.6%, -1.5%), p = 0.913.

Conclusions: FT decreased similarly over a 6-year interval in older HIV-infected and HIV-uninfected men, but morning FT levels were lower among HIV-infected men, but not afternoon/evening levels. These data may suggest a loss of diurnal variation in FT among HIV-infected men.

755 Inflammatory Biomarkers in Chronic HIV Disease Predominantly Associate With Monocyte Activation

Eleanor M. P. Wilson[1], Amrit Singh[1], Kathy Huppler Hullsiek[2,3], Keith Henry[2,3], Ken Lichetenstein[4], Pragna Patel[5], John T. Brooks[5], Irini Sereti[1], Jason V. Baker[2,3]
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Background: We have previously shown soluble biomarkers of inflammation, including an IL-6/D-dimer composite score, independently predict non-AIDS related morbidity and mortality. We explored associations between select biomarkers and cellular immunophenotypes to identify potential mechanisms of excess inflammation among HIV-infected adults.

Methodology: Baseline plasma specimens from SUN Study participants were analyzed for levels of IL-6, hsCRP, sCD14, sCD163, and D-dimer. We performed immunophenotyping for markers of T cell activation and maturation (HLA-DR, CD38, CX3CR1, CD28, CD57) and monocyte activation and migration (CCR2, CD14, CD16, tissue factor [TF], CX3CR1, CCR5). We evaluated associations between cellular phenotypes and soluble markers by Spearman rank correlation. Linear regression was used to estimate the percent change in plasma biomarker level for each 5 unit difference in cellular phenotype, after adjustment for: age, gender, race, smoking, diabetes, treatment for hypertension or hyperlipidemia, hepatitis, CD4 cell count, and HIV RNA <400 copies/mL. Due to multiple comparisons, we defined significance as p-value ≤0.01.

Results: Participants' (n=670) median age was 41 years and CD4 count 471 cells/μL; 76% were male, 44% smokers, 88% on ART, and 72% had HIV RNA <400 copies/mL. Correlations of biomarkers with select cellular phenotypes are shown (Table). In fully adjusted models, a 5 unit greater frequency of CD14++CD16+ monocytes was associated with 11.4% higher IL-6 (p<0.001), 27.5% higher D-dimer (p<0.001), and 10.9% higher hsCRP (p=0.004); a corresponding difference of monocytes expressing CCR2 was associated with 6.9% lower D-dimer (p=0.003) and CCR5 with 1.4% higher sCD163 (p<0.001). Of T-cell subsets, greater frequencies of CD4+HLADR+CD38+ T-cells were independently associated with higher sCD163 (5.1%, p<0.001) and CD8+CD28+ T-cells with lower sCD163 (3.0%, p=0.001) and D-dimer (1.2%, p=0.001). Finally, an IL-6/D-dimer clinical risk score was positively associated with CD14++CD16+ monocytes (p<0.001) and inversely with CD8+CD28+ T-cells (p=0.009) in adjusted models.

Conclusions: Plasma biomarkers that strongly predict clinical risk for non-AIDS morbidity were consistently and strongly associated with monocyte activation phenotypes and modestly with T-cell maturation, but not CD8+ T-cell activation, phenotypes. These findings may help direct treatment strategies to control persistent inflammation in chronic HIV disease.

756 Extrinsic Pathway Coagulation Factors Are Associated With Mortality During Treated HIV Disease

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Background: We previously reported that HIV replication increases non-hepatocyte dependent procoagulant factors and decreases hepatocyte-dependent pro- and anticoagulant factors, resulting in a procoagulant state. Here we explore mortality risk associated with these changes in the context of treated HIV disease.

Methodology: In a nested case-control study of the SMART and ESPRIT control arms (randomized to continuous antiretroviral therapy), we evaluated all-cause mortality associations with 9 extrinsic pathway factors (listed in Table); 6 are hepatocyte products (FII, FVII, FIX, FX, antithrombin, protein C). Three controls were matched per case on enrollment date, age (+/- 5yrs), study, and country. Odds ratios (OR) with 95% confidence intervals (CI) for 4th vs. 1st quartile of each marker were estimated using conditional logistic regression accounting for matching factors and adjusting for gender and race. To study the combined effect of the hepatocyte-dependent factors, individual biomarkers for each case/control set were ranked and combined over the 6 biomarkers to obtain a "Hepatocyte Score". Additional covariates studied included: hepatitis co-infection, diabetes, cardiovascular disease, and baseline CD4, HIV RNA, and IL-6.

Results: Among cases (n=134) and controls (n=388), respectively, median CD4 count was 454 and 495 cells/mm3, and 65 and 77% had viral suppression at baseline. Median factor (F) levels and mortality OR are listed (Table); findings include: 1) mortality increased with higher FV and FVIII levels (non-hepatocyte procoagulant cofactors), 2) mortality was inversely related to FVII levels, protein C (anticoagulant), as well as the composite hepatocyte score; mortality association for the score was not attenuated after adjustment for all covariates (OR 0.38; p=0.01), 3) When restricted to participants with viral suppression at entry, FV (OR 1.97; p=0.05), FVIII (OR 2.28, p=0.03), FVII (OR 0.35, p<0.01) and protein C (OR 0.38, p=0.02) remained associated with mortality 4) Adjusting specifically for IL-6 levels attenuated FV and FVIII, but not FVII or Protein C, associations.

Conclusions: Findings support that hypercoagulation contributes to disease risk via alterations in the profile of extrinsic pathway coagulation factors, mediated by inflammation (e.g., FVIII) and hepatocyte dysfunction (e.g., protein C). Studies are needed to further clarify mechanisms by which alterations in coagulation biology leads to disease among treated HIV patients.

Extrinsic Pathway Coagulation Factors and Mortality Risk				
CoagulationMarker	Cases (n=134)Median (IQR)	Controls (n=388) Median (IQR)	Mortality OR* 4th vs. 1st QRT (95% CI)	p-value
F V (%)	109 (87-135)	98 (85-120)	2.13 (1.23-3.69)	0.007
F VIII (%)	148 (110-189)	128 (100-160)	2.68 (1.45-4.95)	0.002
TFPI ng/mL	27 (21-35)	26 (21-32)	1.27 (0.71-2.27)	0.42
Hepatocyte Score			0.39 (0.20, 0.77)	0.007
F II (%)	100 (85-116)	105 (92-121)	0.63 (0.35-1.13)	0.12
F VII (%)	94 (77-112)	102 (82-123)	0.49 (0.26-0.93)	0.03
F IX (%)	96 (82-113)	97 (84-111)	0.95 (0.53-1.71)	0.87
F X (%)	92 (78-104)	92 (80-107)	0.68 (0.38-1.22)	0.19
Antithrombin (%)	126 (109-141)	129 (114-143)	0.80 (0.45-1.42)	0.44
Protein C (%)	109 (91-126)	117 (100-134)	0.54 (0.30, 0.98)	0.04
F = factor; TFPI = tissue factor pathway inhibitor*adjusted for age, gender, race, study (SMART or ESPRIT) and date and country of enrollment				

757 Correlates of Inflammatory Markers After One Year of Suppressive Antiretroviral Treatment (ART)

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Background: Elevated levels of inflammatory markers such as interleukin (IL)-6 are associated with HIV-associated non-AIDS morbidity and death. Traditional risk factors such as substance use, obesity, triglycerides, cholesterol and fasting glucose levels are likely increased in HIV+ adults, and may be causally related to inflammation. We examined the cross-sectional association between a panel of inflammatory markers, and metabolic and other risk factors in a well-treated HIV+ adult population.

Methodology: A previously described case-control study was performed on HIV+ adults enrolled in the ACTG-ALLRT cohort who were ART naïve at study entry, received a modern ART regimen, and were virally suppressed (<400 copies/ml) at year 1 of ART. This analysis examined the controls that were the event-free comparator population. Spearman correlations (unadjusted and partial) evaluated biomarkers and selected behavioral, metabolic and anthropometric factors at year 1.

Results: Subjects (N=315) were 85% male; mean age was 44 years. At year 1, 59% had CD4 > 350 cells/mm3, 89% had HIV RNA ≤ 50 copies/ml. After adjusting for CD4 and other factors, levels of plasma IL-6, soluble tumor necrosis factor receptors (sTNFR)-I and II, interferon gamma inducible protein-10 (IP-10), soluble CD14 (sCD14), and D-dimer positively correlated with age (p<.0001). IL-6 positively correlated with waist circumference (r=0.22, p<.001), waist-hip ratio (r=0.15, p<.01), # cigarettes/day (r=0.19, p<.01) and fasting glucose (FG) (r=0.25, p<.001). Correlations for waist circumference, smoking and FG were significant even after adjustment for each of the other factors. IL-6 levels increased as the number of metabolic syndrome components increased (r=0.15, p<.01). sCD14 correlated with BMI (r=-0.12, p=0.03) and smoking (r=0.29, p<.001). sTNFR-I correlated

with waist-hip ratio (r=0.21, p<.001) and smoking (r=0.18, p<.01). sTNFR-II correlated with waist circumference (r=0.15, p=0.01), waist-hip ratio (r=0.21, p<.001), smoking (r=0.24, p<.001), FG (r=0.14, p=0.03) and triglyceride levels (r=0.20, p<.001). None of factors examined gave significant correlations for D-dimer and IP-10.

Conclusions: As in the general population, increased age, increased central obesity and smoking are associated with increased levels of soluble inflammatory markers in HIV+ virally suppressed patients. These findings underscore the relationships between inflammation and behavioral, anthropometric and metabolic risks in treated HIV infection. Future studies should focus on determining the mechanisms for these associations, and whether the impact of inflammation on disease progression is independent of these factors.

758 Pro12Ala Polymorphism Is Associated With Metabolic Disturbance in HIV/HCV Coinfected Patients

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Background: Peroxisome proliferator-activated receptor gamma-2 gene (*PPARγ2*) rs1801282 (Pro12Ala) polymorphism has been associated with lower risk of metabolic disturbance and atherosclerosis. The aim of our study was to analyze the association between the *PPARγ2* rs1801282 polymorphism and metabolic disturbance in human immunodeficiency virus (HIV)/Hepatitis C virus (HCV) coinfected patients.

Methodology: A cross-sectional study in 257 non-diabetic HIV/HCV-coinfected patients from Hospital Gregorio Marañón (Madrid, Spain) was carried out between September 2000 and July 2009. Genotyping was performed by using GoldenGate® assay with VeraCode® Technology in Centro Nacional de Genotipado (CeGen). Besides, were analyzed serum lipids (cholesterol, triglycerides, high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), LDL-C/HDL-C ratio, and atherogenic index (AI)), and homeostatic model assessment (HOMA) values. Only 207 patients were performed liver biopsy, which were classified according to escala METAVIR score, and in 109 of 207 patients were evaluated serum adipokines (leptin, adiponectin, resistin, plasminogen activator inhibitor-1(PAI-1), hepatic growth factor (HGF), and nerve growth factor (NGF)) by multiplex LINCOPLEX™ assay with Luminex 100™ analizer. The genetic association study was carried out according to a dominant genetic model of G allele (CC vs. CG/GG), which was the model that best fit to our data. Univariate and Multivariate Generalized Linear Models (GLM) were used to study the *PPARγ2* polymorphism effect on different clinical variables (lipid profile and IR).

Results: rs1801282 CG/GG genotype (Ala variant) was associated with low values of cholesterol (arithmetic mean ratio (AMR)=0.87 (95% of confidence interval (95%CI)=0.79; 0.96); p=0.004), LDL-C (AMR=0.79 (95%CI=0.68; 0.93); p=0.003), LDL-C/HDL-C (AMR=0.83 (95%CI=0.71; 0.99); p=0.034), and AI (AMR=0.84 (95%CI=0.75; 0.99); p=0.042). Furthermore, rs1801282 CG/GG genotype (Ala variant) was associated with low values of HOMA (AMR=0.71 (95%CI=0.50; 0.99); p=0.048) among patients with significant liver fibrosis (F≥2). Moreover, rs1801282 Ala variant was also associated with low serum values of HGF (AMR=0.61 (95%CI=0.39; 0.94); p=0.028), and NGF (AMR=0.47 (95%CI=0.26; 0.84); p=0.010).

Conclusions: The presence of *PPARγ2* rs1801282 CG/GG genotype (Ala variant) was associated with a protective effect for metabolic disturbance versus CC genotype in HIV/HCV coinfected patients. Thus, *PPARγ2* rs1801282 polymorphism may play a significant role in the development of metabolic disorders in HIV/HCV coinfected patients, and might have an influence on the cardiovascular risk.

759 Predictors of Incident Hypertension in HIV-Positive Adults Over 24 Months On ART in South Africa

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Background: As the current HIV population ages and access to antiretroviral therapy (ART) increases in resource-limited settings, the number of patients developing non-communicable chronic diseases on ART will also increase. In view of limited research on this topic in resource-limited settings, we sought to examine predictors of hypertension in a large urban HIV clinic in South Africa.

Methodology: Prospective study of hypertension over 24 months on ART among 12376 ART naïve adults initiating ART at Themba Lethu Clinic in Johannesburg between April 2004-2011. Patients with hypertension at ART initiation were excluded. We used Cox proportional hazards regression to examine demographic and clinical characteristics at ART initiation in relation to incident hypertension. We first defined hypertension as systolic >140 and/or diastolic blood pressure (BP) >90 mmHg and/or documentation of hypertensive medication. We then categorized it as mild (systolic BP 140-159.9 and/or diastolic BP 90-99.9 mmHg) or moderate/severe (systolic BP ≥160 and/or diastolic BP ≥100 mmHg). Person-time started at ART initiation and ended at the earliest of hypertension, loss, death, transfer or completion of 24 months of follow-up.

Results: Among 17 378 eligible patients, 29% (5002) had documented hypertension at ART initiation. The remaining 12 376 were predominately female (62%) and on stavudine-lamivudine-efavirenz (75%). At ART initiation patients had a median age of 36 years (IQR: 31-42), median CD4 count of 94 cells/mm^3 (IQR: 35-166), median systolic blood pressure of 113 mm/Hg (IQR: 103-123) and median diastolic blood pressure of 73 mm/Hg (IQR: 66-80). By 24 months, 2116 (17%) developed hypertension, of whom 1857 (88%) were mild and 259 (12%) were moderate/severe. Regression models showed older patients (≥40 years), males, and patients with a BMI ≥25 kg/m^2 had an increased rate of hypertension over 24 months (Table). Results for mild hypertension were similar, while results for moderate/severe hypertension showed a higher hazard for patients ≥50 years and those with a BMI ≥35 kg/m^2

Conclusions: 20% of patients in our cohort developed hypertension within 24 months on ART. Obese patients (BMI ≥30kg/m^2) and those older ≥40 years of age should be targeted for frequent BP monitoring and identification of other cardiovascular risk factors in order to implement lifestyle modifications and pharmaceutical therapy as indicated to help prevent myocardial infarction, heart failure, stroke and kidney disease.

Table. Predictors of hypertension after 24 months on Antiretroviral Therapy at Themba Lethu Clinic, Johannesburg, South Africa (n=12 376)

		Hypertension 24 Months			Mild Hypertension 24-month			Moderate/Severe Hypertension 24-month		
		Hypertension (n, %)	Crude HR (95% CI)	Adjusted HR (95% CI)	Hypertension (n, %)	Crude HR (95% CI)	Adjusted HR (95% CI)	Hypertension (n, %)	Crude HR (95% CI)	Adjusted HR (95% CI)
Initiating NRTI	tenofovir	288 (14.3)	1.0	1.0	263 (13.0)	1.0	1.0	21 (1.0)	1.0	1.0
	stavudine	1868 (18.0)	1.2 (1.1-1.4)	1.3 (1.1-1.4)	1594 (15.4)	1.1 (1.0-1.3)	1.2 (1.0-1.3)	2.8 (2.3)	2.1 (1.4-3.4)	2.2 (1.4-3.5)
Initiating NNRTI	efavirenz	1957 (17.1)	1.0	1.0	1686 (14.7)	1.0	1.0	232 (2.0)	1.0	1.0
	nevirapine	199 (21.4)	1.2 (1.1-1.4)	1.5 (1.3-1.7)	171 (18.4)	1.2 (1.0-1.4)	1.5 (1.3-1.8)	27 (2.9)	1.4 (1.0-2.1)	1.8 (1.2-2.6)
Age at ART initiation (yrs.)	18-24.9	50 (8.1)	0.5 (0.4-0.7)	0.6 (0.4-0.8)	40 (6.5)	0.5 (0.3-0.7)	0.5 (0.4-0.7)	9 (1.5)	0.9 (0.5-1.8)	0.9 (0.5-1.8)
	25-29.9	176 (9.1)	0.6 (0.5-0.7)	0.6 (0.5-0.7)	148 (7.7)	0.5 (0.4-0.7)	0.6 (0.5-0.7)	26 (1.4)	0.8 (0.5-1.3)	0.8 (0.5-1.3)
	30-39.9	900 (15.6)	1.0	1.0	794 (13.8)	1.0	1.0	93 (1.6)	1.0	1.0
	40-49.9	693 (15.6)	1.6 (1.4-1.7)	1.6 (1.4-1.7)	605 (20.0)	1.6 (1.4-1.7)	1.5 (1.4-1.7)	74 (2.4)	1.6 (1.2-2.2)	1.7 (1.2-2.3)
	≥50	337 (32.4)	2.5 (2.2-2.9)	2.5 (2.2-2.9)	270 (26.0)	2.3 (2.0-2.6)	2.3 (2.0-2.6)	57 (5.5)	4.2 (3.1-5.9)	4.3 (3.1-6.0)
Sex	Female	1251 (16.2)	1.0	1.0	1056 (13.7)	1.0	1.0	163 (2.1)	1.0	1.0
	Male	905 (19.4)	1.3 (1.2-1.4)	1.4 (1.2-1.5)	801 (17.2)	1.4 (1.3-1.5)	1.4 (1.3-1.6)	96 (2.1)	1.1 (0.8-1.4)	1.1 (0.9-1.5)
BMI at ART initiation (kg/m^2)	<18	355 (12.8)	0.9 (0.8-1.0)	0.9 (0.8-1.0)	301 (10.8)	0.9 (0.7-1.0)	0.8 (0.7-1.0)	49 (1.8)	1.2 (0.9-1.7)	1.1 (0.8-1.5)
	18-24.9	1168 (16.5)	1.0	1.0	1020 (14.4)	1.0	1.0	129 (1.8)	1.0	1.0
	25-29.9	431 (23.3)	1.5 (1.3-1.6)	1.5 (1.3-1.7)	369 (20.0)	1.4 (1.3-1.6)	1.5 (1.3-1.7)	53 (2.9)	1.6 (1.2-2.2)	1.6 (1.2-2.3)
	30-34.9	140 (27.6)	1.7 (1.5-2.1)	1.8 (1.5-2.2)	119 (23.4)	1.7 (1.4-2.0)	1.8 (1.5-2.2)	16 (3.2)	1.8 (1.1-3.0)	1.9 (1.1-3.3)
	35-39.9	45 (40.5)	2.7 (2.0-3.7)	2.8 (2.0-3.8)	35 (31.5)	2.4 (1.7-3.4)	2.5 (1.8-3.5)	8 (7.2)	4.5 (2.2-9.2)	4.4 (2.1-9.2)
	≥40	17 (42.5)	2.8 (1.7-4.5)	2.8 (1.7-4.5)	13 (32.5)	2.4 (1.4-4.2)	2.4 (1.4-4.2)	4 (10.0)	6.0 (2.2-16.3)	6.0 (2.2-16.5)
CD4 count at ART initiation (cells/mm^3)	>200	213 (18.4)	1.0	1.0	275 (16.0)	1.0	1.0	35 (2.0)	1.0	1.0
	101-200	735 (17.5)	1.0 (0.8-1.1)	1.0 (0.8-1.1)	627 (14.9)	0.9 (0.8-1.1)	1.0 (0.8-1.1)	91 (2.1)	1.0 (0.7-1.4)	1.0 (0.7-1.5)
	51-100	445 (18.2)	1.0 (0.9-1.2)	1.0 (0.9-1.2)	274 (15.3)	1.0 (0.9-1.2)	1.0 (0.9-1.2)	64 (2.6)	1.3 (0.9-2.0)	1.3 (0.8-1.9)
	0-50	660 (16.5)	1.0 (0.9-1.2)	1.1 (1.0-1.3)	681 (14.5)	1.1 (0.9-1.2)	1.1 (1.0-1.3)	69 (1.7)	0.9 (0.6-1.4)	1.0 (0.6-1.5)
Hb at ART initiation (ug/dL)	≥10.0	1645 (18.0)	1.0	1.0	1429 (15.6)	1.0	1.0	187 (2.1)	1.0	1.0
	>10.0	511 (15.8)	1.1 (1.0-1.2)	1.2 (1.1-1.4)	428 (13.2)	1.0 (0.9-1.1)	1.2 (1.1-1.3)	72 (2.2)	1.3 (1.0-1.7)	1.5 (1.1-2.0)
WHO stage at ART initiation	I/II	1281 (18.3)	1.0	1.0	1106 (15.8)	1.0	1.0	149 (2.1)	1.0	1.0
	III/IV	875 (16.2)	1.0 (0.9-1.1)	1.0 (0.9-1.1)	751 (13.9)	0.9 (0.9-1.0)	1.0 (0.9-1.1)	110 (2.0)	1.0 (0.8-1.3)	1.1 (0.8-1.4)

*All demographic and clinical characteristics at ART initiation that were adjusted for in the model are shown in the table

Session P-Q2 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Frailty: Physical Function and Telomeres

762 Frailty, Inflammation and Mortality Among Aging HIV-Infected and At-Risk Injection Drug Users

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Background: Serum measures of inflammation increase with age and have been strongly associated with adverse clinical outcomes among both HIV-infected and uninfected adults. Yet, limited data exists on the potential predictive and clinical utility of aggregate measures of inflammation. Recently, a simple additive index has been validated to best capture the effect of inflammation on mortality among adults 65 years of age and older. Frailty is an age-related syndrome of increased vulnerability to adverse clinical outcomes. Previously, we observed a significant association of frailty with both HIV and mortality risk among aging injection drug users (IDUs). In this study, we evaluated the relationship of frailty with the validated inflammation index and examined the independent effect of this index on mortality.

Methodology: Frailty was defined in the ALIVE cohort of current and former IDUs by the presence of ≥3 of 5 standard criteria: weakness (grip strength), slow gait speed, weight loss, low physical activity, and exhaustion. An inflammatory index score was constructed from serum measures of interleukin-6 (IL-6) and soluble tumor necrosis factor-α receptor-1 (sTNFR1): (log IL-6 + 2*log sTNFR1)/3. Multinomial logistic regression was used to assess the relationship of frailty with inflammation. Mortality was ascertained for the period 2005 through 2010 through linkage to the National Death Index. Cox proportional hazards models were used to estimate the risk (hazard ratios [HR] with 95% confidence intervals [CI]) for all-cause mortality.

Results: Among 1326 subjects, the median age was 48 years, 88% were African American, 457 (34%) were female, and 387 (29%) were HIV+. In separate models, adjusting for sociodemographics, comorbidity, and HIV status, frailty was significantly associated with log IL6 (aOR 1.34; 95% CI, 1.10-1.64), log sTNFR1 (aOR 1.79; 95% CI, 1.11-2.89) and with each unit increase in the inflammatory index score (aOR 2.00; 95% CI, 1.32-3.01). In models adjusting for sociodemographics, comorbidity, HIV and frailty status, the inflammatory index score was independently associated with increased mortality risk (aHR 2.90; 95% CI, 2.18-3.84); for HIV-'s (aHR 2.74; 95% CI 1.88-3.99) and for HIV+'s (aHR 2.55; 95% CI, 1.65-2.95). Similar results were observed adjusting for CD4 count and HIV viral load.

Conclusions: A recently validated, simple, biologically informed inflammatory index is strongly associated with frailty and independently associated with mortality risk among aging HIV-infected IDUs, independent of HIV disease stage. Further studies of the clinical utility, biological underpinnings, and potential therapeutic targets related to this index may ultimately facilitate improved clinical management for aging HIV-infected persons.

763 Brisk Walking Improves Inflammatory Markers in cART-Treated Patients

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Background: Low grade chronic inflammation is a predictor of cardiovascular disease and metabolic problems, which are frequent complications in patients receving combination antiretroviral therapy (cART). The aim of this study is to evaluate the benefit of brisk walking as moderate insensity exercise, with or without strength exercise, on metabolic and inflammatory parameters in cART-treated patients.

Methodology: We enrolled 50, HIV-infected cART-treated, sedentary subjects in a 12-week exercise program, consisting of 3 outdoor sessions/week of 60 min walking at 65-75% of HR (Heart Rate) max with ("walk/strength" group) or without ("walk" group) 30 min circuit training at 65% of 1-RM (Repetition Maximum). Subjects were assessed at baseline (BL) and 12 weeks (W12) by 6-minute walking test (6MWT) and 1-RM test, morphometric measures (BMI, waist, hip and leg circumferences), blood examination (cytometry, fasting total, HDL and LDL cholesterol, tryglicerides, glucose, insulin, AST/ALT, gGT, CPK, HbA1c, CD4 and CD8 cells, plasma HIV-RNA) and body mass distribution by DEXA. We measured traditional markers of chronic immune activation (IL6, d-dimer and sCD14), and IL-18 and myostatin, as potential negative regulators of adipose tissue and muscle homeostasis, respectively. Statistical analysis was performed by Wilcoxon-signed paired rank test and Spearman'scorrelation.

Results: 35/50 subjects (26 men, 9 women; medianage 48 yrs) completed the 12-week program: 21 in the "walk" group and 14 in the "strength-walk" group. At W12, participants showed significant improvement of performance at 6MWT ($P<0.0001$) and in all strength exercises (crunch $p=0.0002$, lat machine $p=0.0002$, chest press $p=0.0007$, leg extension $p=0.014$, sitting calf $p=0.0004$, leg press $p=0.002$); of BMI ($p=0.004$), waist ($p=0.050$) and hip ($p=0.041$) circumferences; total ($p=0.0004$) and LDL cholesterol ($p=0.0004$). Significant level reductions were observed for d-dimer, IL-18, IL-6 and myostatin (Table 1). No intercorrelations were observed between % changes at W12 of each marker.

Conclusions: Moderate intensity exercise improved aerobic fitness and metabolic markers in cART-treated patients, and it was associated with improvement of immune activation markers and, possibly, adipose tissue and muscle homeostasis.

Markers measured in this study			
	BL (median, IQR)	W12 (median, IQR)	p
sCD14 (ng/mL)	802 (682-1044)	866 (659-993)	n.s.
d-dimer (ng/mL)	273 (177-392)	181 (138-341)	0.0002
IL-6 (pg/mL)	9.37 (7.21-10.89)	8.35 (7.46-9.49)	0.05
IL-18 (pg/mL)	28.4 (20.5-33.0)	23.4 (13.7-31.2)	0.01
Myostatin (ng/mL)	20.9 (10.4-27.3)	13.5 (5.1-24.4)	0.006

764 Cell-Mediated CMV Responses in HIV-Infected Persons With Impaired Physical Function

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Background: Immune responses to human cytomegalovirus (CMV) increase with age and HIV-infection and correlate with cardiovascular disease markers. We previously demonstrated greater odds of functional impairment among HIV-infected persons with higher CMV IgG concentrations, immune activation (%CD38HLA-DR on CD8+ T cells) and inflammation (IL-6, TNF-alpha). Here we evaluated the hypothesis that cell-mediated CMV responses were associated with functional impairment and inflammation/activation in persons aging with HIV infection.

Methodology: Case-control study of 45-65 year-old HIV-infected subjects, on antiretroviral therapy >6 months, plasma HIV-1 RNA <48 c/mL. Low function (LF) cases and high function (HF) controls were identified by clinical criteria, and matched by age, gender, and time since HIV diagnosis. CMV-specific T cell responses were determined by the proportion of CD4+ and CD8+ T cells expressing IFN-γafter stimulation with CMV pp65 peptides and described using geometric mean and 95% confidence intervals (CI). Odds of LF was estimated by conditional logistic regression. Associations between continuous variables were described by Spearman correlation.

Results: 30 LF cases were matched to 48 HF controls; mean (SE) age 53 ± 0.8 years; 21% female; 76% Caucasian and 17% Hispanic. Compared to controls cases had similar current CD4 (549 ± 49 vs 639 ± 40 cells/μL, $p=0.16$), lower nadir CD4 (110 ± 27 vs 178 ± 22 cells/μL, $p=0.04$) and greater smoking prevalence (48% vs 20%, $p=0.01$). As previously reported, higher CMV IgG was associated with a 5-fold greater odds of LF (CI 1.5, 17.0) per log10 increase in CMV IgG ($p=0.01$) and was correlated with markers of inflammation: IL-6 ($r=0.37$, $p<0.001$), hs-CRP ($r=0.29$, $p=0.01$), TNF-alpha ($r=0.24$, 0.04); activation: %CD38+HLA-DR+ CD8+ T cells ($r=0.21$, $p=0.07$); and immune senescence: %CD28-CD8+ T cells ($r=0.27$, $p=0.02$). Odds of LF were not significantly different by CMV-specific CD8+ T cells (1.08; 0.92, 1.28; $p=0.35$) or CD4+ T cells (OR 0.99; CI 0.76, 1.29; $p=0.95$). Correlation was detected between CMV IgG and CMV-specific CD8+ T cells ($r=0.30$, $p=0.007$) but not CMV-specific CD4+ T cells ($r=0.17$, $p=0.15$). CMV-specific CD8+ T cells were not correlated with inflammation, activation, or senescence markers; all $r\leq|0.12|$, $p\geq0.31$. CMV-specific CD4+ T cells were correlated with CD28-CD4+ T cells ($r=0.37$, $p<0.001$), but not inflammation or activation markers; all $r\leq|0.11|$, $p\geq0.36$.

Conclusions: Cell-mediated immune response to CMV was not a significant predictor of low physical function and was not associated with inflammation/activation among HIV-infected adults on effective ART. CMV-specific humoral responses are more strongly correlated with functional impairment and related inflammation, activation and senescence.

765 Presence of the Immune Risk Phenotype and Telomere Shortening Among HIV Treated Patients

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Background: Although effective combination antiretroviral therapy (cART) increases levels of CD4+ T-cells, other T-cell phenotypic alterations often persist in the long-term. These phenotypic abnormalities resemble the Immune Risk Phenotype (IRP) observed in elderly uninfected individuals that have a high risk of morbidity and mortality. The IRP consists of immunologic and serologic markers that include: low CD4:CD8 T-cell ratio (<1), high CD28-negative T-cell percentages and CMV IgG seropositivity. The IRP is also associated with immune senescence yet it has never been evaluated among HIV patients. In this pilot study, we investigated the prevalence of the IRP among successfully treated HIV patients and assessed how this phenotype relates to markers of immune senescence such as telomere shortening.

Methodology: The IRP prevalence was evaluated in 126 successfully treated HIV patients and in 21 age-matched controls. Patients and controls were assessed for CMV serology, CD4:CD8 ratio and CD4+CD28- T-cells percentages. All HIV patients had undetectable viral loads at the time of evaluation. Individuals with clinical manifestation of CMV disease were excluded from the study. Telomere length was measured by Flow-FISH analysis in a subset of 24 HIV patients which were categorized into 2 groups based on their IRP status: "HIV-IRP" (n=13) and "HIV-noIRP" (n=11). All comparisons between groups were performed using the Mann Whitney test and p-values <0.05 were considered significant.

Results: We found that 32% (40/126) of the HIV patients (median age [IQR] =53 [47-60]) exhibited the immunologic and serologic characteristics described in the IRP. None of the controls exhibited an IRP profile (median age [IQR] =55 [47-63]). The median relative telomere length (RTL) was shorter in the HIV-IRP group than in the HIV-noIRP group (median RTL [IQR] = 9.9 [8.7-10.7] and 10.9 [10.3-12], respectively). This difference approached statistical significance (p=0.087).

Conclusions: We have shown for the first time that the prevalence of the IRP among successfully treated HIV patients is significantly higher than in age-matched healthy controls. These findings suggest that this immune profile previously identified in elderly uninfected individuals, occurs at a much younger age in HIV patients. We also found that among those with HIV, there may be an association between the IRP and shorter telomere length. However larger studies will be needed to substantiate this finding and to determine whether the IRP may also represent a risk profile associated with higher mortality/morbidity in the HIV population. This is the first study assessing the association between telomere length and the IRP in the context of HIV.

766 Geriatric Syndromes Are Common Among Older HIV-Infected Adults

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Background: Geriatric syndromes such as falls, frailty, and functional impairment are multifactorial conditions used to identify vulnerable older adults. We hypothesized that these conditions would be common among virally suppressed HIV-infected older adults and that both HIV and non-HIV related factors would be associated with the presence of geriatric syndromes.

Methodology: We conducted a cross-sectional study within a San Francisco based research cohort of HIV-infected adults age 50 and older who had an undetectable plasma HIV RNA on cART for at least 3 years. We measured frequencies of four geriatric syndromes: (1) falls (yes/no to fall in past year), (2) urinary incontinence (yes/no based on the International Consultation on Incontinence Questionnaire), (3) functional impairment, and (4) frailty (Fried's criteria). Functional impairment was defined as difficulty with activities of daily living (e.g. dressing, bathing) and instrumental activities of daily living (e.g. shopping, housework). Potential correlates included sociodemographics, number of co-morbidities and non-antiretroviral medications, and HIV specific variables (e.g. proximal and nadir CD4, length of HIV infection, exposure to certain antiretroviral drugs), which were examined in multivariate analyses using relative risk estimation by poisson regression.

Results: 142 subjects were enrolled, of which 94% were male and 63% were Caucasian with a median age of 57 (range 50-74). The median CD4 count was 577 (IQR 393-715), median CD4 nadir was 172 (IQR 50-318), and median length of HIV infection was 22 years (IQR 18-25). 49% had been exposed to zidovudine, stavudine or didanosine. Subjects had a median of 4 (IQR 3-6) co-morbidities and were taking a median of 9 (IQR 5-12) non-antiretroviral medications. 86% of subjects had at least one geriatric syndrome and 54% had 2 or more syndromes. 38 subjects (27%) reported at least one fall, 36 (25%) reported urinary incontinence, and 64 (45%) reported difficulty with at least 1 instrumental activity of daily living. 12 (9%) subjects met the full criteria for frailty, while 79 (56%) met criteria for pre-frailty. Every 50 unit increase in CD4 nadir (RR 0.93, 95% CI 0.88-0.99) and being employed (RR 0.57, 95% CI 0.37-0.89) were associated with a lower relative risk of the composite outcome of 2 or more geriatric syndromes.

Conclusions: In this study population over age 50, more than half of participants had 2 or more geriatric syndromes, which was associated with CD4 nadir. While the role of HIV infection in these syndromes warrants further investigation, the high frequencies of syndromes, especially difficulty with instrumental activities of daily living and pre-frailty, merit consideration of new clinical care paradigms incorporating geriatric medicine principles.

767 Physical Function Impairment On Quality of Life Among Persons Aging With HIV Infection

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Background: Impairments in physical function are seen among aging, HIV-infected persons on effective antiretroviral therapy (ART). The impact of physical function impairments on quality of life (QoL) during ART is unknown.

Methodology: Cross-sectional study of 45-65 year-old HIV-1-infected subjects, on ART >6 months, plasma HIV-1 RNA <48 copies/mL. Medical history, QoL questionnaire (SF-36), and objective physical function assessment for 400-m walk speed (m/sec), power (chair rises/sec), and grip strength (kg) were completed on all subjects. Veterans Aging Cohort Study (VACS) Index scores were calculated as previously described. SF-36 scores were normalized to a population mean of 50 points. Objective physical function, physical activity (>500 versus ≤500 Kcal/week), and VACS scores were used to estimate each QoL subscale in a multivariable linear regression model.

Results: Of 359 subjects, 85% were male, 74% Caucasian, 18% Hispanic, median age 51 (48-56) years, median CD4+ lymphocyte count 551 (361-768) cells/μL, and 5% had detectable HIV-1 RNA. Median SF-36 scores and results of the regression model are shown in the table below. For every 1 m/sec increase in walking pace, we saw an estimated 11.8 point increase in the physical function scale with smaller differences in QoL points across all subscales. For every increase in chair rise pace of 1 rise/sec, we saw an estimated 16.0 point increase in physical function score and 15.0 point increase in social function score with smaller differences in QoL across all subscales. Subjects reporting greater physical activity had QoL scores between 2.8 and 5.7 points higher than those with lower physical activity. A 1 kg increase in grip strength was associated with a 0.2 higher mental health score, but was not significantly associated with differences in other subscales. Inclusion of a comorbidity/mortality index (VACS Index) did not improve the model.

Conclusions: Among aging persons with well-controlled HIV, faster 400-meter walk pace, faster chair rise pace, and greater physical activity were associated with both higher physical and mental QoL, independent of HIV-related mortality risk as estimated by the VACS Index. Targeted exercise programs to increase physical activity and improve speed and power should be evaluated as interventions to improve QoL during ART.

Table. SF-36 Subscale Summary Statistics and Relationship to Physical Function/Comorbidity Assessments by Multivariable Linear Regression Analysis

	Physical Function	Role Physical	Bodily Pain	General Health	Vitality	Social Function	Role Emotional	Mental Health
Median SF-36 Score (Q1, Q3)	50.9 (36.2, 57.1)	56.2 (35.0, 56.2)	46.5 (37.5, 55.9)	48.6 (36.8, 53.2)	46.7 (39.6, 58.5)	46.3 (35.4, 57.1)	55.3 (34.3, 55.3)	50.4 (39.1, 55.0)
Mean difference (95% CI) in SF-36 score per unit difference* in physical function/comorbidity assessment								
400-m walk pace	11.8‡ (8.4, 15.2)	8.4‡ (4.5, 12.3)	7.3‡ (3.3, 11.3)	8.2‡ (4.6, 11.8)	5.1^ (1.4, 8.8)	4.4† (0.3, 8.4)	6.9^ (2.6, 11.2)	4.6† (0.6, 8.6)
Chair rise pace	16.0‡ (9.1, 22.9)	13.8‡ (6.2, 21.5)	11.8^ (3.8, 19.7)	8.77^ (1.6, 16.0)	13.4‡ (6.1, 20.8)	15.0‡ (6.8, 23.2)	12.0^ (3.3, 20.7)	5.4 (-2.7, 13.4)
Grip Strength	0.01 (-0.1, 0.1)	-0.07 (-0.2, 0.06)	-0.1 (-0.4, 0.01)	0.04 (-0.08, 0.2)	0.02 (-0.10, 0.2)	0.01 (-0.2 0.2)	0.1 (-0.01, 0.3)	0.2† (0.01, 0.3)
Physical Activity	4.0‡ (1.7, 6.3)	5.7‡ (3.1, 8.3)	3.5^ (0.8, 6.2)	5.2‡ (2.8, 7.6)	6.1‡ (3.7, 8.6)	4.9‡ (2.2, 7.6)	2.8 (-0.2, 5.7)	4.9‡ (2.2, 7.6)
VACS Index	-0.10 (-0.8, 0.6)	0.08 (-0.7, 0.9)	0.3 (-0.4, 1.3)	-0.2 (-1.0, 0.5)	0.7 (-0.09, 1.4)	0.4 (-0.5, 1.2)	0.2 (-0.8, 1.2)	0.4 (-0.4, 1.2)
Intercept	*17.5 (12.0, 23.1)*	*25.2 (18.9, 31.4)*	*31.6 (25.2, 38.0)*	*24.7 (18.9, 30.5)*	*27.6 (21.7, 33.5)*	*26.4 (19.8, 32.9)*	*21.4 (14.5, 28.4)*	*27.3 (20.8, 33.7)*

*Units used for the above variables : 400-m walk (1 m/sec), chair rise (1 rise/sec), grip strength (1 kg), physical activity (>500 or ≤500 kCal/wk), VACS Index (per 10 points); † p<0.05; ^ p<0.01; ‡ p<0.001

Session P-Q3 Poster Session
Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Diabetes and Insulin Resistance

768 IL-6, hsCRP, and the Development of Type 2 Diabetes Among HIV Positive Patients Taking ART

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Background: Untreated HIV is associated with higher levels of inflammatory markers, and initiation of continuous antiretroviral therapy (ART) results in a decline, but does not normalize these markers. Inflammation is hypothesized to play a role in development of type 2 diabetes; however, clinical data addressing this issue among HIV positive patients have not been reported to our knowledge. We investigated the association of interleukin 6 (IL-6) and high sensitivity C-reactive protein (hsCRP) with the development of type 2 diabetes in HIV positive individuals.

Methodology: This cohort study includes patients from the control arms of the INSIGHT SMART and ESPRIT studies, all of whom were taking ART following randomization. Participants were included if they did not have a history of diabetes at entry and had IL-6 and hsCRP measured at study entry using stored plasma. Hazard ratios (HR) with 95% confidence intervals (CI) per 2-fold higher level of baseline biomarker levels were estimated using Cox regression adjusting for age, gender, race, use of ART, baseline HIV viral load, CD4+ count, body mass index, hepatitis co-infection, and use of lipid- or blood pressure-lowering treatment. Sensitivity analyses were conducted using SMART patients only who also had baseline lipid levels and smoking assessed.

Results: 3,965 patients with median CD4+ count of 523 cells/mm^3 were followed for an average of 4.6 years; 137 patients developed diabetes requiring drug treatment. Higher baseline levels of IL-6, and hsCRP were significantly associated with the risk of developing diabetes. Unadjusted HRs associated with 2-fold higher level of IL-6 and hsCRP were 1.47 (95% CI: 1.26-1.70) and 1.32 (95% CI: 1.20-1.45), respectively. With adjustment for baseline covariates, the associations remained significant (Table). The associations with IL-6 and hsCRP were similar when analyses were restricted to SMART patients and smoking and lipoprotein levels were considered as covariates (HR=1.36; 95% CI: 1.07-1.72 for IL-6 and HR=1.23; 95% CI: 1.07-1.43 for hsCRP).

Inflammatory Marker	Patients who Developed Diabetes (n=137) Median (IQR)	Patients who Did Not Develop Diabetes (n=3,828) Median (IQR)	Adjusted HR for Diabetes Associated with 2-Fold Higher Level of Biomarker*(95% CI)	*P*-value
IL-6 (pg/mL)	2.35 (1.70-3.90)	1.80 (1.14-2.80)	1.30 (1.09-1.56)	0.004
hsCRP (µg/mL)	2.86 (1.63-5.12)	1.52 (0.67-3.52)	1.24 (1.12-1.38)	<0.001

* Adjusted for age, gender, race, BMI, co-infections with hepatitis B or C, CD4+ cell count, HIV RNA level and ART status, use of lipid-lowering drugs, and use of BP-lowering drugs.

Conclusions: Elevated levels of CRP and IL-6 predict the development of type 2 diabetes among HIV positive patients taking ART. These data support a possible link between inflammation and the pathogenesis of type 2 diabetes among HIV positive patients.

769 HbA1c Is A Poor Predictor of Fasting Glycemia in HIV-Infected Men With Low CD4 Count, High MCV and MCH

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Background: Hemoglobin A1c (HbA1c) is the primary index of glycemic control in patients with diabetes and is also recommended for diagnosis. There is limited evidence that among HIV-infected patients, HbA1c values may not accurately reflect glycemia. Using data from the Multicenter AIDS cohort Study (MACS) we assessed HbA1C discordance (observed HbA1c - expected HbA1c) and associated factors among HIV-infected participants.

Methodology: Fasting glucose (FG) and HbA1c were measured at each semi-annual MACS visit since April 1999. All HIV-infected and HIV-uninfected men for whom at least one fasting glucose (FG) and HbA1c pair measurement was available were evaluated. Univariate median regression was used to determine the association between HbA1C and FG by serostatus. The relationship between HbA1c and FG in the HIV-uninfected men was used to determine the expected HbA1c. Generalised estimating equation determined factors associated with the Hb1Ac discordance among HIV-infected men. Clinically significant discordance was defined as observed HbA1c - expected HbA1c ≤-0.5%.

Results: Between 1999 and 2012, 1500 HIV-uninfected and 1357 HIV-infected participants were included with a median of 11 visits for each participant. At the baseline visit, 177 had diabetes mellitus (DM). HIV participants were mostly on antiretroviral therapy (ART) (74%) with a median of CD4 cell count at 486/mm3. At a FG of 125 mg/dL, the median HbA1c among the HIV-infected men was 0.21% lower than among the HIV-uninfected men and the magnitude of this effect increased in with FG> 126 mg/dL. 63% of HIV-infected men had at least one visit with clinically significant HbA1c discordance, which was independently associated with low CD4 cell count (<500/mm3), protease Inhibitor, non-nucleoside reverse transcriptase inhibitor or zidovudine-containing regimen, high mean corpuscular red cell volume and abnormal corpuscular haemoglobin.

Conclusions: HbA1c underestimates glycemia in HIV-infected patients and its use may lead to under treatment of established DM or under diagnosis if used as a diagnostic criterion, especially among those with risk factors for HbA1c discordance.

770 Triglycerides/HDL Ratio and Risk of Developing Diabetes Mellitus During Antiretroviral Therapy

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Background: The aim of our analysis was to evaluate the incidence of diabetes mellitus (DM) and its association with triglycerides (TRG), triglycerides to high-density lipoprotein cholesterol ratio (TRG/HDL) and liver fibrosis (measured by FIB-4) during combination antiretroviral therapy (cART).

Methodology: Patients from the ICONA Foundation study initiating first-line cART between 1997 and 2013 were selected and observed up to new-onset DM or last clinical follow-up. DM was defined as: first of 2 consecutive glucose>126 mg/dl or clinical diagnosis of DM or start of anti-diabetes treatment.

Incidence rate was calculated as number of observed DM after cART initiation divided by person years of follow-up (PYFU). Multivariable Poisson regression was used to determine factors independently associated with DM, including current TRG/HDL in model A and current TRG in model B.

Results: 3,546 patients [males 73.7%, median age 38 yrs (IQR 33-45), median BMI 23.1 (IQR 21.1-25.2), HCV-ab positivity 22.1%] were included in this analysis. Of these, 80 persons developed DM over 13,911 PYFU, corresponding to an incidence of 5.7 per 1,000 PYFU (95%CI 4.6-7.1). Incidence of DM according to most recent TRG and TG/HDL are shown in Table 1. At multivariable analysis (Table 1 model A) most recent TRG/HDL was associated with a significant increase in risk of developing DM while current TRG was associated with developing DM only at crude analysis (Table 1 model B). Advanced liver fibrosis (defined as FIB-4 index >3.25) was also independently associated with higher risk of DM in model A (Table 1) but not in model B (rate ratio [RR] 2.28; 95%CI 0.89-5.85 , p=0.08). However, the association was much stronger among patients without HCV co-infection (RR 5.28; 95%CI 1.25-22.27) than in those with positive HCV-Ab (RR 1.91; 95%CI 0.61-6.0 p-value for interaction=0.02). Other risk factors associated with DM's onset were (model A): Age (per 10 yrs older) (RR 1.44; 95%CI 1.06-1.95), p<0.05), current BMI>30 (4.85; 95%CI 2.38-9.86 , p<0.001), current D4T+3TC use (6.05; 95%CI 1.87-19.63 vs.TDF+FTC, p<0.05), current ATV/rtv use (3.14; 95%CI 1.27-7.78 vs. EFV, p<0.05).

Conclusions: High TRG/HDL ratio predicted the risk of new-onset DM, independently of other traditional risk factors. The use of this simple marker as predictor of the risk of DM merits to be further explored. Advanced hepatic fibrosis estimated using FIB-4 score might be an additional predictor for DM, especially in those with non HCV related liver damage.

Model a	# events	PYFU	IR per 1000 PYFU 95% CI	Crude RR 95% CI	P	Adjusted RR* 95% CI	P
Current TRG/HDL				1.18 # (1.10-1.26)	<0.001	1.63 # (1.32-2.01)	0.000
0-I quartile	8	2155	1.9 (0.7-4.9)				
I-II q	4	2750	2.9 (1.4-5.8)				
II-III q	11	2490	4.4 (2.4-8.0)				
III q-max	21	2391	8.8 (5.7-13.5)				
Not measured	36	4127	8.7 (6.3-12.1)				
Current FIB 4 score							
<1.5	38	10345	3.7 (2.7-5.0)	1.00		1.00	
1.5-3.25	22	1921	11.4 (7.5-17.4)	3.12 (1.84-5.27)	<0.001	1.97 (1.00-3.86)	0.049
>3.25	8	476	16.8 (8.4-33.6)	4.58 (2.14-9.81)	<0.001	2.94 (1.11-7.79)	0.030
Not measured	12	1169	10.3 (5.8-18.1)				
# relative risk expressed per 10 point higher *Controlled for gender, age, nationality, CD4 count before cART, CDC C stage, log_{10} HIV-RNA, HCV co-infection, baseline cholesterol, current BMI, calendar year of cART start, current antiretroviral regimen. I quartile=1.66, II q=2.70, III q=4.54, max=80.56.							
Model b	# events	PYFU	IR per 1000 PYFU 95% CI	Crude RR 95% CI	P	Adjusted RR* 95% CI	P
Current TRG, mg/dl				1.10 § (1.05-1.15)	<0.001	1.06 § (00.99-1.13)	0.077
<=180	45	10456	4.3 (3.2-5.8)				
181-300	19	2409	7.9 (5.0-12.4)				
>=300	16	1047	15.3 (9.4-24.9)				
§relative risk expressed per 50 mg/dl higher *Controlled for gender, age, nationality, CD4 count before cART, CDC C stage, log_{10} HIV-RNA, HCV co-infection, baseline cholesterol, current BMI, current fib4 score, calendar year of cART start, current antiretroviral regimen.							

771 Measuring Physical Activity and its Impact On Insulin Resistance in MACS Men

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Background: Physical activity (PA) has many beneficial effects, including improved fitness, strength, quality of life, and decreased insulin resistance. Several small studies suggest that HIV-infected adults report inadequate PA. We examined the relationship between HIV status, PA and insulin resistance among men in the Multicenter AIDS Cohort Study (MACS).

Methodology: The International Physical Activity Questionnaire (IPAQ short form) was self-administered during MACS visits 53 and 54 (April 1, 2010 to March 31, 2011); we used data from the first administration that could be scored. Per IPAQ protocol, a metabolic equivalents (METs) total score (continuous variable) was calculated by adding MET-minutes/week for all activity performed and a categorical score (low, moderate, and high) was also generated. Concurrent homeostatic model assessment insulin resistance (HOMA-IR) (mmol/L) was calculated as: (fasting glucose x fasting insulin)/22.5. Additional covariates included age, race, BMI, education, smoking, HCV status, history of AIDS, ART, CD4, and VL. Adjusted quantile regression was used to investigate the effect of HIV status on PA (continuous). Adjusted linear regression was used to investigate the effect of PA (categorical) on log-transformed HOMA-IR by HIV status.

Results: 1429 men (661 HIV-infected men, 768 HIV-uninfected men) were included in the analysis. HIV-infected status was significantly associated with higher total MET-minutes/week among men reporting the highest activity levels (75th percentile and up). However, the proportion of men reporting low (24% in HIV-infected vs. 23% in HIV-uninfected), moderate (27% vs. 28%), and high (49% vs. 49%) activity was similar by HIV status. Both HIV-infected status and low PA (vs. high PA) were associated with more insulin resistance ($p<0.0001$ and $p=0.0007$, respectively). Among men with low PA, HIV-infected men had higher HOMA-IR than their HIV-uninfected counterparts with similar activity levels ($p<0.0001$). However, this association was not seen among men in the moderate and high PA groups.

Conclusions: In all men, lower PA was associated with more insulin resistance. However, HIV-infected men with the lowest levels of PA were more insulin resistant then HIV-uninfected men with a similarly low PA. This suggests that low PA may affect health outcomes more in HIV-infected persons compared to HIV-uninfected persons and that PA may need to be increased to a greater extent among HIV-infected persons to achieve the same metabolic benefit.

772 Impact of Randomized Antiretroviral Therapy (ART) Initiation On Glucose Metabolism: ACTG A5224s

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Background: Prior studies have found that early HIV protease inhibitors (PIs) and lipodystrophy contribute to glucose dysregulation. Few randomized trials have evaluated glucose indices in ART-naïve subjects on newer ARTs.

Methodology: A5202 randomized 1857 ART-naïve HIV+ subjects to blinded abacavir/lamivudine (ABC/3TC) or tenofovir/emtricitabine (TDF/FTC) with open-label efavirenz (EFV) or atazanavir/ritonavir (ATV/r). A pre-specified secondary analysis of the metabolic substudy A5224s compared fasting glucose, insulin, and homeostatic model assessment-insulin resistance (HOMA-IR) using 2-sample t-tests, linear regression, and Spearman correlation. Diabetes was defined as 2 fasting glucose values >126 or 2 non-fasting glucose values >200 mg/dL over 1 year.

Results: Overall, 269 non-diabetic subjects enrolled: 85% male, 47% white non-Hispanic, median baseline age 38 years, HIV-1 RNA 4.6 $\log_{10}$ copies/mL, CD4 236 cells/mm^3, glucose 84 mg/dL, insulin 4 µIU/mL, and HOMA-IR 0.77. At 96 weeks, the mean (95% CI) glucose increased by 2.7 (1.1, 4.3) mg/dL, insulin by 0.09 (0.03, 0.16) $\log_{10}$ µIU/mL, and $\log_{10}$ HOMA-IR by 0.11 (0.05, 0.18); all $p<0.05$. Six subjects developed diabetes; glucose changes ranged from -41 to +47 mg/dL. No interaction was detected between nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTI)/PI for any glucose index ($p\geq0.61$). Changes in indices were not significantly different between NRTI arms ($p\geq0.18$). Assignment to EFV resulted in greater glucose increase (mean 4.8; 2.6-7.0 mg/dL) compared to ATV/r (0.4; -1.8-2.6 mg/dL); $p=0.006$. Insulin and HOMA-IR changes were not significantly different ($p\geq0.72$). Multivariable analyses are shown in the table. Glucose change positively correlated with changes in BMI ($r=0.23$, $p=0.001$), lean body mass ($r=0.19$, $p=0.006$), and trunk fat ($r=0.18$; $p=0.010$).

Conclusions: Changes in glucose metabolism were minimal and not significantly different between TDF/FTC and ABC/3TC-based regimens. The small but significantly greater increase in glucose in those assigned to EFV has not been previously reported in a randomized setting of ART-naïve persons and may be mediated by change in BMI. As glucose dysregulation may increase with time on ART, longer studies will be needed to further clarify the clinical significance of these findings.

Table. Multivariate Analyses Examining Effects of Treatment and Clinical Characteristics on Change in Glucose and HOMA-IR over 96 Weeks

		96-week Glucose Change (mg/dL)		96-week HOMA-IR Fold Change	
Covariate	*Reference*	*Estimated mean change (95% CI)*	*p-value*	*Estimated mean fold change (95% CI)*	*p-value*
ABC/3TC	TDF/FTC	2.1 (-1.0, 5.1)	0.18	1.04 (0.77, 1.41)	0.80
EFV	ATV/rtv	5.7 (2.6, 8.7)	<0.001	1.08 (0.80, 1.47)	0.61
Baseline HIV-1 RNA	continuous (per 1 $\log_{10}$ copies/ml higher)	2.4 (0.0, 4.9)	0.047	1.30 (1.04, 1.64)	0.023
96-week BMI change	continuous (per 1 kg/m^2 higher)	0.8 (0.3, 1.4)	0.005		

Covariates included ART regimen, sex, age, race/ethnicity, baseline CD4 and HIV-1 RNA, hepatitis B/C, family history of diabetes, baseline/change in body mass index (BMI) and dual-energy X-ray absorptiometry (DXA) measured lean body mass (LBM), limb and trunk fat. After adjusting for treatment, only variables that remained significant in the final model are shown above.

Session P-Q4 Poster Session
Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**
Lung Disease and HIV

773 HIV Infection Increases Risk of Acute Exacerbations of COPD

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Background: Poorly controlled HIV infection is associated with increased risk of COPD. Acute exacerbations of COPD (AECOPD) are major contributors to morbidity and mortality but are understudied in HIV populations. Within the AIDS Linked to the Intravenous Experience (ALIVE) study, we examined the factors associated with AECOPD among those with and at-risk for HIV infection.

Methodology: ALIVE is an on-going prospective, community-based cohort that began following persons with a history of injecting drugs in Baltimore, MD in 1988. We longitudinally examined 167 individuals who had pre-bronchodilator airflow obstruction (defined as forced expiratory volume in 1 second / forced vital capacity [FEV1/FVC] <0.70) on all spirometry measures performed during follow-up. AECOPD, assessed at each 6 month study visit, was defined as answering "yes" to the question "In the last 6 months, have you had a worsening of your breathing status requiring treatment with antibiotics or steroids?" Multivariable logistic regression with generalized estimating equations was used to identify correlates of AECOPD.

Results: A total of 167 participants with a median of 3 visits (IQR 2-5) over 1.5 years (IQR: 0.5-2.1) were included in analysis. The mean age at baseline was 52 years, 89% were black, 30% female and 32% HIV infected with a median CD4 count of 312 cells/mL (IQR: 193-454) and a median viral load of 40 copies/mL (IQR: 40-3627). After adjusting for gender, comorbidity, and COPD severity, HIV infection was independently associated with a 2.49 increased odds of AECOPD (Table 1). Compared to HIV negatives, HIV-infected persons with undetectable (≤40 copies/mL) and high (>10,000 copies/mL) HIV RNA had increased odds of AECOPD, but intermediate RNA levels were not associated (OR 1.23; 95% CI 0.32, 4.67; p=0.76). CD4 count was not associated with increased odds of AECOPD.

Conclusions: HIV infection was independently associated with increased odds of AECOPD. Increased risk for AECOPD at higher and at lower HIV RNA levels likely reflects both biological (immune dysregulation) and behavioral (access to HIV and COPD care) patterns. Providers should be aware that HIV infection may increase the risk for AECOPD.

Table 1. Correlates of AECOPD

Covariate	Adjusted OR	(95% CI)	p-value
Female	2.67	(1.32, 5.41)	0.006
HIV Infection	2.49	(1.21, 5.10)	0.013
Comorbid disease*†	2.32	(1.17, 4.63)	0.016
Airflow Obstruction			
Mild (FEV1 ≥80% predicted)*	Reference		
Moderate (FEV1 50-79% predicted)*	2.63	(1.13, 6.14)	0.025
Severe (FEV1 <50% predicted)*	5.86	(2.16, 15.85)	0.001

* In previous 6 months
† Defined as a chronic medical disease requiring treatment in the past 6 months.
Abbreviations: AECOPD, Acute Exacerbation of Chronic Obstructive Pulmonary Disease; CI, Confidence Interval; FEV1, Forced Expiratory Volume in 1 second; HIV, Human Immunodeficiency Virus; OR, Odds Ratio

774 Association of HIV Infection and Immune Activation With Decline in Lung Function

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Background: HIV infection may be a risk factor for chronic obstructive pulmonary disease (COPD), characterized by fixed airflow obstruction (AFO) on spirometry. Decline in the forced expiratory volume in one second (FEV1) is greater in current smokers and in COPD at ~60 ml/year compared to the normal ~30 ml/year decline associated with aging; accelerated FEV1 decline is associated with poor health outcomes. We determined differences in FEV1 decline in HIV-infected (HIV+) compared to uninfected (HIV-) individuals, and the relationship of lung function with systemic biomarkers of inflammation, altered coagulation and immune activation.

Methodology: Longitudinal analysis of HIV+ and HIV- subjects matched for current smoking status enrolled 2009-2012 in the Examinations of HIV Associated Lung Emphysema (EXHALE) Study, a substudy of the Veterans Aging Cohort Study. Subjects completed a standardized baseline questionnaire for lung diseases, smoking and other exposures, and repeated spirometry with bronchodilator (BD) every 6-12 months. Plasma interleukin-6 (IL6),

soluble CD14 (sCD14), and D-dimer were measured at baseline. AFO was defined as a ratio of the FEV1 to forced vital capacity (FVC) <0.70. We used multivariable linear regression models to determine the association of HIV or biomarkers with baseline lung function, and generalized estimating equations (GEE) to determine the association of HIV or biomarkers with change in FEV1.

Results: In 168 HIV+ and 147 HIV- subjects, mean age of 54, nearly 60% current smokers, there was no difference in the baseline FEV1 or the prevalence of AFO. However, HIV+ subjects had a 36 ml greater decline in post-BD FEV1 than HIV- subjects (p=0.03) adjusting for age, body mass index, and smoking-pack years, with a median of 3 repeated measures per person over 24 months. Decline in FEV1 was 98 ml/year (standard error [SE] 11) in HIV+ and 62 ml/year (SE 13) in HIV- subjects. Levels of IL6, sCD14 and D-dimer above the group median were independently associated with lower baseline values of FEV1, FEV1/FVC in HIV+ (p<0.05 for all) but not in HIV- subjects in cross-sectional analyses adjusted for race/ethnicity, smoking pack years and injection drug use. Using GEE, sCD14 levels above the group median were independently associated with a greater decline in FEV1 in HIV+ subjects (57 ml/year, SE 22, p<0.01), but not in HIV- subjects in stratified models. In contrast, FEV1 decline was not significantly different by IL6 or D-dimer in either group.

Conclusions: Lung function decline, measured by post-BD FEV1, is accelerated in HIV infection, and is associated with elevated levels of sCD14 in HIV+ individuals. These data suggest that selective innate immune activation may play an important role in the progression of COPD in HIV infection.

775 HIV Infection and Related Biomarkers Are Independent Risk Factors for Radiographic Emphysema

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Background: The association between HIV infection and emphysema remains incompletely understood. We hypothesized that HIV is an independent risk factor for emphysema severity, and explored whether markers of HIV disease and systemic biomarkers of inflammation (interleukin-6 [IL-6]), altered coagulation (D-dimer) and immune activation (soluble CD14 [sCD14]) are associated with emphysema.

Methodology: We performed a cross-sectional analysis of 114 HIV-infected (HIV+) and 89 HIV-uninfected (HIV-) subjects in the Examinations of HIV-Associated Lung Emphysema (EXHALE) study, a pulmonary substudy of the Veterans Aging Cohort Study. All subjects underwent chest CT scan with blinded semi-quantitative interpretation by a radiologist for emphysema severity, graded from 0 to >75% lung involvement, and distribution of emphysema in the upper, mid and lower lung zones. Plasma biomarker levels were measured at enrollment. Demographics, smoking and other exposures were gathered via questionnaires. We generated multivariable logistic regression models to determine the independent risk of HIV with emphysema, defined as >10% lung involvement. We abstracted recent HIV RNA and CD4 cell counts, and nadir CD4 cell counts from VA laboratory data and performed similar analyses to examine the role of HIV related variables and biomarkers amongst HIV+ subjects.

Results: Most HIV+ and HIV- subjects were smokers; those with HIV tended to be older, to have other substance use and prior pulmonary infections. HIV+ subjects were more likely to have greater emphysema severity as well as diffuse and lower lung zone emphysema (Table 1). HIV infection was associated with significantly increased risk for >10% radiographic emphysema in analyses adjusted for pack-years of cigarette smoking (OR 2.24; 95% CI, 1.12 - 4.48). In multivariable analyses restricted to HIV+ individuals, low nadir CD4 (OR 2.98; 95% CI, 1.14 - 7.81) and high sCD14, defined as the upper 25th percentile of values (OR 2.55; 95% CI, 1.04 - 6.22), were associated with increased risk of >10% emphysema. IL-6 and D-dimer levels were not associated with emphysema in HIV.

Conclusions: HIV is an independent risk factor for radiographic emphysema, defined by >10% emphysema on CT scan. Emphysema severity was overall significantly greater among HIV+ individuals. Additionally, among those with HIV, nadir CD4 <200 and elevated sCD14 were associated with emphysema, pointing toward potential pathogenetic mechanisms linking HIV infection with emphysema.

Select baseline characteristics of subjects by HIV status: HIV+ (n=114) vs HIV- (n=89)			
EMPHYSEMA SEVERITY, % None/negligible (<5%)	40	46	p-value 0.011
Trace (5-10%)	27	37	0.011
Mild (11-25%)	19	8	0.011
Moderate (26-50%)	5	8	0.011
Severe (51-75%)	9	1	0.011
Very severe (>75%)	0	0	0.011
EMPHYSEMA DISTRIBUTION, % Diffuse emphysema	28	16	0.037
Upper lung zone	61	53	0.27

Middle lung zone	42	30	0.085
Lower lung zone	30	18	0.052
PLASMA BIOMARKERS, median (IQR) IL-6, pg/mL	1.81 (1.28 - 3.43)	1.23 (0.94 - 2.07)	<0.001
Soluble CD14, ng/mL	1671 (1472 - 2128)	1386 (1171 - 1569)	<0.001

776 Factors Associated With Chronic Obstructive Pulmonary Disease in a High Risk HIV-Infected Cohort

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Background: HIV-infected subjects have been reported to be at higher risk of Chronic Obstructive Pulmonary Disease (COPD) than the general population, due to an increased prevalence and magnitude of exposure hazards, such as smoking, and possible interactions with HIV-infection. We sought to study factors associated with COPD in an HIV-infected cohort with an important smoking history.

Methodology: HIV-CHEST is a multicentre, ongoing prospective study evaluating low dose chest tomography for early lung cancer diagnosis in HIV-infected subjects. A cross-sectional lung function sub-study assessed spirometry and plethysmography in subjects ≥ 40 years, active cigarette smokers or quitted within the past 3 years, ≥ 20 pack-years and with a nadir of CD4 T-cells count < 350/µl. COPD was defined according to the GOLD diagnosis criteria (post-bronchodilator ratio of Force Expiratory Volume in one second (FEV_1) to the Force Vital Capacity (FVC) <0.70, graded from 1 to 4). Logistic regression models evaluated the association between COPD and various factors (table). Factors associated with COPD (p<0.2) in univariate analysis were included in the multivariate analysis.

Results: Of 444 subjects included in the prospective study, 353 had a spirometry. Nineteen subjects were excluded, as post-bronchodilator FEV_1/FVC was not measured. Median age was 50 years (IQR 46-53), 276 (83%) were men, 330 (99%) were under antiretroviral therapy (ART), median duration of ART was 14 years (IQR 6-16), 84 (25%) had a history of intravenous drugs, 95 (28%) were HCV-infected, median pack-years smoking was 30 (IQR 25-39), 116 (35%) had a history of marijuana use, 294 (88%) had a viral load < 50 copies/ml, and median CD4 T-cells at inclusion and nadir were respectively 574 (IQR 396-764) and 178 (IQR 76-261)/µl. COPD was diagnosed in 83 subjects (25%), of whom 45 (54%) and 34 (41%) were respectively grade 1 and 2; in 62 subjects (75%), COPD was unknown before inclusion. Increased age was associated with COPD while elevated CD4 count was protective (Table).

Conclusions: Prevalence of COPD was high in this smoking HIV-infected cohort and COPD was a new diagnosis in the majority of cases. Potential increased risk with marijuana use deserves further studies. COPD active diagnosis through pulmonary function tests should be advocated in ageing HIV-infected smokers, and smoking cessation highly prioritized.

Variable	Univariate analysis		Multivariate analysis		Variable	Univariate analysis		Multivariate analysis	
	OR [CI95%]	p	OR [CI95%]	p		OR [CI95%]	p	OR [CI95%]	p
Sex (woman)	0.85 [0.43;1.67]	0.64			ART duration	1.01 [0.97;1.05]	0.70		
Age (per 10 years increase)	**2.17 [1.44;3.29]**	**<0.001**	**2.34 [1.48;3.70]**	**<0.001**	HCV co-infection	1.62 [0.95;2.75]	0.066	1.45 [0.81;2.62]	0.21
Smoking (per 5 packs year increase)	1.11 [1.00;1.22]	0.046	1.01 [0.99;1.03]	0.30	Nadir CD4 T cells < 200/µl	1.12 [0.68;1.86]	0.65		
History of marijuana use (yes/no)	1.53 [0.92;2.55]	0.10	1.69 [0.96;2.99]	0.071	**CD4 cells (per 100/µl increase)**	**0.89 [0.81;0.98]**	**0.024**	**0.90 [0.81;0.99]**	**0.039**
BMI<18.5 kg/m^2	2.22 [1.07;4.60]	0.032	2.05 [0.94;4.46]	0.071	HIV viral load <50 copies/ml	0.99 [0.46;2.13]	0.98		
History of lung infection/ pneumocystosis	1.87 [0.85;4.10]	0.16	2.07 [0.90;4.80]	0.089					

Factors associated with COPD (n = 334). ART: Antiretroviral Therapy; BMI: Body Mass Index.

Session P-Q5 Poster Session
Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**
Bone Disease: Osteopenia, Fracture Risk, and Osteoarthritis

777 Minimal Change in Bone Density and No Association With HIV Factors Over 12 Months in HIV-Infected Men

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Background: It has been postulated that HIV infection is associated with increased risk of osteoporosis, mainly seen in clinical trials. There is a paucity of data in real clinical cohorts. We assessed factors associated with reduced bone mineral density (BMD) at baseline and 12 months in HIV-infected men in our clinic cohort.

Methodology: Longitudinal study of HIV-infected men assessed BMD at baseline and 12 months. HIV demographics, combination antiretroviral therapy (cART) use and osteoporosis risk factors were identified. Absolute BMD (g/cm^2) at lumbar spine (LS), total hip (TH) and femoral neck (FN) was measured using dual-energy xray absorptiometry (DXA). Reduced BMD was defined as T-score <-1 and >-2.5, and osteoporosis as T-score <-2.5 in men ≥50 years and Z-score <-2 in men <50 years. Men currently or ever taking bisphosphonates were excluded. Change in absolute BMD was assessed using paired t-test. Logistic regression (adjusted for baseline BMD) investigated relationships between risk factors in patients with more than the smallest detectable difference (>SDD) decrease in BMD.

Results: Of 421 men recruited, 21 were excluded for bisphosphonate use. Of 400 men (mean [SD] age 47 [9.8] years, 94% white ethnicity, 93% MSM, diagnosed HIV positive for median [IQR] 9.1 [4.8,15.2] years, median [IQR] CD4 543 [409,694] cells/μL, 92% on cART of whom 88% had HIV RNA <40 copies/mL), 316 had paired DXAs. Baseline prevalence of reduced BMD was 31%, 36% and 47%, and osteoporosis was 10%, 3% and 3% at LS, TH and FN, respectively. Associations with reduced absolute BMD at baseline were low BMI at all sites (p<0.0001), current smoking at TH (p=0.02) and high serum calcium at LS (p=0.02). Over 12 months, mean absolute BMD increased at LS (p=0.006) and decreased at FN (p=0.008), with no significant change at TH (p=0.653) (Table 1). >SDD decrease in BMD occurred in 14%, 10% and 10% at LS, TH and FN, respectively. No factors, including HIV stage, nadir CD4, cART use and type, were associated with >SDD decrease in BMD at any site (all p>0.05).

Conclusions: Although a relatively high proportion of men had reduced BMD, only a minority had a significant decrease over 12 months, with an increase in BMD at LS. We found no association with HIV-related factors, including cART use or type, suggesting that patients on cART have returned to health. Our data suggests that there is no need to alter cART regimens in patients with reduced BMD, but to primarily concentrate on addressing osteoporosis risk factors seen in the general population.

Table 1: Change in absolute BMD at 12 months

Site	Baseline		12 months		p-value*
	N	Absolute BMD mean (SD)	N	Absolute BMD mean (SD)	
Lumbar spine	400	1.144 (0.16)	316	1.149 (0.16)	0.006
Total hip	394	1.002 (0.14)	306	1.007 (0.14)	0.653
Femoral neck	397	0.952 (0.13)	313	0.945 (0.132)	0.008

BMD: bone mineral density; FN: femoral neck; LS: lumbar spine; SDD: smallest detectable difference; TH: total hip
* Paired t-test

778 New Fracture Risk and FRAX 10-Year Probability of Fracture in HIV-Infected Adults

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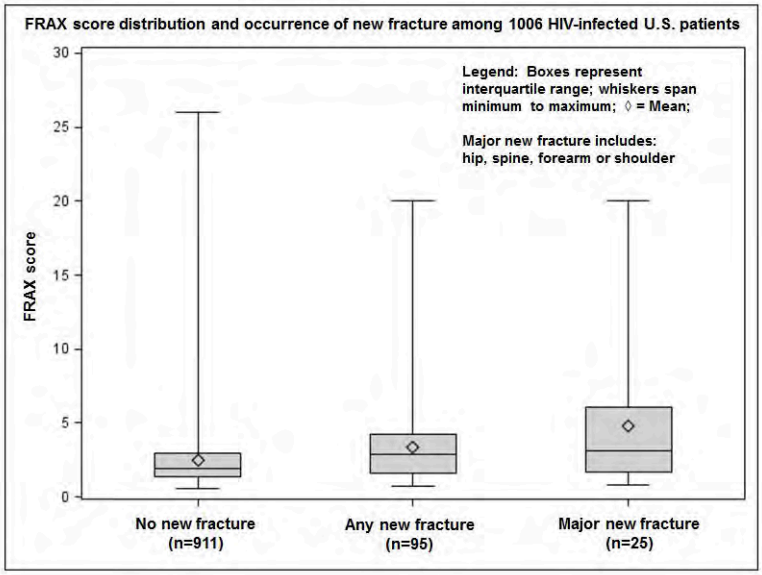
Background: FRAX reliably predicts 10-year fracture risk for adults in the general population. However, its utility for HIV-infected adults, for whom the prevalence of low bone mineral density (BMD) and risk of fractures have been shown to be greater, has not been assessed.

Methodology: Using dual energy X-ray absorptiometry (DEXA) BMD values of the left femoral neck, and clinical data collected prospectively during 2004-2012 from two CDC-sponsored HIV cohorts, we calculated the initial FRAX 10-year risk of a major osteoporotic fracture (i.e., of the hip, spine, forearm, or shoulder). We assessed rates of any new bone fracture and major osteoporotic fracture per 100 person-years (py) of follow-up, stratified by initial FRAX-score intervals, and used Cox proportional hazards models to identify clinical and demographic risk factors for any new fracture.



Results: Among 1006 participants who contributed 5022 py of follow-up, 83% were male, 67% were non-Hispanic white, median age at date of DEXA scan was 42 years [interquartile range (IQR) 35-48], and median CD4+ cell count was 408 cells/mm3 [IQR 255-600]. Participants had median (IQR) values of 0.90 g/cm2 for BMD (IQR: 0.80-1.00) and 1.9 for FRAX score (IQR: 1.4-3.2); median FRAX scores were higher for those who had any subsequent new fracture vs. those who did not (Wilcoxon rank sum test: p<0.01). (Figure). During a median of 4.2 (IQR 3.0-7.7) years of observation after initial DEXA, 95 participants (9.4%) had any new fracture: 7.1% occurred among persons with FRAX score <3% (1.39 per 100py) and 15.3% among persons with FRAX score ≥3% (3.27 per 100py). New major osteoporotic fractures were observed among 1.5% of persons with FRAX score <3% (0.30 per 100py), and among 4.9% (1.04 per 100py) of persons with FRAX score ≥3%. In multivariate analyses, having a prior fracture (adjusted hazard ratio [aHR] 2.02, 95% confidence interval [CI]: 1.09-3.71), older age (aHR 1.30 per 10 years, 95% CI: 1.04-1.62), and lower BMD (aHR 0.14 per g/cm2, 95% CI: 0.03-0.59) were associated with risk of any new fracture. In a separate model, having FRAX score ≥ 3% vs. FRAX of < 3.0% was associated with any new fracture (HR 2.31, 95% CI: 1.54-3.46).

Conclusions: In a large convenience sample of relatively young HIV-infected U.S. adults, a FRAX score ≥3%, low baseline BMD, history of prior fracture, and increased age were significantly associated with elevated risk of new fracture.

779LB Bone Density Changes After Antiretroviral Initiation With Protease Inhibitors or Raltegravir

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Background: The initiation of antiretroviral therapy (ART) leads to a 2-6% loss of bone mineral density (BMD) over 48-96 weeks which depends in part on the specific medications used. The effect of integrase inhibitors on BMD with ART initiation and how it compares to the changes seen with protease inhibitors (PIs) have not been clearly established.

Methodology: We compared the percentage change in BMD at the lumbar spine, total hip, and total body over 96 weeks in HIV-infected treatment-naive participants randomized equally to open labeled Tenofovir Disoproxil Fumarate-Emtricitabine (TDF/FTC) plus Atazanavir-Ritonavir (ATV/r), Darunavir-Ritonavir (DRV/r), or Raltegravir (RAL) in a substudy of AIDS Clinical Trials Group A5257 (N= 1809) with randomization stratified by substudy participation. BMD was measured using standardized dual-energy x-ray absorptiometry (DXA) and centrally read. We used linear regression with reverse Helmert contrasts to compare the 96-week percentage change in BMD in the two PI arms (ATV/r vs DRV/r) and, if no difference was found, the BMD changes in the combined PI arms were compared to those in the RAL arm. Primary analyses were intent-to-treat, adjusted for the stratification factors of baseline cardiometabolic risk and HIV-1 RNA.

Results: Three hundred and twenty eight participants were randomized and had baseline DXA scans. At baseline, 90% were male and 44% were white, non-Hispanic; the median HIV-1 RNA load was 4.55 $\log_{10}$ copies/mL; age was 37 years; CD4 count was 349 cells/μL. At week 96, the mean percentage changes from baseline in spine and hip were statistically significant in all arms (p>0.001) and similar in the PI arms (Spine: ATV/r -4.0% v DRV/r -3.6%, p=0.42; Hip: ATV/r -3.9% v DRV/r -3.4%, p=0.36), but were greater in the combined PI arms than the RAL arm (Spine: -3.8% v -1.8%, p<0.001; Hip -3.7% v -2.4%, p=0.005). The percentage changes in total body BMD were small, but statistically significant in all of the arms (p<0.001 for all), but the magnitude of the change was greater with ATV/r than DRV/r (-2.9% v -1.6%, p=0.001) or RAL (v -1.7%, p=0.004), but not different between the DRV/r and RAL arms (p=0.72). As-treated analyses led to similar results.

Conclusions: In ART-naïve, HIV-infected individuals initiating ART with TDF/FTC, 96 week BMD losses at the lumbar spine and total hip were similar with the PIs, ATV/r and DRV/r, whereas the integrase inhibitor, RAL, had significantly less BMD loss at these sites than the combined PIs arms. In contrast, total body BMD loss was slightly greater with ATV/r than DRV/r.

780 Hand Osteoarthritis, a Joint Disorder Frequent and More Severe in HIV-1 Patients: METAFIB-OA Study

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Background: Osteoarthritis (OA) is one of the most frequent joint disorders, causing chronic pain and functional disability. Accelerated aging and metabolic syndrome (MetS) are common among HIV-infected patients, both of which are risk factors for OA. We investigated whether HIV-1 patients have OA more frequently than the general population and identified risk factors for hand OA (HOA) in the context of HIV.

Methodology: A case control study was designed that included HIV-infected patients with MetS (IDF/AHA criteria) and aged 45 - 65. They were paired with HIV-infected controls without MetS on age, gender, HIV-RNA level and duration of HIV infection. A hand radiograph was performed and analyzed by two independent readers. HOA was diagnosed if the Kellgren-Lawrence score (KL) was ≥2 on ≥1 joint. Thumb base OA (i.e., rhizarthrosis [RZ]) was also evaluated. Structural radiographic severity of HOA, reflecting OA deformity, was assessed by the sum of KL scores across all joints and by the number of joints having KL≥2 on both hands. Prevalence of HOA was compared to that of the literature. Logistic and linear regression models were used to determine risk factors of HOA.

Results: 301 patients [88% male, mean age (SD): 53.4 (5.0) years, mean estimated duration of HIV-infection: 18 (7) years] were included, of whom 152 were cases and 149 were controls. Overall HOA prevalence was 55.6% and was higher in MetS+ (64.7%) than MetS- patients (46.3%), p=0.002. RZ was also more frequently observed in MetS+ patients (26.1 vs 14.1%, p=0.01). Concerning the severity of HOA, mean (SD) sum of KL score was higher

in MetS+ (6.8, 0.9) than MetS- patients (3.7, 0.5), p=0.002. Results were similar for the number of affected joints [MetS+: 3.2 (0.4) vs MetS-: 1.8 (0.2); p=0.002]. Prevalence of HOA was higher in the HIV-infected population than the general population in the same age group (56% for men in the present study vs. 38% in the Framingham study).

In multivariable analysis, the presence of MetS increased the risk of HOA (OR=2.23, 95%CI: 1.26-3.96), even after adjustment on age, as for RZ (OR=1.86, 95%CI: 0.98-3.45). MetS was also associated with more severe HOA: in multivariate analysis, it was independently correlated with the sum of KL scores (β=2.1; p=0.04) as well as with the number of affected joints (β=1.02; p=0.04). No association was identified between HOA and previous/current exposure to protease inhibitors or HIV characteristics (viral load, CD4 count at inclusion and nadir, T4/T8 rate, duration of HIV infection).

Conclusions: HIV-1 patients more frequently exhibit HOA than the general population of the same age and are at-risk of more severe HOA, particularly in case of MetS.

781 Low Bone Mineral Density Is Associated With Increased Risk of Incident Fracture in HIV+ Adults

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Background: Although the prevalence of both low bone mineral density (BMD) and bone fractures are increased among HIV-infected adults compared with the general population, no study has yet characterized their causal association in the context of HIV infection.

Methodology: We analyzed available dual energy X-ray absorptiometry (DEXA) values of the hip (left femoral neck) and clinical data collected prospectively during 2004-2012 from two CDC-sponsored HIV cohort studies, the HOPS and the SUN Study. We assessed factors associated with low BMD (osteopenia or osteoporosis, defined by T-scores of -1.0 to >-2.5, and ≤ -2.5, respectively), using the Jochkheere-Terpstra test for ordered alternatives for continuous variables and the Cochran-Armitage test for categorical variables. We analyzed the association of low BMD with subsequent incident fractures using Cox proportional hazards regression.

Results: Among 1008 patients (median age 42 [interquartile range (IQR)35-48] years, 83% male, 67% non-Hispanic white, median CD4+ cell count [CD4] 408 cells/mm3 [IQR 254-598]), 36.3% (n=366) had osteopenia and 2.9% (n=29) osteoporosis. During 5,032 person-years of observation after DEXA scanning, 95 incident fractures occurred, predominantly rib/sternum (n=18), hand (n=17), foot (n=15) and wrist (n=11). Low BMD was significantly (p<0.05) associated with age, lower nadir CD4, history of fracture, and male-male sex HIV transmission risk. In unadjusted analyses, age, current or prior tobacco smoking, hepatitis C co-infection, history of fracture, and low BMD (osteopenia or osteoporosis) were significantly associated with increased hazard of a new fracture. In multivariable analyses, only osteoporosis (adjusted hazard ratio [aHR] 3.04, 95% confidence interval [CI] 1.47-6.30) and age (aHR 1.35 per 10 years, 95% CI 1.07-1.70) remained associated with incident fracture.

Conclusions: In a large convenience sample of relatively young HIV-infected adults in the U.S., low baseline BMD and increasing age were strongly associated with elevated risk of incident fracture, highlighting the potential value of DEXA screening in this population.

782 A Randomized Open Label Study for Comparing Two Doses of Zoledronic Acid in HIV Infected Patients

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Background: An increasing proportion of HIV-infected patients need treatment for osteoporosis. The best management of this problem is not well-known.

Methodology: This is a randomized, controlled, pilot study to compare the benefit of a biennial use of zoledronic acid with the standard dosage, the annual use, in HIV-infected patients with osteoporosis. A total of 31 caucasian subjects were randomized (2:1), 10 at Control group and 21 to Zoledronic group; at week 48, subjects from the Zoledronic group were reallocated to Annual group (n= 12, 5 mg per year, 2 doses in 2 years) or Biennial group (n=9, one dose in 2 years). Changes from baseline to week 96 in bone mineral density (BMD) for the lumbar spine (L1-L4) and total femur, determined by dual-energy x-ray absorptiometry, were compared between groups, as well as changes in serum alkaline phosphatase, serum procollagen type 1 amino-terminal propeptide (P1NP) and urine N-telopeptide of type 1 collagen (NTx). Mann-Whitney test was used to compare the percentage of change in BMD between groups; McNemar test when the variables are categorical, and by Wilcoxon test in case of non normal variables were used for intragroup comparisons.

Results: At week 96, the percentage of change in hip BMD was 2.12% (-0.12; 3.08) in Control group, 5.16% (3.06;6.74) in Annual group and 4.47% (1;5.58) in Biennial group (p=0.042 between Control and Annual group). Lumbar spine BMD decreased -1.74% (-2.56;3.60) in Control group, increased 7.90% (4.20;16.57) in Annual group and 5.22% (2.02;7.28) in Biennial group (p=0.003 between Control and Annual group; p=0.017 between Control and Biennial group). NTx (p=0.006) and P1NP (p=0.005), significantly decreased in Annual group. Biennial group showed a significant decrease from baseline to 48 week in P1NP (p=0.036), and a trend to significance in NTx (p=0.05), but not between baseline to week 96. No differences between Annual and Biennial groups were detected in any parameter at week 96. Two patients from Zoledronic group suffered grade 1 asthenia and two had fever within 48 hours after the infusion administration, one of them with grade 1 and other grade 2 of intensity. All symptoms reverted with paracetamol or ibuprofen administration. No discontinuations of the study were observed due to adverse events drug-related.

Conclusions: The use of biennial zoledronic acid presented similar bone benefit than the annual administration after 96 weeks of follow up in terms of BMD and bone markers. The biennial administration of zoledronic acid may be an alternative in the treatment of osteoporosis in this population.

783 Mechanism of Bone Disease in HIV and HCV: Impact of Tenofovir Exposure and Severity of Liver Disease

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Background: Both HIV and HCV infections are associated with an increased risk of osteoporotic fractures. The mechanisms underlying this higher risk are incompletely elucidated. In this analysis, we explore the effects of HIV, HCV and HIV/HCV co-infection on bone health, and assess the relative contributions of TDF exposure and severity of liver disease.

Methodology: This prospective, cross-sectional study recruited 298 male volunteers with HIV, HCV, HIV/HCV co-infection and non-infected controls. All HIV infected patients were virologically suppressed on HAART. Subjects underwent bone mineral density (BMD) testing by DXA scan and measurement of fasting bone turnover markers (BTM) (serum C-telopeptide [CTX] and osteocalcin [OC]). The aspartate aminotransferase-to-platelet ratio (APRI) score was calculated as an indirect marker of hepatic fibrosis. Impact of HIV and HCV infections on BMD was evaluated in multivariate models adjusting for APRI score, BTM, TDF exposure (current, past or never), or duration of TDF use, respectively. All models controlled for age, race and BMI.

Results: Table 1 presents the multivariate analyses of the associations of HIV and HCV infections on femoral neck BMD. HIV and HCV independently predict lower femoral neck BMD, controlling for age, race and BMI (model 1). APRI did not significantly impact BMD or attenuate the association between HIV or HCV and BMD (Model 2), with similar results observed when analysis was restricted to HCV and HIV/HCV patients (not shown). The effect of HIV on BMD is likely mediated through increased bone turnover: HIV patients had higher levels of CTX ($p<0.005$) and OC ($p<0.001$). Furthermore, controlling for OC (model 3) or CTX (not shown) attenuated the association of HIV with BMD. HCV infection did not impact OC or CTX, but was associated with increases in regulatory cytokines OPG ($p<0.001$) and RANKL ($p<0.005$). Among HIV and HIV/HCV patients, TDF exposure (current or past) (model 4) and duration of TDF use were associated with lower BMD ($p=0.0234$). After controlling for TDF exposure, the association of HIV disease with lower BMD was significantly attenuated, suggesting that the observed HIV impact is largely mediated by TDF exposure. Similar associations were observed for total hip BMD.

Conclusions: The impact of HIV on BMD appears to be explained (at least in large part) by TDF exposure and higher bone turnover. HCV association with BMD is independent of the severity of liver disease, as measured by APRI score.

Multivariate models examining the impact of HIV and HCV on femoral neck BMD				
	Model 1 (HIV, HCV, BMI, Race,Age)	Model 2 (Model 1 + APRI score)	Model 3 (Model 1 + serum OC)	Model 4 (Model 1 + TDF exposure)
HIV	-0.035 (p=0.035)	-0.035 (p=0.038)	-0.027 (p=0.11)	0.080 (p=0.070)
HCV	-0.039 (p=0.013)	-0.043 (p=0.016)	-0.043 (p=0.0069)	-0.040 (p=0.011)
APRI score	N/A	0.003 (p=0.89)	N/A	N/A
Osteocalcin	N/A	N/A	-0.0028 (p=0.014)	N/A
TDF Current Use	N/A	N/A	N/A	-0.12 (p=0.006)
TDF Past Use	N/A	N/A	N/A	-0.12 (p=0.028)

784 Low Bone Mineral Density (BMD) Among Ugandan HIV-Infected Patients On Failing First-Line ART

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Background: Both HIV infection and use of ART are associated with increased risk of low BMD. There have been few studies of BMD in sub-Saharan Africa. We examined the prevalence of osteopenia and osteoporosis and factors associated with low BMD among patients failing first-line ART in Kampala, Uganda.

Methodology: Sub-study of the Europe - Africa Research Network for Evaluation of Second-line Therapy, EARNEST trial, a large randomized trial of three different second-line ART strategies in protease inhibitor - naïve patients with evidence of first-line ART failure in 5 African countries. BMD was measured using Dual energy x-ray absorptiometry scans (DXA) at lumbar spine (LS) and hip. Data on potential risk factors for low BMD i.e age, CD4 cell count, plasma viral load, Body mass index (BMI), prior ART regimens, alcohol use, and dietary calcium intake were collected. Low BMD was defined as T-score < -1, with osteoporosis and osteopenia less than -2.5 and between -2.5 and -1 respectively. Logistic regression was used to identify factors associated with low BMD (T-score < -1).

Results: 181/1200 EARNEST participants from 3 sites in Uganda were enrolled into this sub-study. Of these ,125 (69%) were female (16 (12.8%) post-menopausal) , median (interquartile range, IQR) baseline values were: age 35 (31-41) years, duration of 1st line ART 3.7(2.7-5.0) years (30 (16.7%) had

used TDF), CD4 67 cells (35-151), and viral load log 4.9 (4.5-5.3), and a low (<18.5 kg/m2), and high (≥ 25 kg/m2) BMI were present in 19 (10.5%) and 44 (24.3%) of subjects. Median (IQR) BMD for lumbar spine and left hip were 0.94(0.86-1.03) and 0.91(0.83-0.99) gms/cm2 respectively. A total of 89/175 (50.1%) and 44/176 (25%) had low BMD at the lumbar-spine and hip respectively. The prevalence of osteoporosis was 8% at the LS and 1.1% at the hip while osteopenia was present in 46.6% and 27.1% at the LS and hip respectively. Low BMD at lumbar spine was associated with both low BMI (adjusted odds ratio [AOR] 3.48; 95% Confidence interval (CI) 1.08-11.2), and high BMI (AOR 0.42; 0.20-0.88) as compared to normal BMI, and use of TDF in first-line regimen (AOR 2.23; 95% CI 0.95-5.28, p= 0.06). At the Hip, a low BMI was predictive of low BMD, (AOR 4.12; 1.51-11.3) while overweight was protective, (AOR 0.39; 0.14-1.07). Age, gender, and CD4 cell count were not associated with low BMD.

Conclusions: More than half of the Ugandan patients failing first line ART had low BMD but osteoporosis was present in < 10%. The prevalence of low BMD in general and osteoporosis was comparable with cross-sectional data from Europe and US. However, in the 10% with a low BMI, there was a 3.5 fold increased risk of low BMD. Subjects with a low BMI and those receiving TDF have an increased risk of low BMD and may need bone health evaluation and close monitoring of their BMD while on ART.

Session P-Q6 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Hepatic Fibrosis and Other Hepatic Complications

785 Abacavir and Didanosine Enhance Susceptibility To Acetaminophen-Induced Hepatotoxicity

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Background: Liver mitochondrial toxicity induced by nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) is usually associated with disrupted mitochondrial DNA replication. However, mitochondrial dysfunction can also be generated by other mechanisms unrelated to inhibition of Pol-γ. We have analysed the acute effects of clinically relevant concentrations of the most widely used NRTIs on the function of mitochondria and have assessed their impact on the viability of hepatic cells. To explore a possible synergism with other drugs whose hepatotoxicity is attributed to the acute undermining of mitochondrial function, we have also evaluated the effects of NRTIs in combination with acetaminophen (APAP).

Methodology: Parameters of mitochondrial function (oxygen consumption, mitochondrial membrane potential - $\Delta\psi$m -, reactive oxygen species - ROS - production, ATP levels) and cellular proliferation/survival (cell count, cell cycle, viability) were assessed in Hep3B cells treated (1-24h) with the pyrimidine analogues Lamivudine, Zidovudine and Emtricitabine, the purine analogues Abacavir (ABC) and Didanosine (ddI), or the nucleotide analogue Tenofovir. Further experiments were performed in the presence of different concentrations of APAP. Data were presented as mean+/-SEM, and their statistical significance versus vehicle was analyzed by one-way ANOVA.

Results: Clinical concentrations of ABC and ddI, but not of the other NRTIs, produced an immediate and significant decrease in mitochondrial function, expressed by a concentration-dependent inhibition of oxygen consumption, an increased production of ROS, and a reduction of $\Delta\psi$m and intracellular ATP levels. This mitochondrial dysfunction did not compromise cell survival, as the aforementioned parameters returned to previous values after 24h treatment. However, co-administration of these drugs with APAP concentrations below those considered toxic in hepatic cellular models significantly exacerbated the deleterious effects of both treatments on mitochondrial function (30-40% reduction of $\Delta\psi$m with respect to single treatment) and cellular viability (10-20% decrease with respect to each drug).

Conclusions: Among the NRTIs evaluated, only ABC and ddI were deleterious to the mitochondria of hepatocytes, though they did not compromise cell survival at the doses and periods in question. However, liver injury was clearly present when either one of these two purine analogues was administered in combination with subtoxic concentrations of APAP. Our findings are of relevance given the frequent use of APAP by patients taking NRTIs and call for caution regarding the use of these antiretrovirals in combination with other hepatotoxic stimuli owing to mitochondrial interference.

786 Liver Fibrosis Is Not Uncommon in HIV-Infected Patients Without Viral or Alcoholic Hepatitis

Anchalee Avihingsanon[1, 2], Salyavit Jitmitraparp[3], Vorapot Sapsirisavat[1], Tanakorn Apornpong[1], Tawan Mengthisong[1], Stephen Kerr[1, 4], Gail V. Matthews[4], Sharon R. Lewin[5, 6], Kiat Ruxrungtham[1, 7], and the HIV-NAT 006 study team.

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Background: Liver fibrosis in HIV-infected individuals is mostly attributable to hepatitis B (HBV) or C (HCV) co-infection. An association between significant liver fibrosis and diabetes mellitus in an HIV-uninfected population has been reported, but this phenomenon in HIV mono-infected patients has not been well described, and few studies of liver fibrosis in HIV mono-infection have been published from Asia. We determined the prevalence of liver fibrosis assessed by transient elastography (TE, Fibroscan®) and its predictors, among our HIV-infected patients on long term combination antiretroviral therapy (cART) at HIV-NAT, in Bangkok.

Methodology: Liver stiffness measurement (LSM) was assessed by TE in 586 (57.5% male) HIV-infected patients without HBV/HCV co-infection; subjects with transaminitis >10x upper limit of normal were excluded from analysis. LSM values greater than or equal to 7.2kPa were defined as abnormal. Multivariate logistic regression was performed to identify factors associated with abnormal LSM. Predictor covariates included age, gender, metabolic syndrome, cART regimen, duration of cART, alcohol intake, and smoking.

Results: At the time of LSM assessment, median age was 43 years and 21% of patients were aged >50 years. Median (IQR) duration on cART was 11 (6-15) years; median CD4 cell count was 573 (447-730) cells/mm3, median ALT was 27 (20-40) U/L and 95% of patients had plasma HIV RNA <50 copies/mL. Abnormal LSM was observed in 10.9% (64/586) patients and of these, 6 had scores >13kPa indicating cirrhosis. Diabetes mellitus was diagnosed in 18.4% (108/586) patients: 22% (24/108) of patients with diabetes mellitus had abnormal LSM versus only 8% (40/478) of non-diabetic patients (p<0.001). In addition, 24% and 8% of patients with BMI>25kg/m2 and BMI<25kg/m2 had abnormal LSM, respectively. In multivariate analyses, male gender (adjusted odds ratio [OR] 2.10, 95% confidence interval [CI] 1.15-3.80; P=0.015), BMI>25kg/m2 (OR 3.79, 95%CI 2.13-6.73, P<0.01), and diabetes (2.67, 95%CI 1.46-4.88, P=0.001) were independently associated with abnormal LSM. Didanosine use was not significant in univariate models.

Conclusions: The prevalence of abnormal LSM among our HIV-infected patients without HBV or HCV in a setting of relatively low of alcohol consumption and long duration of cART is substantial. Diabetes, being overweight and male gender were significantly associated with liver damage in this cohort. Since liver fibrosis may progress to cirrhosis, hepatocellular carcinoma and cardiovascular morbidity, diabetic patients and overweight patients should be evaluated for the presence of liver fibrosis. Early diagnosis will enable interventions for modifiable risk factors, including diet, exercise and weight loss.

787 Association Between Dideoxynucleoside Analogues (d-Drugs) and End-Stage Liver Disease (ESLD)

Lene Ryom[1], Caroline A. Sabin[2], Peter Reiss[3], Wafaa El-Sadr[4], Antonella D. A. Monforte[5], Stephane De Wit[6], Matthew Law[7], Ole Kirk[1], Andrew N. Phillips[2], Jens D. Lundgren[1], on behalf of the D:A:D Study Group

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Background: Whilst some antiretroviral (ARV) drugs, including d-drugs (stavudine [d4T], didanosine [ddI], zalcitabine [ddC]), may cause hepatotoxicity, their association with clinically defined ESLD remains unknown. Whilst rarely used in resource-rich settings, d-drugs are still used in some resource-limited settings.

Methodology: D:A:D participants were followed from 1/2/2004 to the earliest of ESLD (variceal bleeding, grade III/IV hepatic encephalopathy, hepatorenal syndrome, liver transplant), death, 6 months after last visit or 1/2/2012. Poisson regression described associations between ESLD and cumulative use of d-drugs, other nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), non-NRTIs (NNRTIs), and possible confounders (table), and considered whether any drug effects were reversed upon cessation.

Table: Associations between current and cumulative exposure to d-drugs and rate of ESLD

			Adjusted for:	
			Exposure to other NRTIs, PIs & NNRTIs	Exposure to other NRTIs, PIs & NNRTIs & potential confounders[c]
	Rate /1000 PY[a] (95% CI[a])	Relative rate[b] (95% CI)	Relative rate (95% CI)	Relative rate (95% CI)
Never received d-drugs	0.042 (0.031-0.052)	0.75 (0.41-1.38)	0.74 (0.40-1.36)	1.35 (0.73-2.49)
Currently on d-drugs	0.086 (0.050-0.122)	Ref.	Ref.	Ref.
Stopped d-drugs & off for:				
≥0, <2 years	0.167 (0.111-0.222)	2.28 (1.32-3.94)	2.31 (1.33-4.02)	2.01 (1.17-3.48)
≥2, <4 years	0.144 (0.093-0.196)	1.90 (1.09-3.32)	1.97 (1.12-3.47)	1.91 (1.09-3.36)
≥4, <6 years	0.172 (0.113-0.230)	2.23 (1.29-3.85)	2.38 (1.36-4.16)	2.45 (1.40-4.28)
≥6, <8 years	0.114 (0.066-0.183)	1.51 (0.79-2.86)	1.66 (0.86-3.20)	1.75 (0.91-3.38)
≥8 years	0.067 (0.033-0.119)	0.91 (0.44-1.91)	1.01 (0.47-2.18)	1.09 (0.51-2.36)
Cumulative exposure (/year) to d-drugs	n/a	1.07 (1.01-1.12)	1.07 (1.01-1.14)	1.07 (1.01-1.13)

[a]PY: person-years; CI: confidence interval; [b] adjusted for time since stopping d-drug and cumulative exposure to d-drug; [c]Age, injection drug use as mode of HIV acquisition, previous AIDS diagnosis, viral hepatitis C/B coinfection, latest CD4 count, time since stopping d-drug and cumulative exposure to d-drug; no significant associations were seen between ESLD and calendar year, gender, cohort, smoking status, ethnicity or latest HIV RNA level and so models do not include adjustment for these factors.

Results: Over 252,660 person-years (PY), 204 persons experienced ESLD (incidence 0.81/1000 PY [95%CI 0.70-0.92]). Most common ESLD manifestations were encephalopathy (43%) and variceal bleeding (30%); for 91% the underlying cause was viral hepatitis and/or alcohol use. After adjustment, longer d-drug use was associated with increased ESLD rates (overall adjusted rate ratio 1.07 [95% CI 1.02-1.12]/year; d4T 1.10 [1.04-1.16]; ddI 1.06 [1.00-1.12]; ddC 1.07 [0.92-1.24]). In contrast, no associations were seen with longer use of other NRTIs (1.03 [0.98-1.08]), PIs (0.99 [0.95-1.05]) nor NNRTIs (0.99 [0.93-1.05]). Of 19,033 persons on d-drugs, 90% stopped their use at least once, with only 22% of the PY in those exposed to d-drugs being in current users. Those stopping d-drugs had higher ESLD rates than those currently on d-drugs; this effect did not wane in the first 8 years after cessation (table). Other ESLD risk factors were older age (>35 vs. <35 years: 2.20 [1.20-4.03]), latest CD4 (0.77 [0.74-0.80] /50 cells higher), hepatitis C (1.66 [1.08-2.55]) and hepatitis B (2.63 [1.63-4.25]) coinfection and injection drug use acquisition mode (4.45 [3.22-6.14]). There was no evidence that the d-drug effect was modified by hepatitis status (p>0.1 for interaction).

Conclusions: Cumulative use of d-drugs, but not other ARV drugs, was associated with increased ESLD rates, which were not reversible upon cessation. The higher rates in those stopping d-drugs may suggest selective discontinuation in those at highest risk of ESLD. Our results suggest that d-drugs should be avoided if possible, particularly in those with viral hepatitis.

788 Microbial Translocation, Immune Activation, Apoptosis and Liver Fibrosis in the MASH Cohort

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Background: Microbial translocation and immune activation occurs as HIV disease progresses and has been linked with the development of liver disease. Most of these studies however, have been done *in vitro* and in animal models. Our objective was to investigate the pathways of liver fibrogenesis, including microbial translocation, apoptosis, and cytokine activation in HIV mono-infected and HIV-HCV co-infected adults in the Miami Adult Studies on HIV (MASH) Cohort.

Methodology: After obtaining informed consent in a subset of the MASH cohort participants, blood was collected at baseline and 12 months later for indices of liver fibrosis (FIB-4 and APRI), bacterial translocation (plasma LPS), immune activation (soluble CD14), pro-fibrotic cytokine (TGF-β1), and hepatocyte apoptosis (cytokeratin-18 [CK-18]). FIB-4 and APRI were calculated [age (years) x AST (U/L)]/[PLT (10^9 cells/L) X $ALT^{1/2}$ (U/L)], and [AST (x upper limit of normal range) x 100]/platelet count (10^9 cells/L)], respectively. LPS was determined using the Limulus Amebocyte Lysate kit (Lonza, Wackersville, MD). Soluble CD14 and TFG-β1 were measured using Quantikine ELISA kits (R&D, Minneapolis, MD). Plasma levels of CK-18 were determined by M30 Apoptosense ELISA kit (PEVIVA, Bromma, Sweden). Questionnaires were used for demographics.

Results: Among 80 participants, the mean age was 46.65±7.77, 65% were male, and 75% were black non-Hispanic; 87% were on ART and 25% were HIV/HCV co-infected. Liver fibrosis progressed faster in HIV/HCV co-infected than in than in HIV mono-infected participants [FIB-4 (2.21±SD 1.61 vs 1.21±SD 0.44, p=0.02), APRI (0.64 ±SD 0.64 vs. 0.29 ±SD 0.11, p=0.03)]. In a linear regression analysis faster progression of liver fibrosis using either FIB-4 or APRI was associated with higher CK-18; for FIB-4 (β=11.027, p=0.038) and sCD14 (β=0.0006, p=0.029); for APRI the association was CK-18 (β=47.449, p=0.005) and sCD14 (β=0.0002, p=0.042). Soluble CD14 was associated with TGF-β1 (β=2.330, p=0.001). Using mixed models to evaluate change over time, increase in sCD14 was predictive of faster liver fibrosis [FIB-4 (β=0.0005, p=0.040), APRI (β=0.0002, p=0.043)]. Faster liver disease progression was associated with higher levels of CK-18 over time for both FIB-4 and APRI (β=16.756, p<0.001, and β=37.940, p<0.001). All analyses were controlled for age, gender and CD4 cell count.

Conclusions: Advancement of liver fibrosis estimated by FIB-4 and APRI was associated with increased bacterial translocation, immune activation, hepatocellular apoptosis, and increased level of a pro-fibrotic cytokine TGF-β-1, over a period of one year. Larger studies are warranted to increase the understanding of liver fibrogenesis in order to identify pro-fibrotic targets.

789 Cumulative Exposure To Ritonavir-Boosted Atazanavir Is Associated With Cholelithiasis

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Background: The effect of long-term treatment with ritonavir-boosted atazanavir (ATV/r) on cholelithiasis formation is unknown.

Methodology: A single-center, cross-sectional study was conducted to elucidate the prevalence of cholelithiasis in patients with HIV-1 infection who underwent abdominal ultrasonography between January 2004 and March 2012. Uni- and multi-variate logistic regression analyses were applied to estimate the effects of >2 years of ATV/r exposure on cholelithiasis as the primary exposure.

Results: Of the 890 study patients, 84 (9.4%) had >2 years of ATV/r exposure. Cholelithiasis was twice more frequently diagnosed in those treated for >2 years with ATV/r [15 (18%) of 84 patients] than in those treated for <2 years [72 (8.9%) of 806 patients] (p=0.018). Univariate analysis showed a significant association between >2 years of ATV/r exposure and cholelithiasis (OR=2.216; 95%CI, 1.206-4.073; p=0.010), and the association almost persisted in multivariate analysis (adjusted OR= 1.806; 95%CI, 0.922-3.537; p=0.085). Treatment for >2 years with ritonavir-boosted lopinavir (LPV/r) and ritonavir-boosted darunavir (DRV/r) was not associated with cholelithiasis in uni- and multi-variate analysis { >2 years exposure to LPV/r [n=148 (16.6%)]: OR 1.246, 95% CI 0.710-2.185, p=0.443; adjusted OR 1.221, 95% CI 0.674-2.214, p=0.510} { >2 years exposure to DRV/r [n=29 (3.3%)]: OR 1.067, 95% CI 0.316-3.601, p=0.916; adjusted OR 0.641, 95% CI 0.173-2.377, p=0.506}. Additional analysis showed that >1 year exposure to ATV/r [n=124 (13.9 %)] was significantly associated with cholelithiasis (OR 1.857, 95%CI 1.073-3.214, p=0.027), whereas >1 year exposure to LPV/r and DRV/r was not.

Conclusions: Long-term treatment of patients with HIV-1 infection for >2 years with ATV/r was associated with increased risk for cholelithiasis compared to patients with shorter exposure. Long-term exposure to ATV/r appears to increase the risk of cholelithiasis in patients with HIV-1 infection.

Multivariate analysis: the risk of long-term (>2 years) treatment with ATV/r on cholelithiasis						
	Model 1 crude (n=890)		Model 2 adjusted (n=890)		Model 3 adjusted (n=851)	
	OR	95% CI	OR	95% CI	OR	95% CI
>2 years of atazanavir/r exposure	2.216	1.206-4.073	2.096	1.131-3.883	1.806	0.922-3.537
Age per 1 year increment¶			1.009	0.980-1.039	1.028	1.008-1.049
Female sex			2.005	0.921-4.368	2.183	0.986-4.834
Body mass index per 1 kg/m2 increment					1.001	0.983-1.020
Cirrhosis¶					6.947	2.133-22.63
Diabetes mellitus					1.017	0.417-2.481
HIV viral load per log10/ml increment					0.900	0.717-1.129
Duration of ART per 1 year increment					1.030	0.983-1.080

790 Prevalence of Liver Fibrosis Based On Non-Invasive Markers Among HIV-Infected Patients in Zambia

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Background: Liver-related mortality is anticipated to increase as HIV-infected individuals live longer in sub-Saharan Africa (SSA). Data on the epidemiology of liver fibrosis, an early form of chronic liver disease, from these populations are scarce. Using FIB-4 index and AST-to-platelet ratio index (APRI), we estimated the prevalence and factors associated with having significant fibrosis among HIV-infected Zambians.

Methodology: Using central laboratory testing data from Lusaka public-sector HIV care facilities, we identified patients with measurements of liver transaminases (AST and ALT) and platelet count within 90 days of enrollment. Among patients with available measurements, we calculated FIB-4 index and APRI using published formulas. We determined the proportion with significant liver fibrosis, defined as having either a FIB-4 >3.25 or APRI >1.5. Using multivariable logistic regression we assessed demographic and medical characteristics associated with fibrosis including age, sex, CD4+ T-cell count, and hepatitis B virus (HBV) status.

Results: Of the 87,458 patients who enrolled from July 2006 to July 2008, 35,551 (40.6%) patients had available laboratory testing at enrollment to assess liver fibrosis. The median age of patients was 33 years (interquartile range [IQR], 27-39 years) and 58.2% were women. At enrollment, median CD4+ T-cell count was 220 cells/mm3 (IQR, 103-386 cells/mm3). Only 372 (1.1%) were screened for HBV co-infection with a hepatitis B surface antigen assay. The median FIB-4 index was 0.94 (IQR, 0.61-1.46) and the median APRI was 0.38 (IQR, 0.25-0.64). Significant liver fibrosis was present in 3,008 (8.5%; 95% confidence interval [CI], 8.2-8.8%]) of patients. A 5-year increase in age (adjusted odds ratio [AOR], 1.02; 95% CI, 1.00-1.06), male sex (AOR 1.95; 95% CI, 1.72-2.20), and CD4+ T-cell count <200 cells/mm3 (AOR 3.14; 95% CI, 2.75-3.59) were associated with having liver fibrosis. Among those screened, HBV co-infection was also associated with having fibrosis (AOR 2.92; 95% CI, 1.03-8.28).

Conclusions: Among HIV-infected adults enrolling in HIV care in urban Zambia, nearly 9% may have significant liver fibrosis, a risk factor for liver-related death. In many SSA settings where liver biopsy is rarely available, dedicated HIV cohorts are needed to investigate the utility of non-invasive liver fibrosis assessment.

791 Significance of Alcohol Abuse Diagnosis vs Other Risk Factors for Advanced Liver Fibrosis by FIB-4

H. Nina Kim[1], Heidi M. Crane[1], Carla V. Rodriguez[1], Stephen Van Rompaey[1], W. Christopher Mathews[2], Michael Mugavero[3], Kenneth H. Mayer[4], Katerina Christopoulos[5], Sonia Napravnik[6], Mari M. Kitahata[1]

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Background: Liver disease has emerged as a major cause of non-AIDS-related death among patients with HIV. Given the limitations of liver biopsy, noninvasive markers of hepatic fibrosis such as FIB-4, an index derived from age, platelet count and aminotransferase levels (ALT, AST), have been validated and shown to predict both severity of fibrosis and clinical outcomes. We studied current alcohol use as measured systematically across sites by a self-reported clinical assessment, alcohol history as captured by clinician-recorded alcohol diagnoses over time, and other factors such as viral hepatitis and their associations with advanced fibrosis as represented by FIB-4 >3.25 in a large clinical cohort of patients across the U.S.

Methodology: All 8,220 patients in the CNICS cohort across 6 sites who completed self-reported assessments as part of routine care and had at least one set of FIB-4 labs were included. The most recent assessment data and lab values were used. Current alcohol use was categorized using AUDIT-C scores. We defined alcohol abuse diagnosis as any diagnosis of alcohol dependence or abuse recorded over time. We examined associations using logistic regression.

Results: Median age was 45 years, 86% were men, and 53% white, 25% black. 354 (4.3%) of the 8,220 patients and 168 (14%) of the 1,166 chronic hepatitis C (HCV) HIV co-infected patients had high FIB-4 scores >3.25. 16% reported high current alcohol use (AUDIT-C scores ≥5 for men, ≥4 for women). 20% of patients had an alcohol abuse diagnosis. Factors independently associated with FIB-4 >3.25 (Table) included: an alcohol diagnosis, chronic HCV, chronic hepatitis B (HBV), age >40 years, diabetes, most recent HIV plasma viremia >500 copies/mL, and CD4 nadir <200 cells/mm3. A high AUDIT-C score was associated with high FIB-4 only when the analysis was restricted to patients currently drinking; when alcohol abuse diagnosis was added to the model, this association was attenuated and no longer statistically significant. Neither alcohol variable modified the effect of chronic HCV on FIB-4.

Conclusions: In a large diverse population of HIV-infected patients with multiple comorbidities, we identified several independent risk factors - chronic HCV or HBV, diabetes, HIV viremia, older age and low nadir CD4 - for advanced hepatic fibrosis. While adjusting for these factors, alcohol history as measured by diagnoses appears to be an overall more robust predictor of liver fibrosis than current alcohol use measured by the AUDIT-C.

Risk Factors Associated with FIB-4 Score >3.25		
	Bivariate Analysis	Multivariable Analysis
Factor	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Chronic hepatitis C	6.2 (5.0-7.7)	4.1 (3.2-5.3)
Age > 40 years	5.4 (3.7-7.8)	4.7 (3.1-7.0)
HIV viral level >500 copies/ml	2.1 (1.7-2.6)	2.6 (2.0-3.4)
CD4 nadir 200-499 cells/mm3	1.8 (1.0-3.0)	1.6 (0.9-2.9)
CD4 nadir	4.2 (2.5-7.1)	2.7 (1.5-4.8)
Alcohol dependence/abuse	4.8 (3.9-6.1)	3.1 (2.4-3.9)
Chronic hepatitis B	2.5 (1.7-3.6)	2.1 (1.3-3.2)
Diabetes mellitus	2.3 (1.7-3.0)	1.8 (1.3-2.5)

Session P-Q7 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Renal Disease: ART, Genetic Factors, and Long Term Outcomes

792 Predictors of Progression, Stabilisation, or Improvement of eGFR After Chronic Renal Impairment

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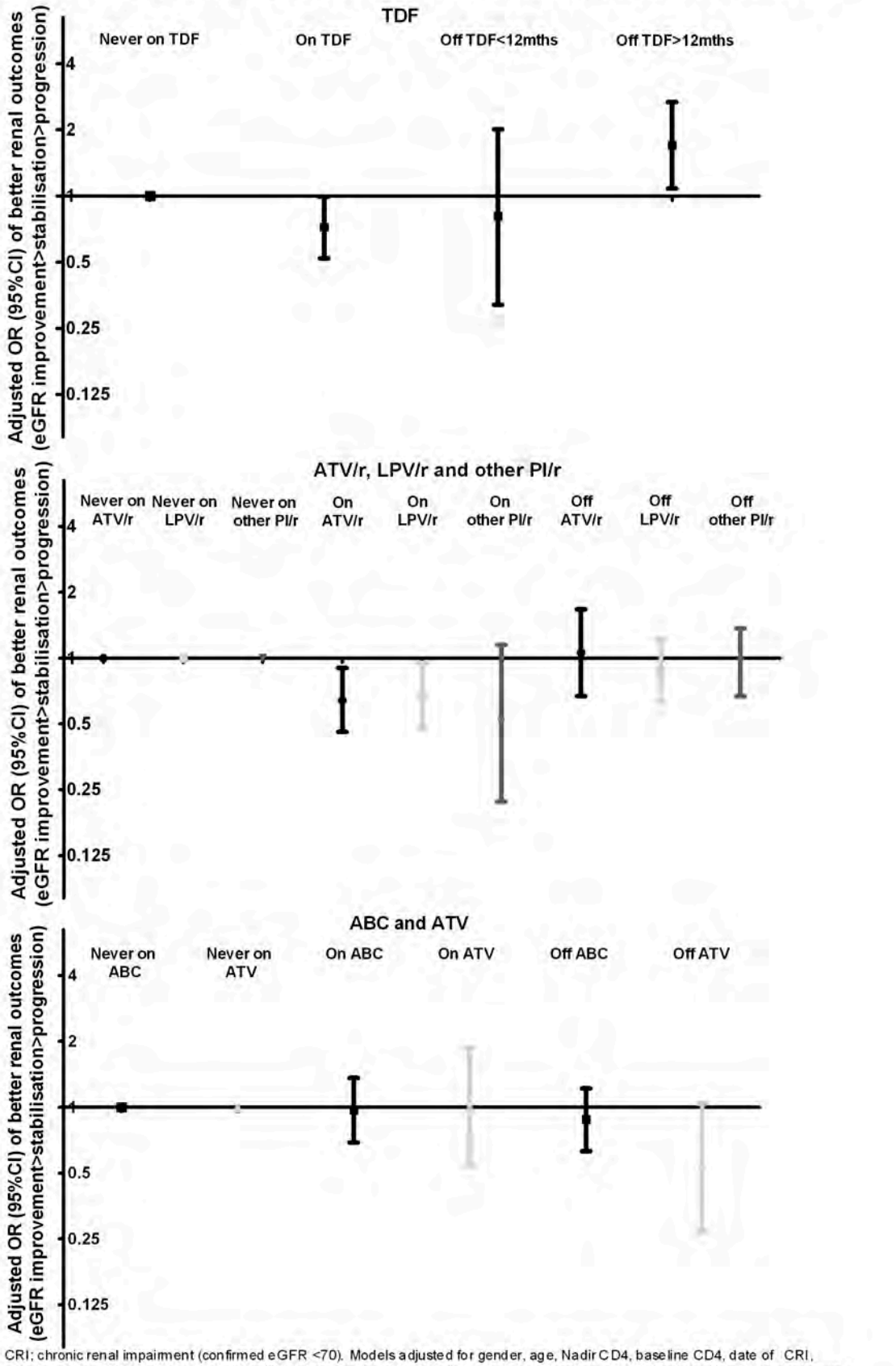
Background: Knowledge of eGFR outcomes after chronic renal impairment (CRI) in HIV-positive persons and its relationship to antiretroviral drug (ARVs) use is limited. Prior studies have shown increased tenofovir (TDF) discontinuation at eGFR<70 mL/min/1.73m^2 limiting the value of eGFR≤60 as a CRI cut-off.

Methodology: D:A:D participants were followed from eGFR>80 (Cockcroft-Gault) after 1/1/2004 to CRI, defined as 2 consecutive eGFR≤70 (>3 months apart), thus ensuring an eGFR decline of ≥10 before CRI. The median of all (and minimum 2) eGFRs at 12-24 months after CRI was compared to the median eGFR defining CRI, and eGFR changes were grouped into: improvement (increase >+10), stabilisation (-10 to +10) and progression (decrease >-10). Multinomial regression assessed odds of better eGFR outcomes (assuming improvement is better than stabilisation, which in turn is better than progression) adjusting for use and discontinuation of TDF, atazanavir (+/- ritonavir, ATV/r), lopinavir (LPV/r), other boosted protease inhibitors (PI/r) and abacavir (ABC), as well as demographics, HIV-related factors, HCV status and traditional renal risk factors (figure).

Results: Of 1237 persons developing CRI, 23.2% improved eGFR, 69.0% stabilised and 7.8% progressed at 12-24 months after CRI. Those on TDF at time of CRI had lower odds of better eGFR outcomes compared to those never exposed to TDF, while those off TDF for >12 months at time of CRI had higher odds of better outcomes (figure). Similar trends were seen for ATV/r, LPV/r and other PI/r, but not ATV or ABC. Censoring follow-up for nephrotoxic ARVs used concomitantly (i.e. those on TDF for concomitant ATV/r use) showed similar results. Older persons (adjusted odds 0.61/10 yrs [95%CI 0.50-0.70]) and those with slowly declining eGFR prior to CRI (0.72 [0.55-0.96], ≤10 vs. >10/yr) had significantly lower odds of better eGFR outcomes, while those with diabetes for >5 yrs had marginally significant lower odds compared to non-diabetics (0.61 [0.36- 1.05]). No HIV-related factors were associated with better eGFR outcomes.

Conclusions: Use of TDF, ATV/r, LPV/r and other PI/r, older age, diabetes and slowly declining eGFR were associated with decreased odds of better eGFR outcomes in HIV-positive persons after CRI. TDF discontinuation prior to CRI was associated with better eGFR outcomes, suggesting TDF associated eGFR decline may be halted or reversed with early cessation. There was some suggestion that this may also be true for ATV/r, LPV/r and other PI/r.

ARV Use at CRI and Adjusted Odds Ratios of Better Renal Outcomes



CRI; chronic renal impairment (confirmed eGFR <70). Models adjusted for gender, age, Nadir CD4, baseline CD4, date of CRI, eGFR at CRI, eGFR slope prior to CRI, HCV status (unknown, negative, positive: anti-HCV positive & HCV-RNA positive/unknown), diabetes (no, yes<5 years, yes>5years), hypertension (>150/>100), prior cardiovascular disease, use (never on, currently on, currently off) of TDF, ATV/r, ATV, LPV/r, other PI/r and ABC. Indinavir use after 2004 was limited and use was only included to account for possible confounding.

793 Spectrum of HIV-Associated Kidney Disease in the Era of Combination Antiretroviral Therapy

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Background: Immune complex kidney disease (ICKD) has become the dominant pathology in renal biopsy series of HIV+ patients. The natural history of ICKD and risk factors for ICKD remain poorly studied.

Methodology: We reviewed consecutive renal biopsies (1998-2012) of HIV+ patients attending eight clinics in the UK. ICKD was defined by the unequivocal presence of glomerular immunoglobulin deposits and corroborated, where available, by the presence of electron dense deposits on electron microscopy. We compared patients with ICKD to those with HIV-associated nephropathy (HIVAN) and patients in the UK CHIC cohort. Kaplan-Meier analysis was used to estimate progression to end-stage kidney disease (ESKD), and Poisson regression analysis to examine factors associated with ICKD and HIVAN in the UK CHIC cohort.

Results: Of the 250 diagnostic biopsies, 88 showed ICKD and 67 HIVAN. ICKD comprised a spectrum of patterns including membranous (n=17), membrano-proliferative (n=5) and ICKD-not otherwise specified [NOS] (n=34); these groups displayed considerable overlap in both glomerular morphology and location of deposits and were hence considered together as 'core' ICKD. The remaining ICKD biopsies showed IgA nephropathy (n= 26) and lupus (n=6) nephropathy; these patients were analyzed separately and excluded from the present analyses. Patients with ICKD and HIVAN differed by ethnicity (black: 54% vs. 98%), median known duration of HIV (6.2 vs. 0.1 years), degree of immunodeficiency (median CD4 nadir 155 vs. 54, median CD4 at biopsy 382 vs. 116 cells/mm^3) and severity of kidney disease at biopsy (median eGFR 53 vs. 22 mL/min/1.73m^2) ($p<0.001$ for all). At biopsy, 59% vs. 41% of patients had initiated combination antiretroviral therapy (ART) ($p=0.01$) and 66% vs. 34% had HIV RNA <200 c/mL ($p=0.0008$); at 1 and 5 years post-biopsy, 4% vs. 29% and 13% vs. 45% of patients had progressed to ESKD ($p<0.0001$ for both). Of the 31,483 patients in the UK CHIC cohort, 32 developed HIVAN and 44 ICKD during follow up. In multivariable analyses, black ethnicity (IRR 2.23 [1.13, 4.40]) and HIV viraemia (1.48 [1.17, 1.86] per $\log_{10}$ increase in HIV RNA) were associated with 'core' ICKD, and black ethnicity (IRR 9.94 [3.69, 26.75]), HIV viraemia (1.35 [1.02, 1.79]), and current CD4 cell count (0.78 [0.68, 0.88] per 50 cell increase) with HIVAN.

Conclusions: This is the first study to demonstrate a relationship between HIV replication and ICKD. Compared to HIVAN, ICKD was associated with less advanced immunodeficiency and a lower rate of progression to ESKD. The observed association with HIV viraemia for both 'core' ICKD and HIVAN may imply a pathogenetic role of HIV replication and its associated immune activation; it also suggests that suppressive ART may reduce the risk of developing these types of kidney disease.

794 Renal and Metabolic Safety of Initial HIV-1 Therapy in Resource-Limited Settings

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Background: Convenient dosing, potency, and low toxicity profile support use of tenofovir disoproxil fumarate (TDF) as the preferred first line nucleotide reverse transcriptase inhibitor (NRTI) in combination regimens for HIV-1 treatment. However, renal and metabolic safety of TDF compared to other NRTI in resource-limited settings has not been well described.

Methodology: Secondary analysis within the ACTG A5175/PEARLS trial, examining the renal and metabolic safety outcomes between participants randomized to zidovudine/lamivudine plus efavirenz (ZDV/3TC + EFV) and TDF/emtricitabine plus EFV treatment arms. Adverse event analysis included occurrence of renal abnormalities (Grade ≥ 3 serum creatinine levels or calculated creatinine clearance [CrCl] by Crockoft-Gault method < 50 ml/min), renal and metabolic serious non-AIDS defining events (SNADEs) at study follow up. Logistic regression explored association between baseline covariates and renal abnormalities. Wilcoxon tests compared serum creatinine with urine dipstick results every 24 weeks and response profiles analysis for CrCl levels over time.

Results: Twenty-one of 1045 participants developed renal abnormalities through 192 weeks (Table 1); 71% were in TDF arm ($p=0.08$). History of diabetes (OR: 10.7, 95% CI: 2.2-52.1), history of AIDS event (OR: 2.7, 95%CI: 0.95-57.4) and a lower baseline CrCl (OR: 3.1 per each 25 ml/min decline, 95% CI: 1.8-6.1) were each associated with development of renal abnormalities. Renal SNADEs occurred in 4% of patients, the majority were urinary tract infections (79%). Renal failure was recorded in 4/42 patients with renal SNADEs and only one event was attributed to TDF use. Serum creatinine levels did not significantly differ to urine dipstick results (normal versus abnormal) at any time point. Significantly lower CrCl values were observed in patients receiving TDF compared to ZDV, but magnitude of difference was small (medians ranging from 98 vs. 106 ml/min at 24 weeks; $p < 0.001$, to 103 vs. 106 ml/min at 96 weeks; $p=0.07$, repeated measures analysis from baseline $p=0.05$). Serious metabolic diagnoses were rare but higher in the ZDV arm (3 vs. 20 cases; $p< 0.001$).

Conclusions: TDF use was not associated with a significant risk of renal abnormalities or serious renal events compared to ZDV in this randomized, multinational study. However, slightly larger declines in CrCl, of unknown clinical importance, were observed with TDF use over time.

Table 1. Baseline Characteristics of Study Population: By Renal Abnormalities at Follow up (N=1045)

Characteristic	Renal Abnormality		P value
	No (N=1024)	Yes (N=21)	
Randomized Treatment Arm, n (%)			
A (ZDV/3TC + EFV)	513 (50)	6 (29)	0.076 (a)
C (TDF/FTC + EFV)	511 (50)	15 (71)	
Age in years, median (IQR)	34 (29, 40)	41 (32, 51)	0.006 (b)
Sex, n (%)			
Female	474 (46)	9 (43)	0.755 (c)
Male	550 (54)	12 (57)	
Body Mass Index (Kg/m²), median (IQR)	22.5 (20.2, 25.3)	21.6 (18.9, 24.4)	0.275 (b)
Screening CD4 cell count (cells/uL), median (IQR)	167 (89, 229)	145 (75, 215)	0.461 (d)
Plasma HIV-1 viral load (log^{10} copies/mL), median (IQR)	5.0 (4.6, 5.4)	5.3 (4.7, 5.5)	0.234 (d)
History of AIDS related diagnoses, n (%)			
No	916 (89)	16 (76)	0.053 (c)
Yes	108 (11)	5 (24)	
History of Hypertension, n (%)			
No	967 (94)	19 (90)	0.437 (c)
Yes	57 (6)	2 (10)	
History of Diabetes, n (%)			
No	1,014 (99)	19 (91)	<0.001 (c)
Yes	10 (1)	2 (9)	
Creatinine Clearance by CG (ml/min), median (IQR)	99.0 (81.6, 121.1)	77.4 (67.5, 92.0)	<0.001 (d)
Abnormal urine dipstick*			
No	935 (91)	16 (76)	0.133
Yes	39 (4)	2 (10)	

** Urine dipstick positive for protein (2+ or higher) or glucose (1+ or higher)*
(a) Fisher's Exact Test; (b) Exact Wilcoxon Test; (c) Chi-Square Test; (d) Wilcoxon Test
Abbreviations: CG (Crockoft-Gault), ZDV (Zidovudine), 3TC (Lamivudine), EFV (Efavirenz), TDF (Tenofovir), FTC (Emtricitabine), IQR (Interquartile range)

795 Risk Factors for Atazanavir (ATV)-Associated Urolithiasis: A Case-Control Study

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Background: Urolithiasis have been reported in patients treated with ATV. Risk factors, clinical features and outcome of ATV-associated urolithiasis have not been fully investigated.

Methodology: From January 2008 to December 2012, we collected all cases of ATV-associated urolithiasis among HIV-infected patients receiving ATV-containing regimens in Paris. A case-control study was then performed with cases defined as adults in whom an ATV-containing urolithiasis had been identified by spectroscopic analysis. Three controls per case were randomly selected among patients treated with ATV-based regimens for at least 6 months and no history of ATV-associated urolithiasis. Patients characteristics, treatment and outcome were retrieved from medical charts at diagnosis and 6-12 months later. An univariate logistic regression analysis was carried out to identify factors associated with the occurrence of ATV-containing urolithiasis and all factors with p-value < 0.20 were kept for a multivariate model selection.

Results: Thirty cases were analyzed. Patients were mostly men (87%), with a median age of 45.5 years, a median CD4 cell count of 443 cells/µL. 97% had plasma HIV RNA levels < 50 cp/mL. Median time between the initiation of ATV-containing regimen and the diagnosis of urolithiasis was 3.1 years [IQR: 2.2-3.8]. Clinical symptoms leading to diagnosis were flank pain in 90% and hematuria in 63%. At diagnosis, renal failure (MDRD creatinine clearance <60 mL/min) was reported in 16/30 (53%) of patients. Ureteroscopic treatment was required in 48% (14/29) of patients and a double J catheter was left in place in 29% (8/28) of cases. 6-12 months after the episode, creatinine clearance remained < 60 mL/min in 5/13 (38.5%) patients.

Factors associated with urolithiasis in the univariate analysis were a history of urinary lithiasis (OR=6.86 (95% CI=2.35, 20.03), p<0.001), the use of ritonavir as ATV-booster (OR=9.38 (95% CI: 1.21, 72.9), p<0.04), previous indinavir use (OR 3.25 (95%CI: 1.33, 7.96), p<0.01), duration of exposure to ATV (OR=1.37 per year (95% CI=1.04, 1.79), p<0.03) and serum bilirubin levels (OR=2.08 per 2-fold increase (95% CI=1.19, 3.61), p<0.01). The final

multivariate model identified serum bilirubin (OR=2.66 per 2-fold increase (95% CI=1.35, 5.21), p<0.01) and duration of exposure to ATV (OR=1.42 per year (95% CI=1.04, 1.93), p<0.03) as independent risk factors.

Conclusions: Although rare, ATV-containing urolithiasis can be associated with severe renal dysfunction and may require surgical treatment. A high serum bilirubin level and long exposure to ATV-containing regimens are independent risk factors for this complication.

796 Single Nucleotide Polymorphisms in UGT1A1 Associate With Atazanavir-Related Nephrolithiasis

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Background: Ritonavir-boosted atazanavir (ATV/r) is a widely used antiretroviral drug though it can cause nephrolithiasis. The aim of this study was to determine the association between polymorphisms in genes encoding proteins that take part in metabolizing process of ATV and drug transporters, and ATV/r-associated nephrolithiasis in HIV-1-infected patients treated with ATV/r.

Methodology: The 20 single nucleotide polymorphisms (SNP) in the ABCB1, NR1I2, UGT1A1, SLCO1B1, and CYP3A5 genes were examined in case patients with ATV/r-induced nephrolithiasis (n=31) and controls (n=47). Case patients were those with a clinical diagnosis of nephrolithiasis while on ATV/r, based on new onset of acute flank pain plus one of the following: 1) new-onset hematuria, 2) documented presence of stones by either abdominal ultrasonography or computed tomography, 3) confirmed stone passage. Control patients were consecutively enrolled among those with >2 years of ATV/r experience in whom nephrolithiasis did not occur. Genotyping was performed by allelic discrimination using TaqMan 5'-nuclease assays with standard protocols. Associations between alleles and ATV/r-associated nephrolithiasis were tested by univariate and multivariate logistic regression analyses.

Results: None of patient characteristics variables (sex, age, body weight, body mass index, CD4 count, renal function, serum uric acid, co-administration of tenofovir, history of nephrolithiasis and indinavir use) was associated with ATV/r-associated nephrolithiasis. Multivariate analyses adjusted with sex and age showed a significant association between ATV/r-associated nephrolithiasis and three SNPs located in the shared UGT1A1-3'UTR region: any G allele at position 339 (rs1042640, adjusted OR=5.704; 95%CI, 1.592-20.44; p=0.008), any G allele at position 440 (rs8330, adjusted OR=5.704; 95%CI, 1.592-20.44; p=0.008), and any T allele at position *211 (rs10929303, adjusted OR=3.660; 95%CI, 1.163-11.52; p=0.027). The distribution of all other SNPs, including the UGT1A1*28 allele was not different between case and control patients.

Conclusions: This is the first study to identify the association between SNPs in UGT1A1 and atazanavir-associated nephrolithiasis. Atazanavir-treated patients with these SNPs might be at higher risk of atazanavir-associated nephrolithiasis than those without.

Association of atazanavir-related nephrolithiasis with SNP in UGT1A1			
	Adjusted OR	95% CI	P value
UGT1A1			
any G allele at 339	5.704	1.592-20.44	0.008
any G allele at 440	5.704	1.592-20.44	0.008
any T allele at *211	3.660	1.163-11.52	0.027

797 Atazanavir and Tenofovir Attenuate the Benefit of Antiretroviral Therapy On Cystatin C: ACTG A5224

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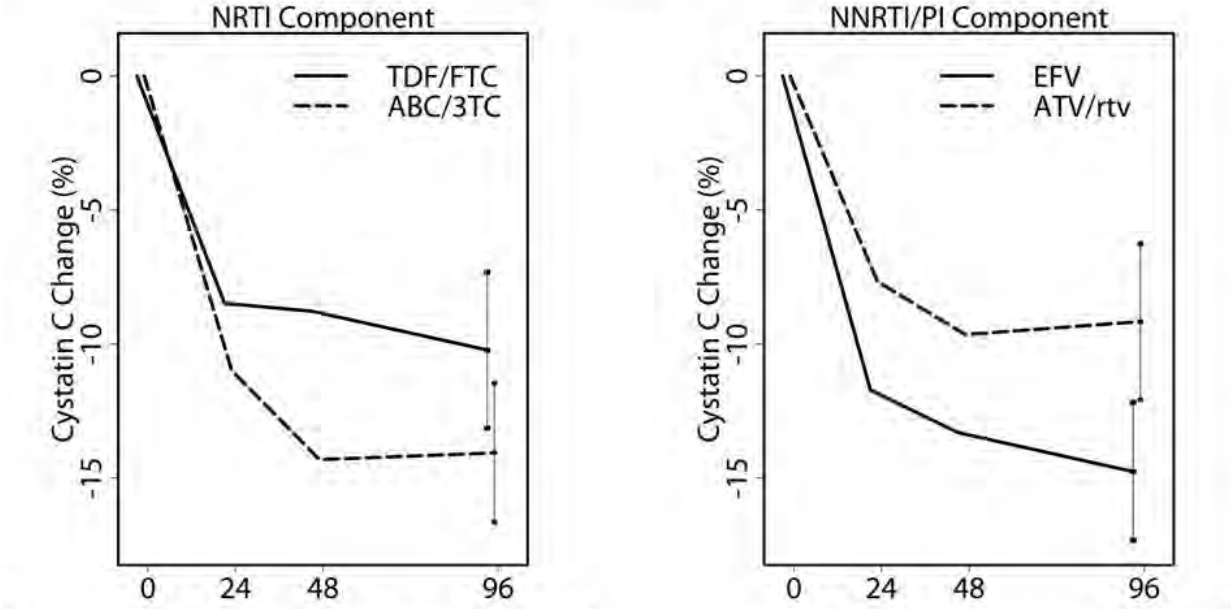
Background: Plasma cystatin C is a biomarker of kidney function thought to more accurately reflect glomerular filtration rate (GFR) than serum creatinine. Whether inflammation affects cystatin C concentrations is controversial. The differential effects of antiretroviral therapy (ART) on cystatin C are poorly understood.

Methodology: ACTG A5224s was a substudy of A5202 which randomly assigned 1857 ART-naïve HIV-infected adults to blinded abacavir/lamivudine (ABC/3TC) or tenofovir/emtricitabine (TDF/FTC) with open-label efavirenz (EFV) or atazanavir/ritonavir (ATV/r). The factorial design was analyzed with one- and two-sample t-tests and multivariable linear regression was used to analyze changes in plasma cystatin C from 0 to 96 weeks. Spearman correlations were used to analyze baseline and change relationships between cystatin C and biomarkers of inflammation.

Results: Of 269 substudy participants, 85% were male and 66% White non-Hispanics; baseline mean(standard deviation) CD4 count was 236(165) cells/mm3 and cystatin C level 0.89(0.17) mg/L. On average, cystatin C decreased significantly over 96 weeks within each arm (p≤0.003). ATV/r and TDF/FTC use were each associated with significant or marginally significant attenuation of the beneficial effects of ART on cystatin C (Figure, no evidence of treatment interaction). In a multivariable regression model, higher baseline HIV-1 RNA, assignment to ABC/3TC, and to EFV were independently associated (p<0.05) with greater % decreases in cystatin C. At baseline, cystatin C was positively correlated with biomarkers of inflammation and endothelial activation: high sensitivity C-reactive protein (r=0.25), interleukin-6 (r=0.34), soluble intercellular adhesion molecule (r=0.36), soluble vascular cell adhesion molecule (r=0.54), tumor necrosis factor-α (r=0.57), and soluble TNF-α receptor-I (r=0.70, all p<0.001). Reductions in cystatin C from 0 to 96 weeks correlated with reductions in inflammatory biomarkers (r=0.39 to 0.58, p<0.001) except for hsCRP (p=0.89) and IL-6 (p=0.24).

Conclusions: The beneficial effect of initiating ART on kidney function as measured by plasma cystatin C levels is attenuated by boosted ATV and TDF/FTC when compared to EFV and ABC/3TC containing regimens, respectively. Decreases in plasma cystatin C after ART initiation may result from improved GFR, but may also be due to decreased systemic inflammation.

Figure: Mean (95% CI) percentage change in plasma cystatin C concentration from 0-96 weeks by treatment group. The intention to treat analysis is displayed below the graphs (p value for between-group difference).



	TDF/FTC N=134	ABC/3TC N=135	p value
Absolute 0-96 week change	-0.10 mg/L (-0.13, -0.08)	-0.14 mg/L (-0.16, -0.11)	0.098
Percent 0-96 week change	-10.2% (-13, -7.5)	-14.1% (-16.8, -11.3)	0.053

	EFV N=139	ATV/r N=130	p value
Absolute 0-96 week change	-0.14 mg/L (-0.17, -0.12)	-0.09 mg/L (-0.12, -0.06)	0.011
Percent 0-96 week change	-14.8% (-17.4, -12.1)	-9.2% (-12.0, -6.4)	0.005

798 A Chronic Kidney Disease Risk Score To Determine Tenofovir Safety Among HIV+ Male Veterans

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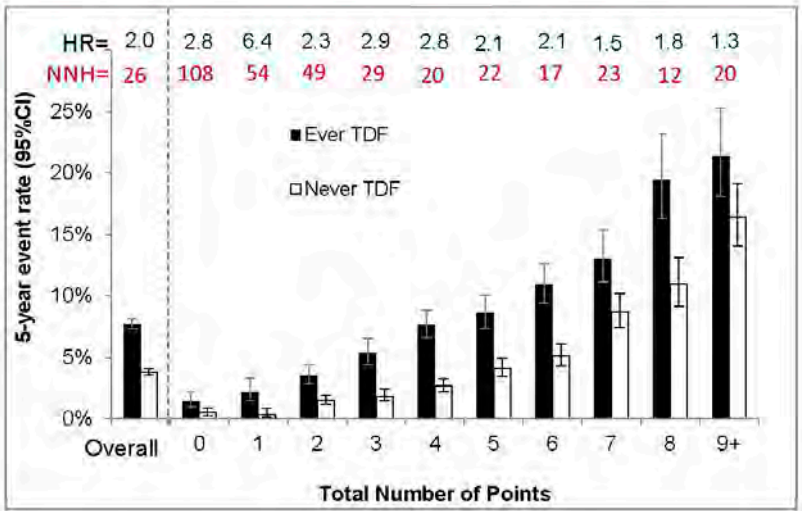
Background: Tenofovir disoproxil fumarate is a widely used antiretroviral for HIV infection that has been associated with an increased risk of chronic kidney disease (CKD). Our objective was to derive a scoring system to predict 5-year risk of developing CKD in HIV-infected adults, and to estimate differences in risk associated with the use of tenofovir.

Methodology: 21,590 HIV-infected men from the Veterans Health Administration aged 18 to 86 years (mean age 47; 54% black) who initiated antiretroviral therapy from 1997-2010 contributed 193,771 years of follow-up. Our outcome was time to first occurrence of CKD, defined as estimated glomerular filtration rate <60ml/min/1.73m2. We developed a point-based score (the VA HIV CKD, or "VHC" risk score) using multivariable Cox proportional hazards models, with weighted point values assigned using regression coefficients from the model.

Figure: Five-year CKD risk by number of VHC points among tenofovir ever and never users



We assessed traditional kidney risk factors and HIV-related factors for CKD, using stepwise backward selection (significance level of α=0.05) to remove candidate covariates.

Results: Median follow-up was 6.3 years, during which 2,059 CKD events occurred. The dominant contributors to the VHC risk score were traditional kidney risk factors (age, glucose, systolic blood pressure, hypertension, triglycerides, proteinuria), although CD4 cell count was also a component. HIV RNA levels were not associated with increased CKD risk in the final model. The overall 5-year event rate was 7.7% in tenofovir users and 3.8% in non-users (adjusted HR=2.0, 95%CI: 1.8-2.2). The VHC Cox model identified a progressive increase in the risk of CKD, with 5-year risks in non-users of tenofovir ranging from <1% (0 points) to 16% (≥9 points), and risks from 1.4% to 21.4% among tenofovir users. Although hazard ratios for tenofovir were higher in those with fewer points (HR=2.8 for 0 points, HR=1.3 for ≥9 points), absolute risk and number needed to harm were worst in those with greater points (NNH=108 for zero points, 20 for ≥9 points). Longer tenofovir exposure was associated with a higher overall 5-year CKD event rate (11.1% for ≥2 years vs. 6.3% for <2 year of exposure), resulting in an NNH of 6 in those with ≥2 years and ≥8 points.

Conclusions: The VHC risk score can be used to predict an HIV-infected individual's absolute risk of developing CKD over five years, and may facilitate clinical decision making around tenofovir use.

799 Genetic Variants of ABCC2 and ABCC10 Are Associated With TFV-Induced Proximal Tubular Dysfunction

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Background: Tenofovir (TFV) is an effective and widely used treatment for both HIV and hepatitis B virus infection. However, it's use in some patients leads to proximal renal tubular dysfunction (PRTD). We aimed to determine the association between polymorphisms in genes encoding drug transporters and PRTD in Thai patients treated with TFV.

Methodology: PRTD was defined as the presence of at least 2 of the following: phosphaturia (total excretion of phosphate >1200 mg per day, or renal tubular reabsorption of phosphate (TmP/GFR) <2.6 mg/dL), uricosuria (FE of uric acid >15%), or non-diabetic glucosuria (urine glucose >300 mg per day or positive urine glucose with plasma glucose <120 mg/gL). Nine single nucleotide polymorphism (SNPs) in the ABCC2, ABCC4, ABCC10, and SCL22A6 genes were determined in 358 Thais taking TFV-based antiretroviral regimens. Genotypes were determined by allelic discrimination using the Tagman 5′-nuclease assay. Associations between genotypes, subject demographic, disease and treatment characteristics and PRTD were analysed by univariate and stepwise multivariate logistic regression.

Results: Out of 358, 67 (18.7%) patients met the criteria of PRTD. After adjusting for age and a history of diabetes, multivariate analysis demonstrated a significant association between PRTD and genotype CC at position 24 (adjusted odds ratio [OR] 2.38; 95% confidence interval [CI] 1.28-4.45, P=0.006); genotype GG at position 1249 (OR 3.54; 95%CI 1.18-10.59, P=0.024) and genotype CC or CT at position 2759 (OR 2.56; 95%CI 1.26-5.21, P=0.009).

Conclusions: We found a significant association between SNPs in ABCC2 and ABCC10 and TFV-induced proximal tubular dysfunction in an Asian population. Pharmacogenetic factors may play a role in the risk of renal toxicity associated with the use of TFV. Close monitoring of renal function is warranted in TFV-treated patients with these SNPs.

800 End-Stage Kidney Disease and Kidney Transplantation in HIV-Positive Patients

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Background: HIV positive individuals are at increased risk of end-stage kidney disease (ESKD). We describe the clinical epidemiology and outcomes of HIV/ESKD in the UK CHIC Study including eligibility for and use of kidney transplantation (KT).

Methodology: Observational cohort study of patients in UK CHIC who received permanent renal replacement therapy between 01/2000 and 12/2011, with follow up to 12/2012. Cases were identified by review of all patients with stage 5 chronic kidney disease and by searching local renal databases. ESKD incidence and prevalence rates were calculated, Poisson regression was used to identify factors associated with ESKD, Kaplan-Meier methods to estimate survival rates, and the log rank test to compare survival curves.

Results: Of 27817 patients, 112 (0.4%; median age 38 years, male 69%, black ethnicity 64%, HIV-associated nephropathy 46%, median eGFR at baseline 22 mL/min/1.73m^2) had a diagnosis of ESKD. Throughout the 12 year study period, the ESKD incidence remained stable at 1.12 (95%CI 0.80, 1.44) and 0.23 (0.15, 0.31) per 1000 person-years of follow up for patients of black and non-black ethnicity respectively. The ESKD prevalence increased from 4.4‰ in 2000/2001 to 10.7‰ in 2010/2011 among black individuals (p=0.01) and remained stable around 1.8‰ for non-black ethnicities (p=0.78). Factors associated with ESKD in multivariable analysis were: black ethnicity (IRR 2.72 [95%CI 1.38, 5.37]), age (1.42 [1.12, 1.81] per 10 years), CD4 cell count (0.93 [0.88, 0.99] per 50 cells increase), HIV load (0.44 [0.23, 0.84] per log10 copies/mL), hepatitis B (2.73 [1.27, 5.86]) and hepatitis C (2.50 [1.09, 5.77]) co-infection. From 2005 onwards, kidney transplantation (KT) was increasingly used to treat ESKD so that by 12/2012, of the 71 patients still alive and under follow up, 31 (44%) were post-KT, 27 (38%) were being worked up or awaiting KT (pre-KT), and 13 (18%) were permanently unsuitable for KT. During this period, the one and five year survival estimates were similar for patients pre-KT and post-KT (100% and 94% at one year, and 89% and 85% at five years respectively, p=0.53), while survival for those unsuitable for KT was substantially worse (83% and 46% at one and five years, p<0.0001).

Conclusions: In the era of combination antiretroviral therapy, the incidence of ESKD has remained stable while the prevalence in black patients continues to increase. Low mortality was observed among patients with ESKD who were eligible for transplantation irrespective of whether they were maintained on dialysis or successfully transplanted. As the majority of patients have advanced kidney disease at the time of HIV diagnosis, ESKD prevention strategies should include efforts to diagnose HIV infection earlier, especially in those of black ethnicity.

Session P-Q8 Poster Session
Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Obesity: ART and Animal Models

801 Maraviroc, a CCR5 Antagonist, Alters Gut Microbiota Composition in a Mouse Model of Obesity

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Background: Changes in intestinal microbiota, through their effects on energy homeostasis and inflammation, could contribute to the development of several pathologies. Preservation of gut microbiote composition arises as a promising tool to prevent the development of different disorders such as obesity. Maraviroc (MVC), a CCR5 antagonist approved for the treatment of HIV-infected patients, have showed neutral or even beneficial effects on liver and adipocyte metabolism, suggesting beneficial actions in overweight/obese HIV-infected patients. However, MVC impacts on gut microbiota have not been analyzed yet. The aim of this study was to investigate the effects of MVC on gut microbiota composition in a mouse model of obesity.

Methodology: A total of 32 male C57BL/6 mice were randomly assigned to one of the following groups: a) Control group (chow diet), b) MVC group (chow diet plus 300 mg/L MVC in the drinking water) c) High-fat diet group (HFD) or d) HFD+MVC group. Body weight and food intake was recorded every 2-3 days. All mice were euthanized after 16 weeks of treatment and cecal contents were removed to study gut microbiota composition. We analyzed by real time PCR four orders from the most dominant phyla in gut.

Results: As expected, HFD induced a significant increase in body weight gain ($p<0.001$). MVC showed a tendency to decrease this body weight gain despite the HFD ($p=0.06$). Mice fed with a HFD showed a significant increase in the expression of Enterobacteriales in comparison with the controls ($p<0.001$). MVC treatment induced a significant decrease in the mRNA levels of this order in both control and HFD mice ($p<0.001$). HFD induced a significant decrease in Bacteroidales and Clostridiales mRNA levels ($p<0.05$ and $p<0.001$ respectively). MVC decreased the expression of Bacteroidales in the group of animals fed with a control diet ($p<0.05$) while a tendency to increase the expression of this order was observed in HFD mice ($p=0.05$). No direct effects were observed on Clostridiales after MVC supplementation, although a slightly decrease was observed in HFD mice. Finally, HFD significantly increased the mRNA levels of Lactobacillales ($p<0.05$) while no significant effects were observed after MVC supplementation, although a tendency to decrease the expression levels of this order was observed in HFD mice.

Conclusions: This is the first study that demonstrates the ability of MVC to modify gut microbiota composition. Whether the changes in gut microbiota induced by MVC are associated with the lower body weight gain observed, is still unknown. Our results suggest that some MVC actions seem to be dependent on diet composition and the metabolic status of animals. If these facts should be taken into account when we design antiretroviral regimens must be further investigated.

802 Low Pre-ART CD4+ T Cells, Female Sex, and Atazanavir Use Increase Obesity Risk After Starting ART

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Background: Obesity prevalence in the United States has increased in recent years. Obesity increases the risk for metabolic diseases and conflicting data exist about the relationship between higher body mass index (BMI) and CD4+ T-cell responses to antiretroviral therapy (ART).

Methodology: We evaluated the incidence and risk factors for development of obesity in >3000 ART-treated HIV-infected adults initiating combination ART in randomized AIDS Clinical Trials Group (ACTG) studies who were followed long-term with standardized evaluations as part of the ACTG Longitudinal Linked Randomized Trials (ALLRT) cohort. Cox regression models were used to examine baseline factors and randomized ART associated with incident obesity (BMI ≥30 kg/m^2) after starting ART.

Results: 2900 participants with pre-ART BMI <30 kg/m^2 were followed a median of 4.3 years (Q1, Q3: 2.1, 7.4) after starting ART. Subjects were excluded for missing baseline BMI values (N=11) and pre-ART BMI ≥30 kg/m^2 (N=475). Subjects were 85% male, 45% non-Hispanic white, and had median pre-ART age of 38 years, pre-ART CD4+ T-cells of 211 cells/μL and HIV RNA of 4.8 $\log_{10}$ copies/mL. Median pre-ART BMI was 23.8 kg/m^2 (Q1, Q3=21.6, 26.1) in males and 24.1 kg/m^2 (21.3, 26.3) in females. A total of 645 (22%) subjects developed obesity. In univariate and multivariable models, female sex (Hazard Ratio [HR]=1.88, 95% Confidence Interval [CI]=1.56-2.27), pre-ART BMI 25-≤30 kg/m^2 (HR=7.66, 95% CI=6.35-9.23 relative to BMI 18.5-<25 kg/m^2) and pre-ART CD4+ T-cells ≤50 (hazard ratio HR=3.21, 95% CI=2.27-4.54 relative to CD4 >500) and 51-200 (HR=2.12, 95% CI=1.52-2.98 relative to CD4 >500) were significantly associated with an increased risk of obesity (all $p<0.0001$). In multivariate analyses that included baseline age, sex, race, BMI, and CD4+ T-cells, use of atazanavir (N=521) was associated with an increased risk of incident obesity (HR=1.29, 95% CI=1.01-1.64) versus non-protease inhibitor (PI)-containing regimens (N=1527) ($p<0.04$). Neither stavudine or zidovudine use was associated with obesity risk in multivariate analysis, compared to regimens without nucleoside reverse transcriptase inhibitors (HR=0.71, 95% CI=0.43-1.18; and HR=0.76, 95% CI=0.48-1.22; respectively).

Conclusions: Earlier initiation of ART may help reduce the incidence of obesity in ART-treated individuals. Females were at significant risk for obesity in this cohort, suggesting that perhaps they should be targeted for interventions to minimize unhealthy weight gain associated with initial ART use. While atazanavir has previously been reported to minimize dyslipidemia compared to other PIs, an association with greater obesity risk may contribute to poor health outcomes.

803 Obesity or Hypertension at ART Initiation and Outcomes Amongst HIV Patients in South Africa

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Background: Aging, antiretroviral therapy (ART) and HIV infection itself have all been associated with increasing rates of chronic comorbidities in HIV patients but there are limited data on chronic disease risk factors and HIV treatment outcomes in resource-limited settings. We evaluated the association between high body mass index (BMI) or hypertension at ART initiation and mortality, loss to follow-up (LTF), and immunological and virologic response among HIV positive patients on treatment in South Africa.

Methodology: Prospective cohort study over 4 years among ART naïve adults initiating ART in Johannesburg between April 2004 and July 2009. ox regression was used to model the association with mortality and LTF of BMI (<18, 18 24.9, 25-29.9 and ≥30kg/m^2) and blood pressure (BP) grouped as normal (systolic <140 and diastolic <90 mmHg), mild (systolic 140-159.9 and/or diastolic 90-99.9 mmHg) and moderate/severe (systolic ≥160 and/or diastolic ≥100 mmHg). Linear and log-binomial regression were used to evaluate associations with CD4 increase and viral load ≥400 copies/mL, respectively. For mortality and LTF, person-time started at ART initiation and ended at the earliest of death, LTF, transfer or dataset close (July 2013).

Table 1. Crude and adjusted relative risks of the association between BMI or BP at ART initiation and death, loss to follow-up and mean CD4 change from ART initiation at 12 and 48-months post ART initiation in Johannesburg, South Africa (n=9693)

		12 months		48 months	
Variable		**No. Events (%)**	**Adjusted HR* (95% CI)**	**No. Events (%)**	**Adjusted HR* (95% CI)**
		Death			
BMI (kg/m^2)	<18	161 (8.0)	1.6 (1.3-2.0)	297 (14.8)	1.4 (1.2-1.7)
	18-24.9	233 (4.2)	Reference	519 (9.3)	Reference
	25-29.9	55 (3.7)	0.9 (0.7-1.3)	119 (7.9)	0.9 (0.7-1.1)
	≥30	39 (6.4)	1.8 (1.3-2.6)	66 (10.9)	1.3 (1.0-1.8)
BP at ART initiation	normal	450 (5.0)	Reference	910 (10.2)	Reference
	mild	28 (5.0)	1.0 (0.7-1.5)	64 (11.4)	1.1 (0.9-1.5)
	moderate/severe	10 (5.5)	1.1 (0.6-2.1)	27 (14.8)	1.4 (1.0-2.1)
		Loss to follow-up			
BMI (kg/m^2)	<18	281 (14.0)	1.4 (1.2-1.6)	538 (26.8)	1.3 (1.2-1.5)
	18-24.9	548 (9.8)	Reference	1185 (21.3)	Reference
	25-29.9	126 (8.4)	0.9 (0.8-1.2)	262 (17.4)	0.9 (0.7-1.0)
	≥30	33 (5.4)	0.6 (0.4-0.9)	84 (13.8)	0.7 (0.6-0.9)
BP at ART initiation	normal	922 (10.3)	Reference	1925 (21.5)	Reference
	mild	52 (9.3)	1.0 (0.7-1.3)	112 (19.9)	1.0 (0.8-1.2)
	moderate/severe	14 (7.7)	0.8 (0.4-1.4)	32 (17.5)	0.9 (0.6-0.9)
		CD4 Response			
BMI (kg/m^2)	<18	6.9 (-12.7, 10.9)		-17.2 (-12.9, 48.3)	
	18-24.9	Reference		Reference	
	25-29.9	-1.0 (-12.7, 10.9)		17.7 (-12.9, 48.3)	
	≥30	8.6 (-7.3, 24.5)		40.7 (-12.4, 93.8)	
BP at ART initiation	normal	Reference		Reference	
	mild	-6.0 (-19.7, 7.6)		29.8 (-15.3, 74.8)	
	moderate/severe	-8.2 (-27.4, 11.0)		3.9 (-71.2, 79.1)	

*All models were adjusted for age and gender and clinical characteristics at ART initiation (CD4 count, hemoglobin, tuberculosis and WHO stage)

**Absolute mean change in CD4 count from ART initiation

Results: 63% of the 9693 patients included were female and the majority (92%) initiated stavudine-lamivudine-efavirenz. At ART initiation median (IQR) CD4 count was 86 cells/mm^3 (33-154), BMI 21.4 kg/m^2 (19.0-24.5), systolic BP 116 mm/Hg (105-128), and diastolic BP 76 mm/Hg (68-85). By 48 months, 1001 (10%) patients died and 2069 (21%) were LTF. We found patients with a BMI $\geq$30 kg/m^2 had an increase in mortality over 48 months on ART compared to patients with a BMI of 18-24.9 kg/m^2, but lower LTF and improved immune response during follow-up (Table). We found no association between obesity and having a detectable viral load. Patients with moderate/severe hypertension (vs. normal) had a slight increase in mortality (30-40%) over follow-up but no increase in LTF, CD4 response, or having a detectable viral load.

Conclusions: Chronic disease risk factors at ART initiation may be associated with small increases in mortality but appear to be protective against LTF and poor immunological response. Successful management and treatment of comorbidities, specifically amongst obese patients that present with moderate to severe hypertension, may help decrease mortality in HIV infected patients.

Session P-Q9 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Genetic Factors and ART Outcomes

804 Specific Binding Characteristics of HLA Alleles Associate With Nevirapine Hypersensitivity

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Background: Multiple class I and II HLA associations have been described in association with nevirapine (NVP) hypersensitivity reaction (HSR) phenotypes. We tested the hypothesis that peptide binding (PB) properties may be shared between these alleles.

Methodology: HLA-A,-B-,-C, -DR typing was performed on stored DNA from a retrospective case controlled analysis of NVP HSR (ClinicalTrials.gov NCT00310843) using the 454 FLX platform. Univariate and multivariate analyses stratified for race were performed according to HLA class I/II alleles, HLA supertypes and HLA alleles according to PB (Sidney J, Lund O), Kir ligand groupings and HLA B/C haplotypes for cutaneous and hepatitis phenotypes of NVP HSR. *In silico* modelling to simulate HLA binding to NVP was performed with the highest ranked candidates.

Results: HLA -A,-B,-C and -DR typing resolved to four digits (794 samples (controls =524, cutaneous NVP HSR cases =170, hepatitis NVP HSR cases = 100)). Multivariate analysis of cutaneous NVP HSR in Southeast Asians (SEA) associated DR4 supertype(OR=2.9, p=0.015) and alleles with HLA-35/18 PB properties(OR=6.4, p=0.002). HLA-DRB1*01:02 was associated with hepatitis NVP HSR in Caucasians (OR=2.7,p=0.01) whereas carriage of alleles of the PB B46 were protective (OR=0.3, p=0.04). HLA-C*04:01 was associated with cutaneous NVP HSR, including SJS/TEN across all races (p<0.0001, Mantel-Haenszel test; Caucasians: OR=2.8 [1.3-5.9], p=0.009; African Americans: OR=4.0 [1.4-13.0], p=0.02; SEA: OR=9.0 [3.2-24.9], p<0.0001). However, haplotype analysis of HLA-B/C showed pairing of HLA-C*04:01 with HLA-B alleles with B35 and B18 like PB (HLA-B*35:01,B*35:05,B*35:08,B*53:01,B*18:01,B*18:02, B*44:02,B*4403), and this effect was strongest in SEA where carriage of HLA-C*04:01 when paired with the HLA-B alleles(OR=11.8,p=0.0003) was more strongly associated with cutaneous NVP HSR than HLA-C*04:01 carried alone(OR=4.8,p=0.047). This suggests that risk of cutaneous NVP HSR attributed to carriage of HLA-C*04:01 may be enhanced by HLA-B alleles which are in strong linkage disequilibrium. An *in silico* and peptide binding model both suggest that NVP non-covalently binds in the F pocket of HLA-B*35:05 and near the B pocket of HLA-C*04:01. In multivariate analyses, Kir ligand groupings Bw4/Bw6 and C1/C2 did not significantly contribute to the modelling of associations with cutaneous hypersensitivity or hepatitis.

Conclusions: Cutaneous and hepatitis phenotypes of NVP HSR associate with different HLA-B and DR-alleles respectively that share PB characteristics. The pairing of these HLA-B alleles with HLA-C*04:01 appears important for the development of cutaneous NVP HSR, providing a testable model for the immunopathogenesis of NVP HSR.

805 Large-Scale Gene-Centric Exploration of Risk for NRTI/NNRTI-Associated Toxicities in Botswana

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Background: Access to combination antiretroviral therapy (ART) in sub-Saharan Africa (SSA) has expanded due to a large number of national initiatives. Previous studies have shown higher rates of NRTI and NNRTI-related toxicity when comparing patients on ART in SSA with those in resource-replete settings. The Tshepo study is the first to extensively evaluate the association of host genetic factors on ART-related toxicity heterogeneity in SSA.

Methodology: The Tshepo study is a 3-year randomized clinical study following 650 ART-naïve adults (69.4% female) from Botswana who initiated first-line NNRTI-based ART. We conducted a large-scale gene-centric association study on Tshepo participants with sufficient DNA using the Illumina Human CardioMetabolo Beadchips enriched in markers for metabolic and cardiovascular genes (198K), including mitochondrial, ADME, renal, and immune response genes. After quality control, 133,822 SNPs were tested for association with 5 NRTI/NNRTI-associated toxicities in 568 individuals. Of these, 62 had peripheral neuropathy (PN), 20 had NVP-associated hypersensitivity cutaneous reaction (NS), 19 had ZDV-related anemia (ZA), 19 had pancreatitis (PA), and 17 had moderate-severe hyperlactatemia/lactic acidosis (LA). Logistic regressions in an additive model were performed and adjusted for gender, age, CD4, plasma HIV-RNA level, and BMI at baseline, as well as for the first two eigenvectors from the population stratification analysis.

Results: Although no SNP reached the Bonferroni study-wide significance level (P<3.7x10-7), several SNPs met the suggestive significance threshold (P<10-5): rs2503875 (chr10, OR=7, P=5x10-7) and rs7767230 (chr6, OR=9, P=2x10-6) for PN; rs702864 (chr21, OR=6, P=7x10-6), rs2902211 and rs11589503 (chr1, OR=5-6, P=9x10-6) for NS; three chr6 markers (OR=9-10, P=4-7x10-6), and two chr18 markers (OR=9-11, P=5-9x10-6) for PA.

Conclusions: This first large genetic study to evaluate ART-associated toxicity in Africa revealed putative candidate loci for several potentially life-threatening and/or debilitating NRTI/NNRTI-related toxicities with robust effect sizes. These preliminary findings warrant validation and further investigation.

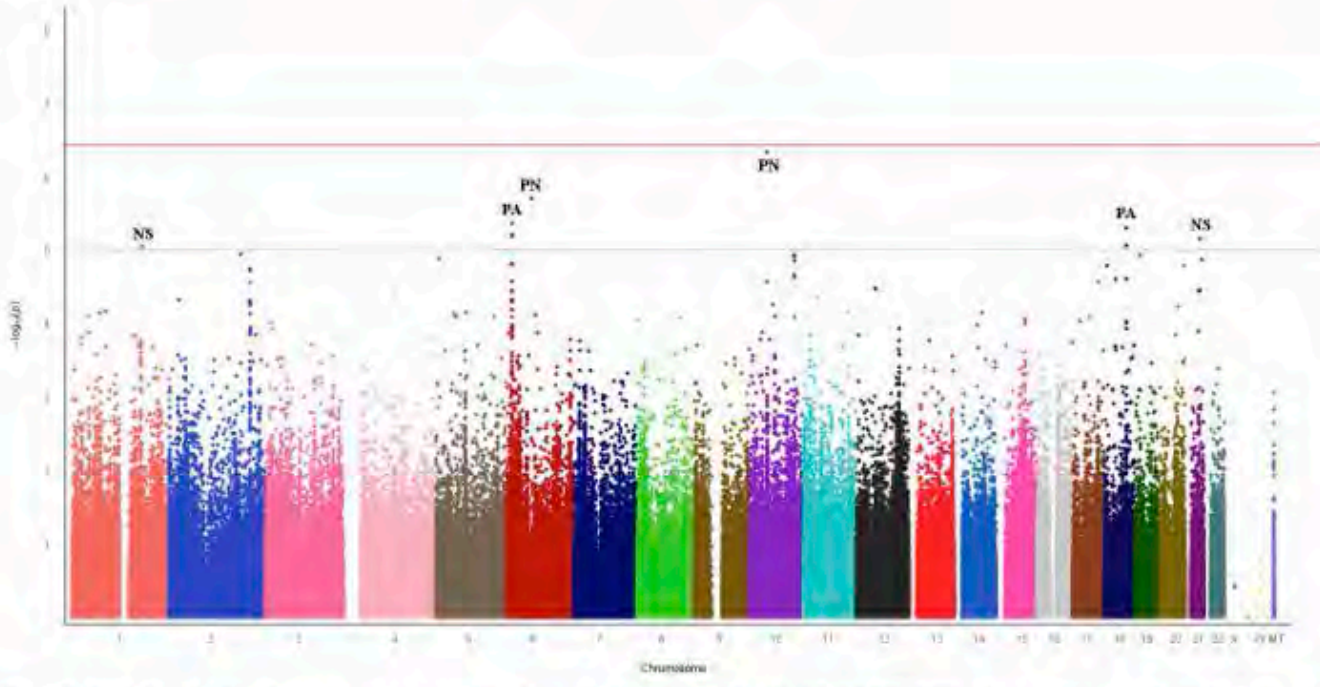

Figure 1: Manhattan plot. Distribution along the chromosomes of -$\log_{10}$(P-values) obtained in each of the 5 NRTI/NNRTI-related toxicities association studies. The red line marks the Bonferroni study-wide significance threshold ($P=3.7x10^{-7}$), and the blue line marks the suggestive significance threshold ($P=10^{-5}$). PA=Pancreatitis, PN=Peripheral neuropathy, and NS=NVP-associated hypersensitivity cutaneous reaction.

Session P-Q10 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

ART and Suicidality

760 Suicide Rates Decrease Among HAART Initiators From 1996 To 2012 in British Columbia, Canada

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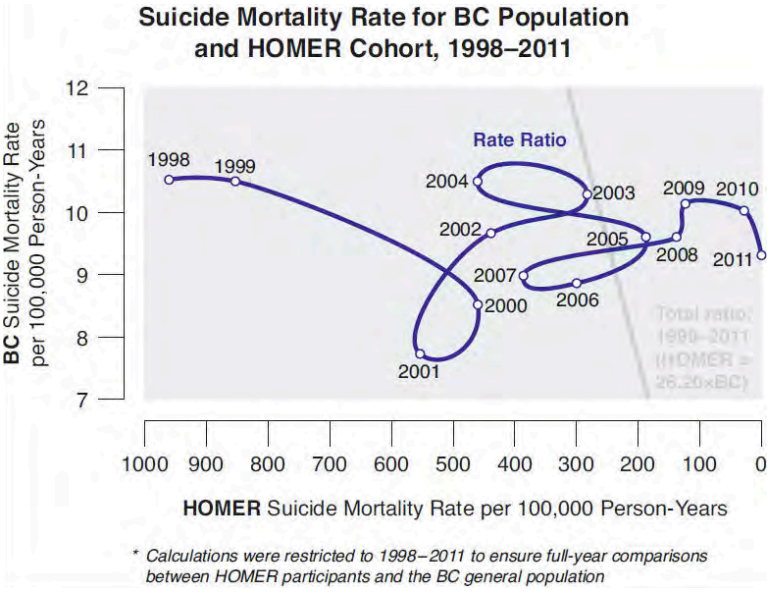
Background: Suicide rates among people living with HIV/AIDS (PLHIV) have been reported at markedly higher levels than in the general population. We sought to evaluate this trend and identify factors associated with suicide among PLHIV who have initiated Highly Active Antiretroviral Therapy (HAART) in British Columbia (BC), Canada.

Methodology: Our analysis was based on all treatment naive individuals who initiated HAART in BC from August 1996 to June 2012. Data on deaths were ascertained from monthly linkages with the BC Vital Statistics Registry. Logistic regression and Cox Proportional hazard models were used to identify factors independently associated with suicide mortality. Suicide was defined by any of the following ICD-10 "cause of death" codes: E850-E854, E858, E862, E868; X40-X42, X46, X47; Y10-Y12, Y16, Y17; E950-E952, X60-X69: E953, X70; E954, X71; E955, X72-X75; E958.1, E958.2; X76, X77; E956; X78, X79: E957, X80; E958.0, X81; E958.5, X82; E958.3, E958.4,



E958.6-E958.9; X83, X84. The variables assessed included: gender, Aboriginal identity, median income, urban versus rural neighborhood, age at death and year of death, ever having been diagnosed with an AIDS-defining illness, ever having had a positive hepatitis C (HCV) diagnosis, HAART adherence in the most recent year, most recent HAART cocktail, number of years on HAART, most recent and nadir CD4, most recent viral load, and history of injection drug use.

Results: Among 5,229 PLHIV who initiated HAART over the study period, 993 (19%) died, of which 82 (8.2%) were from suicide. In 1998, suicide mortality peaked at 961 deaths per 100,000 person-years, a rate 91-fold greater than in the BC population, and then declined to 28 deaths per 100,000 person years in 2010, a rate 3-fold greater than the BC population. No deaths from suicide were reported in 2011, which was the last full year of data for the cohort. The Cox model, which included those who committed suicide and those who remained alive at the end of the study period (n =4318), showed that a history of injection drug use (Adjusted Hazard Ratio [AHR]= 3.95; 95% CI: 1.99-7.86) and never having been diagnosed with an AIDS defining illness (AHR = 4.45; 95% CI: 1.62 - 12.25) were independently associated with time to suicide.

Conclusions: Rates of deaths from suicide declined significantly over the study period. While factors directly related to HIV infection, or type of HAART regimen, were not associated with suicide, other factors related to life style issues, like injection drug use, were.

761 Disproportionality Analysis of Antiretrovirals With Suicidality Using FDA AERS Data

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Background: An analysis of 4 ACTG studies, including 5332 subjects, identified an increase in the hazard of suicidality in efavirenz containing regimens compared to regimens containing atazanavir, atazanavir/ritonavir, lopinavir/ritonavir and zidovudine/lamivudine/abacavir. Rare but serious psychiatric adverse events (AEs), including suicide, have been included in postmarketing reports with efavirenz. We conducted a Multi-Item Gamma Poisson Shrinker (MGPS) disproportionality analysis based on data in the FDA Adverse Event Reporting System (AERS) database to assess the potential association of selected antiretrovirals (ARVs), including efavirenz, with suicidality. AERS primarily includes spontaneous serious AE reports from consumers and healthcare professionals of varying quality with fewer entries from clinical trials.

Methodology: The AERS database (Q3 2012) search included MedDRA preferred terms “completed suicide”, “suicidal ideation”, and “suicide attempt”. In addition to the ARVs, fluoxetine and sertraline, antidepressants with a Black-Box Warning for suicidality, were included as positive controls. The MGPS method can provide a robust estimate of disproportionality measure (reporting above expected frequency) referred to as the EBGM (Empirical Bayesian Geometric Mean), and the corresponding 90% confidence interval (EB05, EB95). The threshold for a potential drug-event signal is generally considered to be EB05 ≥2.

Results: The database included 29,836 AE reports among patients receiving efavirenz, atazanavir, darunavir, etravirine, nevirapine, and raltegravir, including 437 reports of completed suicide, suicidal ideation, and suicide attempt. Efavirenz and all comparator ARVs did not exceed the threshold for identification of a disproportional signal for suicide, suicidal ideation, and suicide attempt (EB05 Scores ≥2; Table). Fluoxetine and sertraline had EB05 Scores ≥2 for suicide, suicidal ideation, and suicide attempt.

Conclusions: This analysis does not show a disproportional signal for suicide, suicidal ideation, and suicide attempt for efavirenz, atazanavir, darunavir, etravirine, nevirapine, and raltegravir. There are limitations to the AERS data, including a lack of certainty that reported adverse events are related to the drug, lack of sufficient detail in the reports, and underreporting of adverse events. Appropriate baseline psychiatric screening and counseling is important when starting patients on any ARV.

Empirical Bayesian Geometric Mean (EBGM) and corresponding 90% confidence interval (EB05, EB95)					
Antiretroviral	**MedDRA term**	**N**	**EBGM**	**EB05**	**EB95**
Atazanavir	Completed suicide Suicidal ideation Suicide attempt	10 31 13	0.21 0.59 0.34	0.13 0.44 0.22	0.33 0.78 0.52
Darunavir	Completed suicide Suicidal ideation Suicide attempt	6 19 9	0.28 0.71 0.51	0.15 0.49 0.30	0.49 1.01 0.82
Efavirenz	Completed suicide Suicidal ideation Suicide attempt	46 70 100	0.52 0.86 1.31	0.41 0.71 1.11	0.66 1.04 1.54
Etravirine	Completed suicide Suicidal ideation Suicide attempt	0 8 4	- 0.78 0.64	- 0.45 0.31	- 1.29 1.23
Nevirapine	Completed suicide Suicidal ideation Suicide attempt	11 33 41	0.18 0.50 0.65	0.11 0.38 0.50	0.28 0.66 0.83
Raltegravir	Completed suicide Suicidal ideation Suicide attempt	1 27 8	0.08 0.98 0.47	0.02 0.71 0.27	0.21 1.31 0.77

Positive Controls	MedDRA term	N	EBGM	EB05	EB95
Fluoxetine	Completed suicide Suicidal ideation Suicide attempt	1206 1268 3428	3.40 3.89 5.68	3.24 3.71 5.53	3.56 4.07 5.85
Sertraline	Completed suicide Suicidal ideation Suicide attempt	917 1585 1203	2.14 3.48 2.70	2.03 3.34 2.57	2.26 3.62 2.83

Session P-R1 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Epidemiology and Transmission of TB

806 High Clonality of *M. tuberculosis* Strains Among MDR-TB Patients in Gauteng, South Africa

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Background: The problem of multidrug and extensively drug resistant tuberculosis (M/XDR-TB) was first highlighted in the 1990's with an outbreak of MDR-TB in New York City, followed a decade later by an XDR-TB outbreak (KZN strain) in Tugela Ferry, South Africa. Both were due to highly clonal, highly resistant strains of M. tuberculosis (Mtb), spread mainly in HIV infected populations. However, the relative contributions to the M/XDR-TB epidemic in South Africa of clonal spread and de novo acquired resistance are unclear. To better understand the dynamics of MDR-TB transmission and resistance amplification in Mtb, we carried out a cluster analysis of Mtb strains from patients initiating treatment for MDR-TB at a referral hospital in Gauteng, South Africa.

Methodology: Mtb isolates from 74 patients were genotyped by IS6110-RFLP and direct DNA sequencing of 9 resistance determining genes: rpoB, katG, mabA-inhA, gyrA, gyrB, pncA, tlyA, rpsL, and rrs. Clusters were defined by 2 or more isolates with an identical IS6110-RFLP. Diagnosis of MDR was confirmed by drug susceptibility testing as part of routine clinical management.

Results: Among the 74 patients, 36% were HIV infected and 29% had been treated for at least one prior TB episode. The Mtb isolates represent 17 strain families and 47 IS6110 genotypes, including 11 (15%) pre-XDR and 1 (1.4%) XDR, with 54% overall clustering (40/74). Pre-XDR and XDR are more clustered (10/12, 83%) than MDR sensu stricto (30/62, 48%). Isolates from HIV-positive patients trend towards more clustering (17/26, 65%, p=0.223) than those from HIV-negative patients (23/47, 49%). The majority of clustering is accounted for by 4 families (26/40, 65%) which comprise 47% of the total Mtb population analyzed. The largest strain family (14/74 isolates, 19%) has the KZN genotype and is highly clustered (10/14, 71%). One pre-XDR isolate is nearly identical to the KZN strain; the other 13 show diverse mutation profiles, as seen in other South African variants, likely due to independent evolutionary trajectories from a less resistant precursor. Our data shows evidence of multiple importations of KZN strains to Gauteng, with further amplification of drug resistance and ongoing transmission in the region. The other 3 highly clustered strains show similar clonal characteristics with evidence of resistance amplification.

Conclusions: MDR-TB is spreading in Gauteng. A few strains of relatively low diversity are predominant in the MDR-TB population and appear to be undergoing resistance amplification. Transmission seems to be responsible for much of the MDR-TB among HIV-positive patients. The KZN strain is circulating in this population and shows evidence of ongoing resistance amplification.

807 Identifying Location of Recent TB Transmission in Rural Uganda: A Multidisciplinary Approach

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Background: Given the substantial burden of undiagnosed TB in sub-Saharan Africa, novel active TB case finding strategies are needed. Location-based TB case finding offers a potentially high yield, community-based approach. However, the precise locations of recent TB transmission events occurring in rural African communities are largely unknown.

Methodology: We recruited all adult residents diagnosed with active TB from July 2012 to June 2013 in Tororo, a rural municipality in Uganda. Active TB cases provided names of household and frequent non-household contacts, sites of residence, health care attendance, work and social activities, and two sputum samples. Household members also provided names of frequent non-household contacts. We performed sputum culture using Lowenstein Jensen and BACTEC MGIT, and used spoligotyping of culture positive specimens to identify recently transmitted TB, defined by genotypic clustering. We analyzed social network structure using Gephi, to identify social ties between TB cases. We mapped and geo-coded GPS locations using ArcGIS by site type (home, work, clinic, social), and identified locations of spatial overlap among genotype-clustered cases to determine likely sites of transmission.

Results: Over one year, 70 adults initiated TB treatment in Tororo; 55 (79%) were enrolled. Of 55 TB cases, 31 (56%) were HIV-infected, 42 (76%) were AFB smear-positive, and 36 (65%) were MTB culture positive. Of 17/36 specimens genotyped to date, 11/17 (65%) belonged to three distinct genotypic clusters. None of the clustered cases shared a home. In one genotypic cluster (cluster A) of three HIV+ women, GPS mapping revealed overlapping social sites - two physically adjacent bars, despite no overlap in social networks, work or clinic sites. In a second cluster of six cases (cluster B), GPS mapping revealed that five genotype-matched cases attended the same medical clinic; the one case not attending this clinic resided next door to another case. No shared household, work or clinic sites, or social network ties were observed in cluster B. Social network analysis revealed ties between at least 2 TB cases in 20/55 (36%) cases.

Conclusions: Using a combination of molecular epidemiology, and geospatial and social network data, we leveraged TB cases diagnosed in clinics to determine the most likely sites of recent TB transmission across a rural Ugandan community. In this analysis, the majority of active TB cases genotyped suggested recent TB transmission that was linked to specific community locations. Connections identified between genotype-clustered TB cases using this multi-domain approach would not have been found using traditional household contact investigation alone.

808 Timing of TB Episodes After the End of Isoniazid Preventive Therapy: Reinfection or Reactivation?

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Background: Isoniazid preventive therapy (IPT) reduces tuberculosis (TB) incidence in high risk populations (HIV-positive and negative), but durability of protection is limited in high burden settings. The underlying mechanism (reactivation of persistent latent TB or re-infection) is not well understood. There are few data on long-term TB incidence after IPT discontinuation. This study aimed to investigate the timing of post-IPT TB incidence and its associated risk factors in a high-TB-risk population with high HIV prevalence (estimated at 29%) in sub-Saharan Africa.

Methodology: Data from a cluster randomized trial of community-wide IPT among gold mine workers in South Africa (the 'Thibela TB' study) were analysed. Participants in the intervention arm who were prescribed isoniazid at least once and who were alive, in the workforce and TB-free 9 months later (corresponding to the intended duration of IPT) were included. TB incidence rates from the end of the intended period of IPT to the end of the follow-up period for the main study were calculated, overall and stratified by follow-up time (per 6 months). Cox regression analysis was used to investigate risk factors for TB incidence and effect modification by follow-up time. A sensitivity analysis used the actual end of IPT (based on prescription dates) as the start of the risk period.

Results: 17,446 participants (96% male, mean age 41 years [yrs; standard deviation 9]) were eligible for the analysis. 541 TB cases were diagnosed during 24,037 person-years at risk (pyar), a median follow-up of 1.4 years. The post-IPT TB incidence rate was 2.3/100 pyar (95% confidence interval [CI], 2.1-2.5) and did not vary during follow-up time (0-0.5 yrs: 2.0/100 pyar [95% CI 1.7-2.3], 0.5-1 yrs: 2.4 [95% CI 2.1-2.8], 1-1.5 yrs: 2.5 [95% CI 2.1-3.0] and ≥1.5 yrs: 2.1 [95% CI 1.6-1.5], P-value 0.12). After adjusting for sex, country of origin and ART use, risk factors identified were older age (30-39 versus ≤29 yrs: adjusted hazard ratio [aHR] 2.2 [95% CI 1.9-4.2], 40-49 yrs: aHR 2.8 [95% CI 1.9-4.2], ≥50 yrs: aHR 2.8 [95% CI 1.8-4.2]), underground mining work (aHR 1.8 [95% CI 1.2-2.5]), living in a mining hostel (aHR of non-hostel versus hostel 0.7 [95% CI 0.6-0.9]) and prior TB disease (aHR 1.9 [95% CI 1.5-2.4]). These factors did not vary importantly over time. The results of the sensitivity analysis did not differ.

Conclusions: TB incidence rates were constant over time since IPT cessation. The risk factors identified are well known and are associated with both reactivation and re-infection disease. No important effect modification of these factors by time was found. These findings do not allow conclusions regarding the mechanism underlying post-IPT TB incidence.

809 HIV and Tuberculosis in Kenya, 2012-2013: Results From a National Survey

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Background: Co-infection with tuberculosis and HIV remains a major cause of morbidity and mortality in sub-Saharan Africa. The 2nd Kenya AIDS Indicator Survey (KAIS 2012) assessed knowledge and experience concerning tuberculosis and HIV at a population level in Kenya, including coverage with treatment services and antiretroviral therapy (ART).

Methodology: KAIS 2012 was a national, population-based, cross-sectional household survey among persons aged 18 months to 64 years conducted from October 2012 to February 2013. Information was collected through household questionnaires and blood samples were taken for HIV testing, CD4+ cell counts and HIV viral load testing at a central laboratory. Respondents were offered home-based HIV testing and counseling and if HIV positive, point-of-care CD4+ T-cell count testing, results of which are not reported here. Kenya's North-Eastern region (HIV prevalence <1%) was excluded because of insecurity. This analysis was restricted to persons aged 15-64 years. Estimates and 95% confidence intervals (CI) were weighted to account for sampling probability and adjusted for survey non response.

Results: Overall, 13,720 persons participated in the survey, of whom 84.8% gave blood. The prevalence of HIV infection was 5.6%. Among persons who had heard of tuberculosis (96.7% overall), 2.0% reported having had the disease; 32.1% of those reporting prior tuberculosis were HIV-infected. Prior tuberculosis was reported by 11.6% of HIV-infected persons compared with 1.4% of HIV uninfected persons (odds ratio 9.4; CI 6.6-12.8). HIV and

tuberculosis co-infection was associated with female sex, geographic origin from Nyanza region, and age range 25-49 years. Significantly more HIV-infected persons with than without prior tuberculosis were in HIV care, accessing ART, or both. For treatment-eligible persons aware of their HIV status and in care, over 95% were receiving ART, irrespective of tuberculosis history. However, including HIV-infected persons unaware of their HIV status and thus not in care, overall ART coverage among those treatment-eligible was 73.9% and 73.3%, respectively, for those with and without prior tuberculosis. Persons with prior tuberculosis accounted for 28.8% of all those on ART.

Conclusions: Two percent of Kenyans reported prior tuberculosis, of whom almost a third were HIV-infected; over one tenth of HIV-infected persons reported prior tuberculosis which was likely a major entry point for HIV testing and HIV care. Persons aware of their HIV status and accessing HIV care had >95% uptake of ART if eligible, but >50% of HIV-infected persons in Kenya are still unaware of their status. Efforts must concentrate on increasing knowledge of HIV serostatus and integrating HIV and tuberculosis services for those living with HIV.

Session P-R2 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

TB Screening and Diagnosis

810 Screening for Tuberculosis in HIV-Infected Nigerian Children With a Urinary Antigen Assay

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Background: Tuberculosis (TB) remains the leading cause of death among HIV-infected children in sub-Saharan Africa. Accurate and prompt identification of TB infection remains challenging, particularly among young children who are often unable to produce sputum. In this study, we evaluated the sensitivity and specificity of the lipoarabinomannan (LAM) TB ELISA for the detection of mycobacteria-specific antigen in urine samples of HIV-infected Nigerian children.

Methodology: As part of routine care, all HIV-infected children enrolling in the APIN/Harvard PEPFAR program undergo routine screening for TB consisting of: clinical evaluation for symptoms or signs of TB infection, chest radiograph, and tuberculin skin testing (TST). In addition, for those children with a chronic productive cough, sputum samples are collected when possible. A composite of these standard TB diagnostic techniques was used as the "gold standard", and compared against results of the urine LAM assay.

Results: 184 HIV-infected pediatric patients were enrolled at two study sites; 40% were female with a median age of 5 years and median baseline CD4+ cell count of 434 cells/mm^3. Almost 36% of patients (66 children) were diagnosed with TB within 3 months after collecting the LAM sample. The sensitivity of the LAM assay to detect the composite diagnosis of TB infection is 10.6% (95% CI 4.7-21.2%), specificity is 97.4% (95% CI 91.9-99.3%), and the PPV is 70% (95% CI 35.3-91.9%). The median CD4 count was 103 cells/mm^3 (IQR, 25-331 cells/mm^3) among children with a positive LAM, compared to 393 cells/mm^3 (IQR, 177-717 cells/mm^3) among those diagnosed with TB but with a negative LAM result.

Conclusions: Although the sensitivity of the LAM assay was low in this population, the relatively high PPV suggests that a positive result may add valuable information to the care of a sick child. However, more sensitive rapid diagnostic methods for the detection of TB in young children are urgently needed.

811LB Massive Diagnostic Yield of HIV-Associated Tuberculosis Using Rapid Urine Assays in South Africa

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Background: Autopsy studies of HIV/AIDS deaths in medical in-patients in sub-Saharan Africa have all reported a high frequency of disseminated tuberculosis (TB), indicating frequent failure of diagnosis. This observational study aimed to identify improved means of rapid TB diagnosis.

Methodology: Unselected HIV-infected medical admissions to a South African district hospital were intensively investigated. Sputum, urine and blood specimens were systematically obtained within the first 24 hours. Multiple additional respiratory and non-respiratory samples were obtained throughout admission as clinically indicated. Sputum samples were tested using fluorescence microscopy, liquid culture and Xpert MTB/RIF (Xpert). Urine samples were tested using Xpert (urine-Xpert of both unconcentrated and concentrated samples) and Determine TB-LAM (urine-LAM). Other non-respiratory samples were cultured. TB diagnoses were defined by detection of Mycobacterium tuberculosis in any sample using culture or Xpert.

Results: HIV-status was ascertained in 1,013 of 1,018 (99.5%) admissions and 585 of 609 (96.1%) HIV-infected patients were enrolled. All those without an existing TB diagnosis (n=427) were included in this analysis. 3,471 TB investigations were done on 1,745 samples from a median of 3 anatomic sites per patient. TB was diagnosed in 139 patients (median CD4 count, 80 cells/μL) and symptoms were very poorly predictive. TB prevalence was 32.6% (95%CI, 28.1-37.2). Disease was extrapulmonary in 83% of cases and pulmonary in just 54% (P<0.001). Using samples obtained in the first 24-hours, the proportions of final diagnoses made by sputum microscopy, sputum-Xpert, urine-LAM and urine-Xpert (30-40 ml concentrated urine) were 19.4%, 26.6%, 38.1% and 59.0%, respectively. Rapid urine tests used together diagnosed 69.1% (96 of 139) of cases. This further increased to 80.6% (112 of 139) of cases when combined with sputum Xpert testing. However, of those with CD4 counts <100 cells/μL, 85.1% (63 of 74) could be diagnosed with urine rapid tests alone.

Conclusions: The prevalence of TB was so high and the presentation so non-specific that routine microbiological investigation for TB should be done in all HIV-infected medical in-patients in high-burden settings. Compared to Xpert testing of one sputum sample alone, the addition of urine-based testing increased the diagnostic yield of the initial TB screen 3.0-fold from 26.6% to 80.6% (P<0.001). Urine-based rapid diagnostics should be considered for routine use in this patient population.

812 Symptom-Based Screening for Tuberculosis Among Pregnant Women Living With HIV in Kenya

Surbhi Modi[1], Joseph S. Cavanaugh[2], Ray W. Shiraishi[1], Barbara Burmen[3], Heather Alexander[1], Kimberly McCarthy[2], Hellen Muttai[4], Kevin P. Cain[5]

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Background: The World Health Organization (WHO) recommends tuberculosis (TB) screening among people living with HIV (PLHIV) using an evidence-based clinical screening algorithm, but limited data exist on its performance among pregnant women. We assessed the performance of the WHO algorithm among women receiving prevention of mother-to-child HIV transmission (PMTCT) services in Nyanza Province, Kenya.

Methodology: We recruited PLHIV who were newly enrolling in HIV care and treatment at 15 facilities between May 2011 and June 2012, including pregnant women from PMTCT services. All PLHIV were screened with the WHO algorithm and provided two or more sputum samples for smear microscopy, liquid culture, and Xpert MTB/Rif (Xpert). TB was defined as any specimen positive for TB by Xpert or culture. We calculated the performance characteristics of clinical screening compared to laboratory diagnostic testing results, stratified by sex and pregnancy status.

Results: Overall, 131 pregnant women were enrolled, representing 28.0% of the 469 women enrolled in the study and 18.2% of all PLHIV included in the analysis. The median age of pregnant women was 25 years (interquartile range: 22-29 years) and 8 (6.1%) had TB. Preliminary analysis shows that sensitivity, specificity, and negative predictive value of the WHO algorithm in pregnant women were 28.6%, 74.8%, and 94.7%, respectively (Table 1).

Conclusions: The prevalence of TB was low among HIV-infected pregnant women compared to other PLHIV. The WHO algorithm missed more than 70% of pregnant women with laboratory-confirmed TB. Symptom-based screening may have limited utility for TB case finding in PMTCT settings.

World Health Organization (WHO) Screening and Tuberculosis (TB) among People Living with HIV, Kenya

Characteristic	Overall Study Population (N = 718)	Pregnant Women (n = 131)	Non-Pregnant Women (n = 338)	Men (n=249)
TB Diagnosis	81 (11.3%)	8 (6.1%)	39 (11.5%)	34 (13.7%)
WHO Algorithm Performance				
Sensitivity	73.7%	28.6%	79.0%	77.4%
Specificity	50.3%	74.8%	45.2%	42.6%
Negative Predictive Value	93.8%	94.7%	94.1%	92.3%
Positive Predictive Value	15.8%	6.3%	16.2%	17.5%
Negative Likelihood Ratio*	0.52	0.95	0.46	0.53
Positive Likelihood Ratio**	1.48	1.13	1.44	1.35

* Negative likelihood ratio is calculated as (1 – sensitivity) ÷ specificity. **Positive likelihood ratio is calculated as sensitivity ÷ (1 – specificity).

813 Highly Multiplexed Detection of Antibodies in Whole Blood During Tuberculosis Infection

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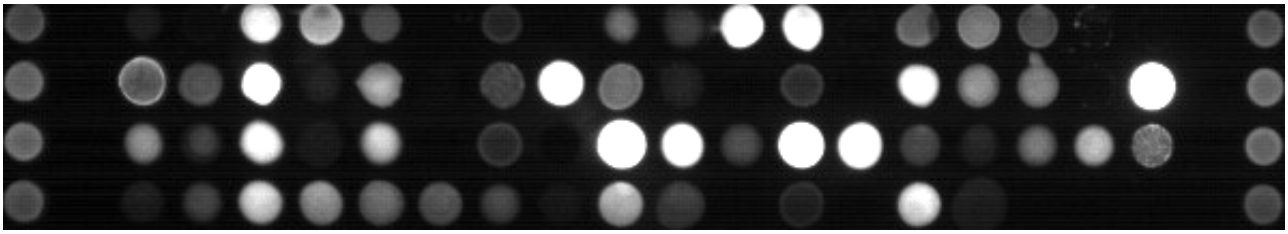
Background: A simple blood test for active TB disease remains a critical unmet need worldwide. Most serodiagnostic assays to date have been based on a single or small number of antigens and have not provided adequate diagnostic accuracy. A hypothesis is that a multiplexed panel of antigen-antibody interactions could provide a signature indicative of active disease. FIND has led a comprehensive TB proteome effort and identified a set of 57 potentially discriminatory antigens. To further down-select to a diagnostic antigen set, it was determined that testing fresh specimens in endemic countries was critical. The portable MBio multiplexed array platform was selected as uniquely suited for this task and a multi-phase clinical research program was initiated. This abstract presents results from the first phase, designed to establish the operational functionality of the MBio system.

Methodology: Disposable assay cartridges incorporating 57 TB proteins and 31 assay controls in a microarray were developed. Cartridges processed with 10 microliters of diluted whole blood or 5 microliters of diluted serum are analyzed on the MBio reader for fluorescence detection of individual antigen-antibody reactivities. A representative image is provided below. To establish performance of the MBio platform, 200 TB suspects were enrolled and tested on systems installed at trial sites in Peru and Vietnam. Endpoints included concordance between the MBio field platforms and a Luminex laboratory reference, indeterminate rate, reliability, and ease of use.

Results: All operational endpoints were met. To compare MBio and Luminex, directional concordance around the mean fluorescence intensity for each antigen was assessed for the collection of frozen serum samples. All antigens showed directional concordance of >75% for all samples, with the majority showing > 90% concordance. The indeterminate rate was 7.4% initially, and after an adjustment of the analysis algorithm, the indeterminate rate decreased to 0.77%. There were zero instrument or software failures over the 673 cartridges tested and user errors were observed in only 2 of 673 cartridges tested.

Conclusions: The MBio system was shown to be a reliable platform for rapidly detecting a large panel of antigen-antibody interactions from whole blood or serum in TB-endemic settings. As a result of this phase I success, the study was advanced to a larger clinical evaluation to investigate diagnostic utility of the array.



814 Performance of the World Health Organization Algorithm for Tuberculosis Screening in Kenya

Surbhi Modi[1], Joseph S. Cavanaugh[2], Ray W. Shiraishi[1], Barbara Burmen[3], Heather Alexander[1], Kimberly McCarthy[2], Hellen Muttai[4], Kevin Cain[5]

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Background: The World Health Organization (WHO) recommends tuberculosis (TB) intensified case finding (ICF) among people living with HIV (PLHIV) using an evidence-based clinical screening algorithm including current cough, fever, night sweats, and weight loss. However, limited data exist on the performance of this algorithm in routine program settings. We assessed the performance of the WHO algorithm alone and with chest radiography among PLHIV in Nyanza Province, Kenya.

Methodology: We recruited PLHIV aged 7 years and older newly enrolling in HIV care at 15 randomly-selected HIV clinics. Patients were screened with the WHO algorithm, underwent chest radiography, and provided two or more sputum samples for smear microscopy, liquid culture, and Xpert MTB/Rif (Xpert). TB was defined as any specimen positive for TB by Xpert or culture. We calculated the performance characteristics of clinical screening compared to laboratory diagnostic testing results.

Results: Overall, 779 PLHIV were enrolled in the study and 718 (92.3%) met criteria for inclusion in the analysis. Median age was 29 years (interquartile range: 24-39 years); 4% were younger than 15 years. Eighty-one patients (11.3%) had TB. Preliminary analysis shows that the sensitivity, specificity, and negative predictive value (NPV) of the WHO algorithm were 73.7%%, 50.3%, and 93.8%, respectively (Table 1). Testing asymptomatic persons with chest radiography increased sensitivity and NPV of the screening algorithm to 90.6% and 96.1%, respectively, but decreased specificity to 32.5%.

Conclusions: By limiting TB diagnostic testing to symptomatic patients, the WHO algorithm missed more than 25% of TB patients. Adding a chest radiograph improved case finding and more reliably identified PLHIV who did not have TB and who should receive isoniazid preventive therapy. Additional analyses including screening performance during follow-up visits are needed.

Table 1. Performance of Clinical Screening for Tuberculosis

Screening Tool	Sensitivity	Specificity	Negative Predictive Value	Positive Predictive Value	Negative Likelihood Ratio*	Positive Likelihood Ratio**
World Health Organization (WHO) Algorithm	73.7%	50.3%	93.8%	15.8%	0.52	1.48
Any cough	53.9%	71.5%	92.6%	19.0%	0.64	1.89
Fever	54.6%	69.8%	92.5%	18.4%	0.65	1.81
Night sweats	46.1%	77.1%	92.0%	20.0%	0.70	2.01
Weight loss	56.6%	69.4%	92.9%	18.5%	0.63	1.85
WHO Algorithm and Chest Radiograph	90.6%	32.5%	96.1%	15.8%	0.29	1.34

* Negative likelihood ratio is calculated as (1 – sensitivity) ÷ specificity.
**Positive likelihood ratio is calculated as sensitivity ÷ (1 – specificity).

815 Diagnosing Extra Pulmonary Tuberculosis Using Xpert MTB/RIF: A Laboratory Algorithm

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Background: South Africa's implementation of XpertMTB/RIF® as the initial diagnostic test for pulmonary tuberculosis (TB) reached national coverage in September 2013. XpertMTB/RIF's use for the diagnosis of extrapulmonary tuberculosis (EPTB) was investigated with the aim of establishing whether EPTB testing should be incorporated into the national testing algorithm.

Methodology: EPTB specimens from 7916 hospitalized patients received over a 6-month period at a high throughput TB referral laboratory in Johannesburg, South Africa were investigated. Large volume specimens were centrifuged, tissue biopsies homogenised and all specimens checked for growth of contaminating bacteria on blood agar. Contaminated samples received NALC-NaOH decontamination prior to liquid culture. Residual specimens (volumes >1ml) after inoculation of culture (n=1175) were tested using XpertMTB/RIF as per the sputum protocol recommended by the manufacturer.

Results: Using culture as the reference standard, XpertMTB/RIF's overall sensitivity was 59% (95% confidence interval [CI] 53, 65) and specificity 92% (CI 90, 94) with the highest sensitivity of 91% (CI 78, 97) for pus, 80% (CI 56, 94) for lymph node aspirates and 51% (CI 44, 58) for fluids (ascitic 59% and pleural 47%). A difference in sensitivity of Xpert was noticed between specimens classified as thick 87% (CI 76, 94) versus clear (watery) 48% (CI 36, 61) appearance. The sensitivity was unchanged when traces of blood 52% (CI 44, 60) or pre-centrifugation 57% (CI 28, 82) were documented among the clear specimens. An additional 124 specimens generated valid results by XpertMTB/RIF but were contaminated by MGIT (10.5%). There was an early diagnosis of rifampicin (RIF) resistance (9.6%) by XpertMTB/RIF in 25/260 cases.

Conclusions: XpertMTB/RIF's performance on EPTB specimens provides very promising results and should be considered for incorporation into National TB guidelines. XpertMTB/RIF is less affected by contaminating bacteria and could significantly reduce laboratory labour and the diagnostic delay of culture for EPTB specimens.

Session P-R3 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Latent TB Screening and Treatment

816 Rifapentine Safety and PK With Novel Dosing Strategies To Increase Drug Exposures for TB: ACTG A5311

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Background: Rifapentine (RPT) is a potent anti-tuberculosis (TB) drug poised to enter Phase 3 trials. Its sterilizing activity and treatment-shortening potential are exposure-dependent. To optimize exposures, RPT must be taken with food, and bioavailability declines with increased dose.

Methodology: This phase 1, two-arm, open-label, multicenter trial in healthy HIV/TB-uninfected subjects investigated two strategies to increase RPT exposures: dividing the dose or giving the drug with an egg (available in many TB-endemic settings). In Arm 1, RPT was administered at 10 mg/kg twice daily (BID) and 20 mg/kg once daily (QD), each for 14 days, separated by a 28-day washout, with randomization of dosing sequence. In Arm 2, 15 mg/kg RPT was given QD with an egg and with a low-fat breakfast, separated by a 28-day washout, with two possible dosing sequences. Intensive pharmacokinetic (PK) sampling was performed after the day-1 and day-14 doses in each dosing period. RPT concentrations were determined by LC-MS/MS. Population PK and PK-toxicity analyses were performed using nonlinear mixed effects modeling in NONMEM. Safety and PK data from Tuberculosis Trials Consortium (TBTC) Study 29X (phase 2 RPT treatment trial) were included in models.

Results: This trial was stopped early because of safety and tolerability concerns. Of 44 subjects, 20 discontinued prematurely, 12 for protocol-defined toxicity (grade 3 or higher adverse event or grade ≥2 rifamycin hypersensitivity (RHS)), including 6 RHS events. Median age and weight were 35 years and 83 kg; 34% were African-American and 27% women. Taking RPT 15 mg/kg with an egg increased population mean steady state AUC ($AUC_{0\text{-}24ss}$) by 47% (RSE 8%) compared to low-fat breakfast. Dividing the dose (10 mg/kg BID vs. 20 mg/kg QD) increased exposures significantly, especially for high doses (e.g. 38% with a daily dose of 1500 mg). $AUC_{0\text{-}24ss}$ in this study were much higher than in TBTC 29X, in which RPT was well-tolerated and patient weights were lower (A5311: 882 for 15 mg/kg QD with egg, 779 mcg*h/mL for 10 mg/kg BID; TBTC 29X: 406 and 582 for 15 and 20 mg/kg QD with food). In a combined A5311/29X analysis, median exposures were similar among individuals with grade 2, grade 3, and no toxicities. Toxicity was more common in A5311 and generally occurred early in treatment. There were no clear exposure-toxicity relationships, though most exposures in A5311 were high.

Conclusions: Two strategies to increase RPT exposures, dividing the dose or giving RPT with an egg, successfully increased RPT exposures 40-50%. Frequent toxicities, including RHS, in HIV/TB-uninfected subjects given high-dose RPT led to early termination of A5311. Limits of tolerability in patients with TB receiving RPT at doses that give similar exposures to those seen in this study remain to be defined.

817 Three Months of Weekly Rifapentine + INH for *M. tuberculosis* Infection in HIV-Infected Persons

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Background: Three months of once-weekly rifapentine 900 mg + INH 900 mg under direct observation (3HP) is at least as effective as 9 months of daily self-administered INH (9H) in HIV-uninfected persons, but there are limited data on the effectiveness of 3HP in HIV-infected populations.

Methodology: We enrolled HIV-infected persons ≥2 years old who were tuberculin skin test positive or close contacts of TB cases, into a prospective, randomized, open-label non-inferiority trial of 3HP (directly observed) vs. 9H (self-administered). HIV-infected participants were enrolled from the U.S., Brazil, Spain, Peru, and Canada between June 2001 and December 2010. Participants were followed 33 months from enrollment, and could not receive antiretroviral therapy (ART) until > 90 days after enrollment. The endpoint was culture-confirmed TB in adults and culture-confirmed or clinical TB in children. The non-inferiority margin was 0.75%.

Results: There were 399 eligible HIV-infected persons enrolled (MITT population): 193 in the 9H arm and 206 in the 3HP arm. There was no significant difference in the proportion of children < 18 years (0.5 vs. 1.5%), history of injection drug use (17 vs. 13%), history of hepatitis C virus infection (14 vs. 11%), median baseline CD4 (524 vs. 496), or receipt of ART > 90 days after enrollment (13 vs. 19%) in the 9H vs. 3HP arms, respectively (P > 0.10 for all). There were 6 TB cases in 471 patient-years (p-y) of follow-up from enrollment in the 9H arm (1.27 per 100 p-y) vs. 2 TB cases in 511 p-y of follow-up in the 3HP arm (0.39 per 100 p-y). Cumulative TB rates were 3.69% vs. 1.01% in the 9H vs. 3HP arms, respectively (difference in cumulative TB rate: -2.68%; upper bound of the 95% CI of the difference: 0.55%). In the per-protocol population, cumulative TB rates were 1.90% vs. 0.56% in the 9H vs. 3HP arms, respectively. Of the 8 TB cases, 6 were pan-susceptible, one was resistant to rifampin + pyrazinamide (*M. bovis*; 3HP arm) and one was resistant to INH + rifampin (9H arm). Among those with CD4+ lymphocyte counts at study entry, the median CD4 was 344 (IQR 271-460) among those who developed TB vs. 512 (IQR 398-704) in those who did not (P = 0.06). Treatment completion was higher in the 3HP (88%) than the 9H (64%) arm (P < 0.001); drug discontinuation due to an adverse drug reaction was similar (3.4%. vs. 4.2%; P = 0.80) in 3HP vs. 9H.

Conclusions: In this study conducted in countries with diverse TB prevalence, among HIV-infected persons who did not receive ART for at least the first 3 months, 3HP was non-inferior to 9H. 3HP had higher treatment completion rates and was well-tolerated. 3HP should be considered for treatment of latent *M. tuberculosis* infection in HIV-infected persons.

818 Effect of HIV On Latent TB Screening of Pregnant Women in Pune, India

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Background: WHO recently recommended isoniazid preventive therapy (IPT) for all HIV-infected pregnant women. Some providers limit IPT to patients with evidence of latent TB infection (LTBI), but the immune changes of both HIV and pregnancy may impact the performance of the most common LTBI tests: the tuberculin skin test (TST) and the IFNγ release assay (IGRA). We compare their performance in HIV-infected and uninfected pregnant women.

Methodology: LTBI screening was done in 128 HIV-infected and 158 -uninfected pregnant women seeking antenatal care at a public hospital in India. Trained staff collected sociodemographics/ medical history and performed IGRA and TST. Agreement using the kappa statistic and percent positivity with binomial exact confidence intervals was calculated. Odds ratios for risk factors of test positivity and discordance were estimated using a logistic regression model adjusting for education, home location, adults in household, TB contact, gestational age (GA), and HIV.

Results: Compared to HIV-uninfected women, HIV-infected women had similar GA (25 vs 26 weeks, p=0.38) and prior IPT (0% vs 0%) but more known TB contacts (7% vs 2%, p=0.03). Median CD4 count for HIV-infected women was 530 cells/mm3 (IQR 393-708); 43 (36%) were on antiretroviral treatment (ART).

All women had higher IGRA positivity than TST whether HIV-infected (29% vs 11%, p=0.01) or not (32% vs 17%, p=0.01). Women with HIV had lower, but not significantly lower, IGRA (29% vs.32% p=0.63) and TST positivity (11% vs 17%, p=0.20) than HIV-uninfected women. In multivariate analysis, positive IGRA was associated with having a TB contact (aOR 2.9, CI 0.9-8.9, p=0.05).

Agreement of TST and IGRA was moderate in HIV-uninfected women (k=0.40, CI: 0.24-0.56) but poor in HIV-infected women (k=0.21, CI 0.02-0.41). There was a trend to lower concordant TST+/IGRA+ in HIV-infected than HIV-uninfected (7% vs 15%, p=0.08) but similar rates of TST-/IGRA- (57% vs 62%, p=0.82) TST-/IGRA+ (18% vs 17%, p=0.92), and TST+/IGRA- (4.6% vs 4.2%, p=0.7). In multivariate analysis, TST-/IGRA+ discordance was associated with having a TB contact (aOR 3.2, CI 1-10, p=0.04). HIV-infected women with TST-/IGRA+ had significantly lower IFNγ concentration than TST+/IGRA+ (1.8 vs 6.4 IU/mL, p=0.02). This was not significant in HIV-uninfected (2.2 vs 4 IU/mL, p=0.12)

Conclusions: Discordance between the IGRA and TST is common in pregnant women_the IGRA returned significantly more positives in both HIV-infected and -uninfected women. HIV-infected women with TST-/IGRA+ discordance had lower IFNγ levels than non-discordant women, suggesting that insufficient IFNγ negatively affects TST performance. The reliance on TST for LTBI screening in antenatal programs may cause >50% of HIV-infected women to miss out on lifesaving IPT.

Session P-R4 Poster Session
Wednesday March 5, 2014, 2:30 PM–4:00 PM Exhibit Hall D
Inflammatory and Immune Activation Markers in TB

819 Baseline Inflammatory and Immune Activation Markers Predictive of TB After ART Initiation

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Background: Incident tuberculosis disease (TB) remains a major cause of mortality after antiretroviral treatment (ART) initiation in resource-limited settings. Pre-ART inflammation and immune activation may impact host risk for TB. Our objective was to determine the association between baseline inflammation and immune activation and risk of pulmonary and extra-pulmonary TB after ART initiation in adults in resource-limited settings.

Methodology: We conducted a nested case-control study (n=332) within the ACTG PEARLS trial of three ART regimens among 1575 HIV-infected treatment naïve adults in 9 countries. Cases were incident TB cases by 96 weeks after ART initiation, and controls were a random sample (stratified by study site) of those who did not develop TB during follow-up. Primary outcomes were associations between pre-ART immunologic and inflammatory marker levels (CRP, ferritin, IFN-gamma, IL-6, IP-10, TNF-alpha, EndoCab IgM, LPS, sCD14) and incident TB. Using univariate and multivariable logistic regression, we calculated odds ratios of association between markers and incident TB. We defined markers according to established cutoff definitions when available and the 75th percentile of measured values when not. Multivariable analyses adjusted for age, sex, study site, treatment arm, baseline CD4, and $\log_{10}$ viral load.

Results: The cumulative incidence of TB at 96 weeks after ART initiation was 4.9% (55 pulmonary and 22 extra-pulmonary TB cases), of which 53% (41 cases) occurred within the first 6 months of treatment. CRP and IP-10 were associated with incident TB in both unadjusted and adjusted analysis (aOR for CRP, 4.12, 95%CI: 2.18-7.77; aOR for IP-10, 1.89, 95% CI: 1.05-3.39). More established TB risk factors, including hypoalbuminemia (aOR 5.24, 95%CI: 2.69-10.20) and hemoglobin <12 g/dL in women or <13 g/dL in men (aOR 2.16, 95%CI: 1.07-4.35) were also significantly associated with incident TB; being overweight or obese versus of normal BMI was inversely associated with incident TB (aOR 0.37, 95%CI: 0.14-0.97).

Conclusions: Incident TB occurs commonly after ART initiation in resource-limited settings. IP-10 and CRP, coupled with traditional risk factors, may have value in identifying patients most at risk for developing TB after initiation of ART. Use of CRP in particular may have added value to identifying those at greatest risk of incident TB post-ART initiation.

Table 1. Associations between markers of inflammation and immune activation and incident TB in the ACTG PEARLS study

Characteristic	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Prior history of TB		
No	1	1
Yes	2.37 (1.33-4.23)	1.09 (0.53-2.26)
Hemoglobin, g/dL		
≥ 12 (f) or ≥ 13 (m)	1	1
< 12 (f) or < 13 (m)	2.78 (1.57-4.96)	2.16 (1.07-4.35)
BMI, kg/m^2		
[18.5-25)	1	1
< 18.5	1.42 (0.64-3.11)	0.93 (0.35-2.44)
≥ 25	0.33 (0.15-0.74)	0.37 (0.14-0.97)
CRP, mg/dL		
≤ 10	1	1
> 10	4.10 (2.67-7.41)	4.12 (2.18-7.77)
EndoCab IgM, MMU/mL		
0.4-380)	1	1
Q4 (>380)	1.37 (0.80-2.36)	1.19 (0.76-2.13)
Ferritin, ng/mL		
≤ 150	1	1
> 150	2.24 (1.34-3.77)	1.72 (0.92-3.21)
IFN-gamma, pg/mL		
Q1-Q3 (0-230)	1	1
Q4 (>230)	1.14 (0.67-1.95)	0.76 (0.42-1.39)
IL-6, pg/mL		
Q1-Q3 (0-300)	1	1
Q4 (>300)	1.06 (0.62-1.81)	0.80 (0.45-1.42)
IP-10, pg/mL		
Q1-Q3 (54-9700)	1	1
Q4 (>9700)	2.51 (1.49-4.23)	1.89 (1.05-3.39)
LPS, pg/mL		
Q1-Q3 (130-7700)	1	1
Q4 (>7700)	0.89 (0.50-1.57)	0.71 (0.38-1.33)
sCD14, pg/mL		
Q1-Q3 (11,000-4,400,000)	1	1
Q4 (>4,400,000)	1.64 (0.97-2.78)	1.40 (0.79-2.46)
Albumin, g/dL		
≥ 3.5	1	1
< 3.5	4.70 (2.68-8.23)	5.24 (2.69-10.20)
TNF-alpha, pg/mL		
Q1-Q3 (0-99)	1	1
Q4 (>99)	2.03 (1.20-3.42)	1.66 (0.94-2.95)

* The adjusted odds ratio represents the independent risk of the added marker characteristic when adjusting for age, sex, treatment, study site, baseline CD4 and baseline viral load. Race was collinear with study site and was not included.

820 MAIT Cells Are Highly Enriched in the Bronchoalveolar Lavage Fluid of Patients With TB

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Background: Mucosal Associated Invariant T (MAIT) cells are a class of non-conventional CD8+ lymphocytes that respond to a broad range of bacterial, mycobacterial and fungal pathogens. They have been defined by their usage of a semi-invariant T cell receptor (TRAV1-2 TRAJ33) and can be activated by microbial riboflavin metabolites presented by the evolutionarily conserved MR-1 molecule. Though found in people who have no history of TB exposure, M.tb-reactive MAIT cells are absent in the peripheral blood of those with active TB. This observation led us to hypothesize that during pulmonary TB MAIT cells leave the peripheral circulation to participate in the lung's mucosal immune response.

Methodology: Bronchoalveolar lavage (BAL) fluid was collected from a cohort of patients undergoing clinically indicated bronchoscopy in Durban, South Africa. Pulmonary TB cases were defined microbiologically (positive M.tb. culture or PCR); controls were defined as having no evidence of inflammatory or infectious lung disease (negative bacterial, fungal and mycobacterial BAL cultures and no eventual diagnosis of sarcoidosis or interstitial lung disease). BAL cells were characterized by flow cytometry to assess the frequency of MAITs (TRAV1-2+) among CD8+ T cells (gated on live, CD14-negative, CD3+ lymphocytes). When sufficient cells were obtained, they were stimulated with CD2/CD3/CD28 beads to assess the production of TNFa and IL-17 by intracellular cytokine staining. When available, matched PBMC were also analyzed for the frequency of peripheral MAIT cells. The Mann-Whitney U test was used to compare frequencies.

Results: In pulmonary TB cases, MAIT cells comprised a significantly higher percentage of lung-resident CD8+ T cells (n=8, median 22.9%, IQR 16.4-33.9%) than in controls (n=11, median 5.0%, IQR 4.3-5.8%, p=0.0005). In contrast, during pulmonary TB, TRAV1-2+ CD8+ T-cells were not expanded in the peripheral blood (n=5, median 5.8%, IQR 5.6-6.2%, p=0.0016). Upon non-specific activation, lung resident MAIT cells in those with pulmonary TB produced very high levels of TNFα and did not produce IL-17 above background.

Conclusions: MAIT cells, an emerging class of innate lymphocytes, are highly enriched in the lungs during pulmonary TB. Interestingly, though it has been shown that HIV severely depletes MAITs in the peripheral blood, here we find MAITs to be comparably enriched in the lungs of both HIV-positive and HIV-negative patients during active tuberculosis. This suggests that MAITs are redistributed to mucosal surfaces rather than destroyed by HIV. Further research the role of MAIT cells in protective immunity against TB is urgently needed; their potential as a novel TB vaccine target should be explored.

821 Vitamin D and TMEM16J Host Variants Associated With TB or Death in HIV-Infected and -Exposed Infants

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Background: While young African children have been severely affected by HIV and TB, host genetic single nucleotide polymorphisms (SNPs) that alter the Vitamin D receptor, affect Vitamin D insufficiency and deficiency (VDID) and pose a potential risk for tuberculosis (TB), have not been well studied.

Methodology: We performed a case-cohort study (total n=346 with a random subcohort of 270) in IMPAACT P1041, a trial in South Africa that evaluated the efficacy of isoniazid prophylaxis on reducing TB disease in 1351 HIV-infected and -exposed, uninfected infants. Vitamin D levels were determined by chemiluminescent immunoassay. Five Vitamin D related SNPs (Bsm-1-G/A [rs1544410], Fok-I-C/T [rs2228570], GC-A/C [rs2282679], DHRC7/NADSYH1-G/T [rs12785878] and CYP2R1-G/A [rs10741657]), and three SNPs in the PKP3-SIGIRR-TMEM16J region associated with TB susceptibility [PKP3 (rs10902158-A/G), PKP3 (rs7105848-T/C), and TMEM16J (rs7111432-G/A)] were assessed by real-time PCR. Primary outcome was time to probable/definite TB by 192 weeks. Secondary outcomes included time to possible, probable, or definite TB; time to latent TB/TB disease; and time to TB or death. Prevalence of VDID, defined as <32 ng/ml, was determined using the random subcohort. To determine the associations between VDID and host SNPs with outcomes, Cox regression was performed.

Results: Median age at Vitamin D draw was 8 months; 11% were ever breastfed; 51% were HIV-infected. VDID prevalence was 26%. There were 138 TB cases (43 definite/probable, and 95 possible) and 26 deaths included in this analysis. Children with VDID had a 77% greater risk of probable/definite TB (HR 1.77, p=0.17). When possible TB was included in the outcome, VDID was associated with a significant increase in TB (HR 1.99, p=0.005). VDID was also associated with any TB or death (HR 2.05, p=0.002). Adjusting for HIV status, season, site, sex, weight-for age z score, breastfed, type of house, mother previous TB diagnosis, age at plasma draw date, and INH/placebo treatment arm, VDID was independently associated with any TB (aHR 1.75, 95% CI 1.01-3.05;p=0.046) as well as any TB or death (aHR 1.76, 95% CI 1.03-3.00; p=0.038). No polymorphism was associated with VDID. In both crude and adjusted models, however, having the TMEM16J G-allele was protective of probable/definite TB (aHR 0.53, p=0.07), any TB (aHR 0.56, p=0.017), any TB/death (aHR 0.59, p=0.016) and any TB/latent TB (aHR 0.58, p=0.009); having GG polymorphism of the PKP3 genetic variant was marginally associated with increased risk of any TB/death (aHR 1.44, p=0.07).

Conclusions: In young children with or without HIV, VDID was associated with nearly a 2-fold increased risk of TB or death. Additionally, specific SNPs that affect innate immunity altered the risk for TB.

822 Latent and Active TB Infection Increase Harmful Immune Activation in Those Co-Infected With HIV

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Background: In HIV infection, surface markers of T-cell activation (CD38, HLA-DR and PD-1) and several soluble markers of inflammation and fibrosis (sCD14, IL-6, IL-8, CRP and hyaluronic acid) have been found to independently predict progression to AIDS and mortality. Co-infections such as CMV have been shown to contribute to immune activation; but the impact of TB, which is widely endemic in the areas hardest hit by the global AIDS epidemic, has not been evaluated. We hypothesized that M. tb. co-infection may be associated with harmful immune activation as measurable by these markers.

Methodology: 84 HIV-positive, antiretroviral naïve individuals from KwaZulu-Natal, South Africa were classified as having no evidence of TB infection (no TB), latent TB infection (LTBI) or active smear-positive pulmonary TB (active TB). Subjects with no TB and LTBI had normal lung parenchyma on CXR and negative M. tb. cultures of induced sputum. Mantoux skin tests and Elispots measuring IFNγ production to M.tb RD-1 peptide pool stimulation were both positive in those with LTBI and both negative in those with no TB. Expression of CD38, HLA-DR, and PD-1 were measured by flow cytometry (median fluorescence intensity) on CD4+ and CD8+ T lymphocytes in the no TB and LTBI groups. Plasma concentrations of the soluble markers were measured by ELISA or multiplexed bead-based immunoassays in all three groups. The Mann Whitney Wilcoxon test was used for comparisons.

Results: All groups were well matched for CD4 and HIV viral load. Subjects with LTBI expressed higher levels of CD38 and PD-1 on CD8+ T-cells and CD38 on CD4+ T-cells compared to those with no TB ($p=0.0014$, $p=0.0443$, and $p= 0.0378$). Those with active TB had elevated plasma levels of CRP, IL-6 and IP-10 ($p=0.0001$, $p=0.0005$, and $p=0.0150$) compared to those with no TB. LTBI was not associated with elevated plasma concentrations of any of the soluble biomarkers.

Conclusions: Both active and latent TB infection elevated markers of immune activation and inflammation that have previously been shown to predict more rapid disease progression in HIV-infected individuals. While elevation of inflammatory markers in active TB is not surprising, it is an important new observation that LTBI can independently increase harmful T-cell activation. These results suggest that in the highly TB- and HIV-endemic settings of Southern Africa, latent TB infection may contribute to HIV disease progression and exacerbate the HIV epidemic. Further work to determine if treatment of LTBI improves lymphocyte activation is needed, as this would provide an additional rationale for the widespread use of isoniazid preventative therapy (IPT) in those with HIV and LTBI.

823 Ex Vivo Fitness of MTB Correlates With Lysozyme Sensitivity in the East-African Indian Lineage

Claire Pardieu[1], Nicola Casali[1], Simon Clark[2], Ann Rawkins[2], Richard Hooper[3], Preya Velji[4], Ximena Gonzalo[4], Jane R. Deayton[5], Francis A. Drobniewski[4]
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Background: Virulence factors (VF) facilitate persistence of Mycobacterium tuberculosis (MTB) and are implicated in the recent emergence of new human MTB isolates. However, some VFs are lineage specific and thus difficult to study. Understanding of VFs is essential for the development of new drugs and vaccines against MTB. We therefore sought to identify new VF/markers of virulence in Central Asian (CAS) clinical isolates.

Methodology: Three large-cluster CAS isolates, designated 6, 14 and 72, from the East-African Indian (EAI) lineage were studied in guinea pigs and human monocyte-derived macrophages (MDMs). References were isolates E and 1, from East-Asian and Euro-American lineages respectively, and also in MDMs unique CAS isolate 40, reference strains H37Rv/Ra, and BCG. Pathogenicity scores (PS) were used to assess the severity of lesions in the lungs of infected animals. PS are derived from blind yet subjective scoring of consolidation, necrosis and calcification. Colony forming units (CFU) recovered from spleen samples of infected animals were used to measure dissemination of isolate within host. MTB intracellular replication ex vivo was measured by qPCR for bacterial gene SigA relative to human gene TERT. Whole-genome sequencing was performed for each CAS, Illumina sequence reads mapped onto the H37Rv genome and single nucleotide polymorphisms (SNPs) identified using ssaha_pileup. To determine in vitro lysozyme (LYZ) sensitivity, CAS isolates and reference strains were plated on 7H10 plates at increasing concentrations of LYZ and CFUs recovered at 3 weeks.

Results: Differences in PS and CFU were observed in vivo but only differences in fitness ex vivo were statistically significant; 72 was the slowest isolate (Figure 1). Comparative genomic analysis revealed 123 unique non-synonymous SNPs as candidates for the observed differential phenotype of 72. Of these, 10 locate in genes previously associated with fitness ex vivo or dissemination in vivo; 3 genes were additionally linked to both acid and LYZ resistance in vitro. Accordingly, sensitivity studies showed that growth of all isolates was inhibited by increasing concentration of LYZ with the strongest correlation seen for isolate 72.

Conclusions: Earlier work linked LYZ sensitivity to MTB fitness and dissemination in vivo, but for Euro-American reference strain H37Rv only. We now describe a similar correlation for EAI clinical isolates. Further work will determine whether genes conferring LYZ resistance are VFs per se.

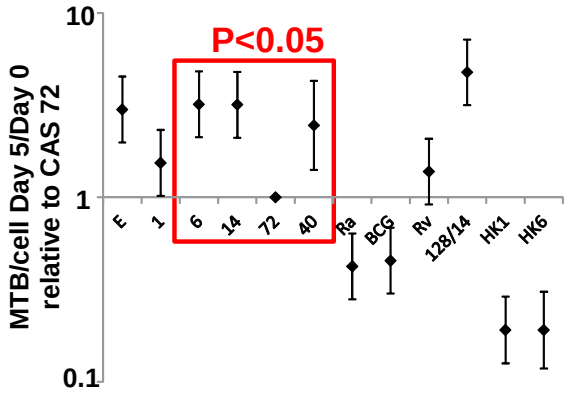

Figure 1. Ex vivo phenotypes of EAI clinical MTB isolates and reference isolates / strains in human monocyte-derived macrophages

824 Polyfunctionality of TB-Specific CD4+ T-Cells in HIV-TB Co-Infection in Latent and Pulmonary TB

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Background: HIV+ persons with latent tuberculosis infection (LTBI) have a 10% annual risk of developing active tuberculosis (TB) compared to a 10% lifetime risk in HIV-uninfected individuals. Mean CD4+ T cell counts of HIV+ patients with pulmonary TB (PTB) are higher than seen with other opportunistic infections suggesting that progression to active TB in this setting is not merely due to CD4+ T cell depletion, but may also be related to functional impairment of CD4+ T cells. There is limited data examining T cell functional signatures in human HIV-TB co-infection. Here we compare CD4+ T cell cytokine profiles and polyfunctionality in response to M. tuberculosis (MTB) antigens between TB uninfected, LTBI and PTB in HIV+ adults.

Methodology: HIV+ adults recruited in Kampala, Uganda were differentiated into 3 groups: PTB (positive sputum smear and/or culture for MTB; n=7), LTBI (>5mm response to the tuberculin skin test (TST) and negative chest x-ray; n=15), or TST- (negative TST and chest x-ray; n=15). Multicolor flow analysis was performed on PBMC stimulated with either PPD, ESAT+CFP10, or SEB, and frequencies of IL-2, IFN-γ and TNF-α secreting cells were determined within the memory subset of CD4+ T cells. Polyfunctionality was determined using FlowJo and SPICE software.

Results: PPD-specific CD4+ T cell secretion of TNF-α and IFN-γ was higher in LTBI compared with TST- group (p=0.001 and p=0.002 respectively). Although LTBI group generally had higher cytokine responses when compared to PTB group, this did not reach statistical significance. Cytokine responses to both PPD and ESAT+CFP10 stimulation correlated positively with TST measured in millimeters (mm). All polyfunctional CD4+ T cell response groups that contained TNF-α correlated with an r>0.43 p<0.01. The polyfunctional CD4+ T cell response profile of MTB-specific CD4+ T cell responses were similar in LTBI and PTB groups with the TNF-α-only secreting cells being the most abundant phenotype. In both groups, PPD-specific cells were less polyfunctional with a greater TNF-α bias than memory cells activated with mitogen.

Conclusions: CD4+ T cell cytokine responses to MTB-specific antigens were significantly higher in LTBI compared to TST- HIV+ adults. ESAT-specific CD4+ T cell responses correlated positively with TST in mm suggesting that TST response in Ugandans, reflective of TB-specific antigen infection with MTB rather than BCG vaccination. Published data suggests polyfunctional CD4+ T cell profiles differ between LTBI and PTB among HIV-uninfected individuals. The fact that we did not observe such a difference in MTB antigen responses in HIV+ subjects suggests that LTBI may represent a more "smoldering" TB state. This may help explain the significantly increased risk of progression to active TB in this population.

Session P-R5 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Impact of ART On TB Risk and Disease

825 Increased Risk of TB and Persistent Immune Deficit With Delayed ART: A Randomized Trial From Haiti

Sean E. Collins[1], Marc Antoine Jean Juste[2], Patrice Severe[2], Serena P. Koenig[3], Rode Secours[2], Oksana Ocheretina[1], Daphne Bernard[2], Allison Dunning[4], Sandra M. Hurtado Rúa[4], Jean W. Pape[1,2]

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Background: The long-term (5 year) effect of early initiation of antiretroviral therapy (ART) versus delayed initiation of ART on immune recovery and risk for tuberculosis (TB) infection in HIV-1 infected individuals is not certain.

Methodology: We conducted an open label randomized controlled trial of immediate initiation of ART in HIV-infected adults with CD4 counts between 200 and 350 cells/mm3 versus deferring ART until the CD4 count was below 200. The primary comparisons were CD4 counts over time and the risk for incident TB during 5 years of follow-up. Generalized estimating equations were used to compare CD4 counts between groups, probability of TB-free survival was calculated using Kaplan-Meier survival methods. Univariate and multivariate Cox proportional hazards regression models were used to estimate the risk of TB as hazard ratios (HR) with 95% confidence intervals. The trial is registered at ClinicalTrials.gov with study number NCT00120510.

Results: 816 participants were enrolled, 408 in each treatment arm. The median age was 40 and 58% of participants were women. The early group started ART within 2 weeks, the deferred group started ART a median of 1.3 years after enrollment. After 5 years, the mean CD4 count in the early group was significantly higher than in the deferred group; 574

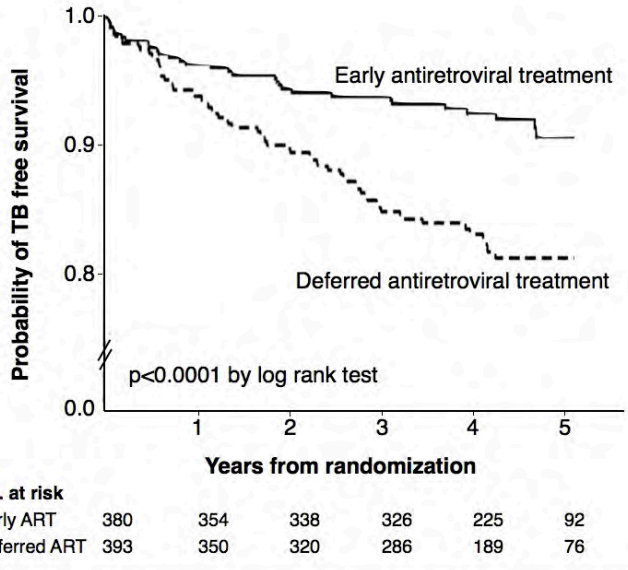

Figure 1: Kaplan-Meier estimates of the probability of tuberculosis free survival from the time of study randomization.

cells/mm3 (95% confidence interval [CI] 545 to 603) versus 451 cells/mm3 (95% CI 419 to 484; p<0.0001). Risk for incident TB was significantly higher in the deferred group five years after randomization (hazard ratio [HR] 2.44 [95% CI 1.56-3.70]; p<0.0001). In a time dependent multivariate analysis, TB risk correlated with lower CD4 counts and with lower Body Mass Index. For each CD4 decrease of 50 cells/mm3 the hazards of incident TB increased by 1.30 (95% CI 1.16-1.43; p<0.0001).

Conclusions: Short delays in ART initiation for HIV-infected adults with CD4 counts of 200 - 350 cells/mm3 can result in long-term (5 year) immune dysfunction and persistent increased risk of tuberculosis.

826 Viral Suppression in HIV-Infected Pregnant Women With and Without TB, South Africa

Jennifer Hoffmann[1], Silvia Cohn[1], Fildah Mashabela[2], Reginah Msandiwa[2], Richard Chaisson[1], Neil Martinson[2], Tshepiso Study Team
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Background: HIV and tuberculosis (TB) are the leading infectious causes of death among women of reproductive age worldwide. In South Africa, the burden of overlapping HIV and TB epidemics is exceptionally high. Nearly 30% of pregnant women presenting for prenatal care are HIV-infected. HIV/AIDS is the leading cause of maternal death in South Africa, responsible for at least 20% of all maternal deaths. Antiretroviral therapy during and after pregnancy is essential for maternal health and prevention of mother to child transmission. We describe the HAART and viral suppression in a cohort of HIV-infected pregnant women with and without TB.

Methodology: Tshepiso is a prospective cohort study of HIV-infected pregnant women with TB (cases) and matched HIV-infected pregnant women without TB (controls) in Soweto, South Africa. Women are enrolled prenatally and followed during delivery, and then mother-infant pairs are followed to one year postpartum for HIV and clinical outcomes.

Results: From January 2011 to September 2013, we enrolled 185 HIV-infected pregnant-women, 61 TB/HIV cases and 124 HIV controls. At enrollment, median age was 28 and 29 years, and median gestational age was 29 and 30 weeks for cases and controls respectively. At baseline, 59% of cases and 57% of controls were taking HAART and the median [IQR] CD4 count was 283 [142,433] and 371 [271,487] for cases and controls respectively (p=0.0009). Among women on HAART, 38% of cases and 62% of controls had undetectable viral load (p=0.02). At delivery 82% of cases and 64% of controls were on HAART with 52% and 86% having an undetectable viral load respectively (p=0.03). One year postpartum 79% of cases and 69% of controls reported taking HAART, only 56% of cases and 60% controls had undetectable viral loads (p=0.76).

Conclusions: Pregnant women with TB/HIV had less viral suppression prenatally and at delivery than those without TB. Uptake of HAART for TB co-infected women was inadequate. Our cohort revealed suboptimal viral suppression at one year postpartum for both cases and controls taking HAART. Option B+ can have a significant impact in improving maternal and infant survival if women are appropriately initiated on HAART and viral suppression is maintained. Our cohort demonstrates the potential programmatic need for additional peripartum adherence interventions and monitoring.

Table 1: Viral Suppression of HIV-infected women on HAART

	TB/HIV Case	HIV Control	*P*
Prenatal Baseline			
n	34	69	
Undetectable n(%)	13(38%)	43(62%)	0.02
Viral Load [IQR]	220 [105,1385]	388 [190,1015]	0.40
CD4 [IQR]	278 [142,406]	348 [263,402]	0.047
One year post-partum			
n	32	52	
Undetectable n(%)	18(56%)	32(60%)	0.76
Viral Load [IQR]	24,898 [2705,57172]	14,065 [2507,121510]	0.99
CD4 [IQR]	433 [331,633]	445 [267,562]	0.93

827 Depleted DHEA-S Reserves Are Associated With Early Mortality After ART Initiation in HIV/TB

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Background: Early mortality post-ART initiation in advanced HIV/TB co-infection is associated with poor pathogen-specific immunologic recovery despite virologic suppression. The active form of dehydroepiandrosterone-sulfate (DHEA-S), DHEA, an adrenal androgen, enhances Th1 responses in HIV/TB and is available as an over-the-counter supplement. We hypothesized that low pre-ART (baseline) DHEA-S levels are associated with early mortality in advanced HIV/TB.

Methodology: We conducted a nested case-control study within a cohort evaluating factors associated with death within 6 months post-ART initiation in ART-naïve adults with HIV/TB and pre-ART CD4 counts <125 cells/μl, in Botswana. Baseline DHEA-S levels (primary exposure) were compared between cases (deaths, n=17) and controls (survivors, n=35). CD4 counts, cortisol, and IL-6 levels were also assessed at baseline (pre-ART) and week 4 post-ART initiation using the rank sum test. Logistic regression was used to adjust for baseline CD4 count and sex.

Results: DHEA-S was significantly lower in cases vs. controls at baseline (0.21µg/ml [IQR 0.11-0.37] vs. 0.45µg/ml [IQR 0.19-0.77]; p=0.007). Adjusting for CD4 count and sex, every 0.1µg/ml higher baseline level of DHEA-S was associated with a 24% decrease in the odds of early mortality (odds ratio, 0.76 [95% CI, 0.59-0.98]). DHEA-S continued to be lower among deaths vs. survivors at week 4 post-ART initiation (p=0.014). Baseline levels of CD4 counts, cortisol, and IL-6 did not differ between deaths vs. survivors. However at week 4 post-ART initiation, change from baseline and absolute CD4 counts were lower, while cortisol and IL-6 levels were significantly higher, in deaths vs. survivors.

Conclusions: Diminished DHEA-S reserves, increased immune activation, and poor immune recovery are associated with increased risk of early mortality in advanced HIV/TB. DHEA has been shown to alter T-regulatory cell function by downregulating FoxP3 expression and enhancing dendritic cell function in vitro, which is essential for mounting protective pathogen-specific immune responses. An inability to effectively fight Mycobacterium tuberculosis in advanced HIV/TB may be in part due to depleted DHEA-S reserves. Exploratory trials of DHEA supplementation to improve immune response and outcomes should be pursued in HIV/TB.

829 Impacts of National ART Initiation Policy Change On Integrated TB HIV Practice in Zomba, Malawi

Kevin D. Bezanson[1], **Adrienne K. Chan[1]**, Monique van Lettow[2], Jean Bourgeois[2], Edson Mwinjiwa[2], Harry Mbewe[3], Martin Kachingwe[2], Donald Cole[4], Sumeet Sodhi[1]
[1]Dignitas International, Toronto, ON, Canada, [2]Dignitas International, Zomba, Malawi, [3]Zomba Central Hosptial, Zomba, Malawi, [4]Dalla Lana School of Public Health, Toronto, ON, Canada

Background: In response to emerging evidence for the safety and clinical benefit of early Antiretroviral (ART) initiation in tuberculosis (TB) patients, the National TB Programme (NTP) in Malawi implemented a change in policy for TB patients co-infected with Human Immunodeficiency Virus (HIV) in September 2011. Clinicians were advised to start ART as soon as possible, rather than delaying initiation until 2 weeks after starting TB treatment. We sought to assess the impact of the policy change on integrated TB HIV program measures and treatment outcomes in a TB HIV clinic at Zomba Central Hospital (ZCH).

Methodology: Routine program data from NTP TB registers and ART Clinic were collected and analyzed for all TB patients enrolled at ZCH April 1, 2011 to April 1, 2012. Univariate comparisons were made between groups enrolled 6 months prior to policy change implementation, and the subsequent 6 months.

Results: All 842 patients were included, 50.2% (n=423) pre, and 49.8% (n=419) post guideline change. No significant differences were found between groups in age, gender, type of TB (pulmonary/extra-pulmonary), or TB episode type (new/retreatment/relapse/failed/return after default).

Program measures of TB HIV integration revealed significantly more patients already on ART being diagnosed with TB in the post-guideline change group, 36.8% (n=154) vs. 30.0% (n=127), p=0.038. Of those not already on ART, rates of HIV testing exceeded 90% and were not different between groups. However, there was a significant improvement post-guideline in HIV positive TB patients initiating ART from 62.6% (n=97) to 74.2% (n=92), p=0.039. Furthermore, in those initiating ART, significantly more did so in less than 2 weeks, increasing from 31.1% (n=33) to 68.1% (n=64), p<0.001.

TB treatment outcomes revealed more patients alive at the end of treatment in the pre-guideline change group 86.3% (n=365) vs. 79.0% (n=331), p=0.005. This was likely due to higher unknown outcomes in the post-guideline change group 9.5% (n=40) vs. 2.8% (n=12), p<0.001, as rates of death were not different between groups.

Conclusions: The national policy change from delayed to early as possible ART initiation in TB patients in Malawi was reflected in clinical practice in our clinic. More patients who tested HIV positive were successfully initiated on ART, and earlier. Increases in patients being diagnosed with TB already on ART were also found, raising the potential that changes in vigilance of TB diagnosis prior to ART initiation occurred as well. These changes did not appear to affect overall mortality. They do suggest an impact of health policy change on service delivery.

830 Does Long-Term ART Reduce TB Rates To Background Population Levels? Data From a National HIV Cohort

Rishi K. Gupta[1,2], Marc Lipman[1], Alison Brown[2], Brian Rice[2], Anton Pozniak[3], Dominik Zenner[2], Lucy Thomas[2], Ibrahim Abubakar[1,2], Valerie Delpech[2]
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Background: Antiretroviral therapy (ART) promotes immune reconstitution and is associated with a time-dependent reduction in HIV-associated tuberculosis (TB) incidence. It is not known if TB rates in individuals on long-term ART remain elevated compared to the background population, particularly in low TB prevalence areas.

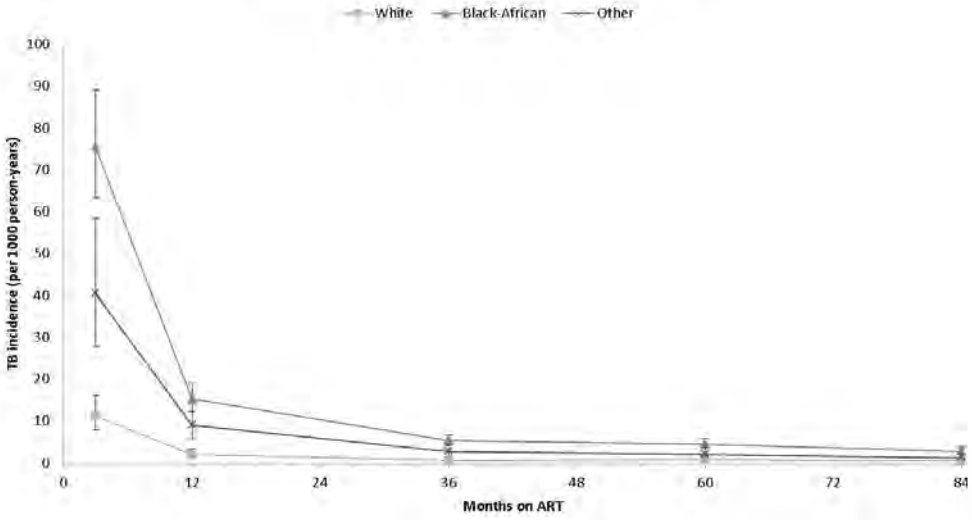
Methodology: National HIV positive cohort records were linked to the national TB register for England, Wales & Northern Ireland. TB incidence in the HIV positive cohort was calculated for 2007-11. This was compared to HIV negative population rates in 2009 (middle year of HIV positive cohort), calculated using Office for National Statistics denominators (minus those seen for HIV care in 2009). TB cases were assumed to be HIV negative if they did not match to a HIV record by 31/12/2011. Data on ART use, most recent CD4 count and ethnicity were available for 99%, 92% and 100% of person-years (PY) respectively.

Results: The HIV positive cohort included 79,919 adults with 231,664 PY of follow up; 50% were white, and 36% were black-African. At cohort entry, median CD4 was 409 cells/µL and 49% were on ART. There were 1,550 TB cases (6.7/1000 PY) during HIV positive cohort follow up; 60% of these were within 3 months of HIV diagnosis. TB incidence was higher in black-Africans than in the white population (13.6/1000 *vs.* 1.7/1000 PY) and declined as time on ART increased [**Fig. 1**]. Lower most recent CD4 count, non-white ethnicity, not being on ART and early ART (0-3 months) were independent risk factors for TB in the HIV positive cohort in multivariate analysis. TB incidence in the HIV positive population during long-term ART (≥5 years) was similar to that in the HIV negative population in black-Africans (2.5/1000 *vs.* 1.9/1000 PY; p>0.05) but was higher than the incidence in the HIV negative population in the white ethnic group (0.5/1000 *vs.* 0.04/1000 PY; p<0.001). This higher TB incidence in the HIV positive white group persisted when the

analysis was restricted to person-time accrued on ART with CD4 ≥500 cells/μL and when white HIV positive patients born abroad were excluded.

Conclusions: TB incidence during l ong-term ART (≥5 years) was similar to that in the HIV negative population in black-Africans but rates were high in this ethnic group, regardless of HIV status. In contrast, incidence during long-term ART in the white HIV positive population, while low overall, was higher than in HIV negative individuals. Underlying reasons for this in this low TB burden setting require further investigation.

Figure 1: Graph showing TB incidence by months on ART, stratified by ethnicity (error bars show 95% confidence intervals).



831 Development of Tuberculosis in HIV-Infected Patients Receiving Successful TARGA

Esteban Martin-Echevarria[1], Sergio Serrano Villar[2], Talía Sainz[2], **Ana Moreno[2]**, Jose Luis Casado[2], Fernando Dronda[2], Maria Jesus Perez Elias[2], Enrique Navas[2], Manuel Rodriguez Zapata[1], Santiago Moreno[2]

[1]Hospital Universitario Guadalajara, Guadalajara, Spain, [2]Hospital Universitario Ramón y Cajal, Madrid, Spain

Background: The incidence of active tuberculosis in HIV-infected patients receiving antiretroviral therapy (ART) is still significantly higher than that observed in the general population. We hypothesized that an optimal immunological recovery may reduce the risk of tuberculosis.

Methodology: Historical cohort study in ART-treated patients without previous diagnosis of tuberculosis. Tuberculosis was diagnosed only if microbiologically proven. Multivariate analyses were performed to identify risk factors associated with tuberculosis.

Results: This study included 1824 patients, with a median follow-up of 473 days. Higher CD4 count gain after ART initiation was a protective factor against active tuberculosis (per each 100 cells/μL increase, OR, 0.683; 95% CI, 0.522-0.894). The maximal protection was observed in patients reaching increments ≥150 cel/μL after 12 months (OR, 0.29; 95% CI 0.11-0.8) or ≥300 cel/μL after 24 months (OR, 0.73; 95% CI 0.71-0.75) of ART. CD4+ cell increase after ART initiation was confirmed as an independent predictor of development of tuberculosis by Cox regression analysis (per each 100 cell/uL at year one, HR 0.63; 95% CI, 0.43 - 0.94; per each 100 cell/uL at year two; HR, 0.57; 95% CI, 0.41 - 0.81). However, there was no association between achieving HIV RNA <50 copies/mL and the risk of active TB (OR, 1.43; 95% CI, 0.68-2.49).

Conclusions: The risk of tuberculosis in patients starting ART is reduced among those with better immunological response and it is unrelated to the virological response. Our results emphasize the need of adjunctive strategies in immunological non-responders in order to minimize the residual risk of tuberculosis.

832 Timeliness of ART Initiation Among HIV-Infected Patients With TB in Sub-Saharan Africa

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[1]ICAP, Columbia University, New York, NY, United States, [2]Department of Epidemiology, Columbia University, New York, NY, United States

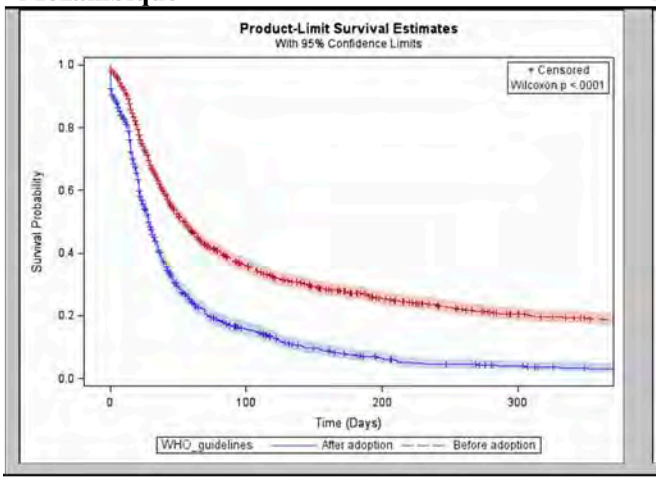
Background: Initiating antiretroviral therapy (ART) early during TB treatment increases survival among people living with HIV (PLWH). 2010 WHO guidelines recommend ART initiation for PLWH as soon as possible after TB treatment initiation, regardless of CD4+ count. Yet, globally, only 48% of PLWH with TB were on ART in 2011.

Methodology: We used routinely-collected data for adult PLWH newly enrolled in HIV care from 05/2003-03/2013 at 74 health facilities supported by ICAP-Columbia University in Mozambique (MZ) and Rwanda (RW) to compare time from enrollment into HIV care to ART initiation in relation to country adoption of 2010 WHO guidelines as follows: 1) Prior to adoption , between ART-eligible patients without and with TB; and 2) after adoption, between ART-eligible patients without TB and all patients with TB at enrollment. "On TB treatment at enrollment" variable was used to identify patients with TB at enrollment. We used stratified Kaplan-Meier survival curves for our analyses.

Results: Of total of 179,086 PLWH enrolled in HIV care, 49,375 (28%) were ART-eligible at enrollment, and 36,508 of ART-eligible (74%) initiated ART. Of all PLWH, 5,014 (3%) had TB at enrollment. PLWH with TB at enrollment had a higher median CD4+ count than ART-eligible PLWH without TB (189 vs. 140 c/mL; p<0.001). Median time to ART initiation for PLWH with TB at enrollment decreased from 55 and 58 days before to 28 and 43 days after WHO guidelines adoption in MZ (p<0.001) and RW (p= 0.015), respectively. In MZ, PLWH with TB had a longer time to ART initiation vs. ART-eligible PLWH without TB prior to WHO guidelines adoption (p<0.001) but a shorter time to ART initiation after guidelines adoption (p<0.001). PLWH with TB at enrollment had a longer time to ART initiation vs. ART-eligible PLWH without TB both before and after WHO guidelines adoption in RW (p<0.001).

Conclusions: In this large cohort, adoption of WHO guidelines was associated with a shorter time to ART initiation for PLWH with TB in MZ and RW. However, as date of TB treatment initiation was not available, time from TB treatment initiation to ART initiation was not assessed. Further efforts are needed to more promptly initiate ART for eligible PLWH, particularly those with TB.

Time to ART initiation among PLWH with TB in Mozambique



Time to ART initiation among PLWH with TB in Rwanda

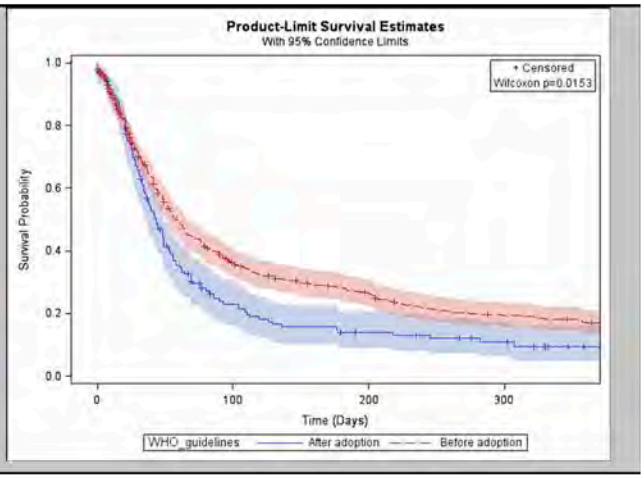


Table 1		
Median days to ART initiation (IQR)	Mozambique	Rwanda
Before 2010 WHO guidelines adoption in country	34 (17-83)	24 (14-45)
PLWH ART-eligible without TB	33 (17-76)	23 (14-42)
PLWH ART-eligible with TB	55 (23-209)	58 (25-205)
After 2010 WHO guidelines adoption in country	35 (19-67)	24 (14-45)
PLWH ART-eligible without TB	36 (20-68)	23 (13-43)
PLWH with TB	28 (15-59)	43 (23-86)

833 Antiretroviral Therapy Initiation and Tuberculosis (TB) Risk in the United States (US) and Canada

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Background: Among HIV-uninfected persons in the US, TB incidence is ~ 3/100,000 person-years (p-y). Previous studies of HIV-infected persons in the US have found rates of ~200/100,000 p-y while on highly active antiretroviral therapy (HAART) and >700/100,000 p-y while not on HAART. HAART decreases TB risk over the long-term, but TB incidence is high shortly following HAART initiation. Previous studies have not assessed TB risk before and after HAART initiation in the same large population of HIV-infected persons from the US and Canada, and therefore both the short- and long term effects of HAART on TB risk in this population.

Methodology: We conducted an observational cohort study among HIV-infected persons in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) from 1998 through 2011. Data were contributed by 11 cohorts and patients were included if they had $\geq$ 2 visits within 12 months. Person-time was contributed from enrollment in NA-ACCORD until first TB diagnosis, loss to follow-up, death, or administrative censoring. TB cases diagnosed after enrollment were included and were defined as culture-confirmed or culture-negative according to Centers for Disease Control and Prevention guidelines. TB diagnosis and diagnosis date were validated via standardized abstraction forms

Results: Among 29,660 HIV-infected patients (158,293 p-y of follow-up), 164 TB cases (102 culture-confirmed, 64 culture-negative) were diagnosed (104/100,000 p-y; 95% CI 88-121/100,000 p-y). Median follow-up was 4.1 years (IQR: 1.8-7.6 years). TB incidence varied according to time from HAART initiation (Table).

Conclusions: In this large North American cohort, TB incidence before HAART initiation was lower than previously described. Consistent with previous studies, TB incidence was highest during the first 6 months following HAART initiation. TB incidence declines after 6 months of HAART exposure, but still exceeds that of HIV-uninfected persons even after 4 years on HAART. This highlights the continued need for vigilance for TB among HIV-infected persons, particularly shortly following HAART initiation.

TB incidence according to time from HAART initiation				
Time Interval	TB cases	Person-Years of follow-up	TB incidence rate per 100,000 person years	95% Confidence Interval
Off HAART	108	72,028	150	123-181
HAART initiation-<3 months	14	5,063	277	151-464
>3 months-<6 months	15	4,746	316	177-521
>6 months-<9 months	5	4,373	114	37-267
>9 months-<1 year	2	4,341	46	6-166
>1 year-<2 years	5	14,529	34	11-80
>2 years-<3 years	5	11,784	42	14-99
3 years-<4 years	5	9,622	52	17-121
>4 years	5	31,806	16	5-37

Session P-R6 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Cryptococcal Disease

834 Prevalence of Cryptococcal Antigen Positivity Among AIDS Patients, United States From 1986-2012

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Background: Cryptococcal meningitis (CM) is the most common cause of AIDS-related mortality in sub-Saharan Africa. CM accounts for between 33% and 63% of all adult meningitis within that region and is responsible for over 500,000 deaths annually; more AIDS-related deaths than tuberculosis. In sub-Saharan Africa, the WHO recommends routinely screening AIDS patients with a CD4 T-cell count less than 100 cells/µl for cryptococcal infection and initiating anti-cryptococcal therapy to prevent CM. The prevalence at which routine cryptococcal infection was found to be cost-effective was 2%. In the United States however there are no such screening recommendations because there is a lack of prevalence data and thus no opportunity for a cost-effective analysis. We aimed to determine the prevalence of cryptococcal infection among advanced AIDS patients in the United States to guide potential updates in the prevention and management of CM.

Methodology: Using stored sera from the Multicenter AIDS Cohort Study and the Women's Interagency HIV Study, we screened specimens from 1,872 participants with CD4 T-cell counts less than 100 cell/µl for cryptococcal infection. We tested serum from participants using the CrAg Lateral Flow Assay (Immy, Inc. Norman, OK), a FDA-cleared test for the detection of cryptococcus antigen (CrAg).

Results: The overall prevalence of CrAg positivity within this population was 2.9% (CI: 0.2-3.8%). The table below describes the results of CrAg positivity by gender, geographical location, and time (pre -HAART and post-HAART). Due to restrictions in table length, Baltimore (3.0%,CI:1.5-6.0%), Chicago (2.3%, CI:0.8-6.8%), and Brooklyn (1.9%, CI:0.6-5.3%) were not included in the table below.

Conclusions: Presently, routine screening for cryptococcal infection is only recommended in AIDS patients with a CD4 less than 100 cell/ul in sub-Saharan Africa. The results from this study suggest the prevalence of cryptococcal infection in the United States is above published cost-effective threshold, varies regionally and may warrant routine screening to detect early infection.

CrAg positivity by gender, geographical location, and time	
Gender	Prevalence (CI)
Males	2.6% (1.7-3.8%)
Females	3.3% (2.3-4.7%)
Location	
Bronx	4.3% (2.2-8.4%)
Pittsburgh	4.2% (2.1-8.3%)
District of Columbia	4.0% (1.7-9.1%)
San Francisco	3.9% (1.5-9.5%)
Los Angeles	3.3% (2.1-5.2%)
Time	
Pre-HAART	3.1% (2.2-4.2%)
Post-HAART	2.8% (1.8-4.2)

835 High Prevalence of Undiagnosed *Cryptococcus* at HIV Diagnosis Across the CD4 Spectrum in Durban

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Background: Early detection and treatment of cryptococcal antigen (CrAg) may decrease morbidity and mortality from cryptococcal meningitis. Based on World Health Organization guidelines, South Africa recommends screening all HIV-infected people with CD4 <100/mm3 for CrAg. The prevalence of cryptococcal infections across varying CD4 counts has not been reported at initial HIV diagnosis. We sought to assess the prevalence of cryptococcal infections, stratified by CD4 count, among newly diagnosed HIV-infected adults attending outpatient clinics in Durban.

Methodology: We enrolled newly-diagnosed HIV-infected adults into a prospective study between October 2011 and January 2013. Participants were recruited from 4 outpatient sites offering HIV testing services, including an urban hospital, a peri-urban hospital, and 2 municipal peri-urban primary health clinics. Eligible participants were ≥18 years old, newly-diagnosed with HIV, not receiving antiretroviral therapy, and initially seeking outpatient care for a variety of complaints. Participants provided a urine specimen in a sterile container that was stored in a -20 °C freezer for later testing. We performed CrAg testing with the rapid CrAg lateral flow assay (Immy Inc., Norman, OK; estimated 98% sensitivity on urine specimens) according to the manufacturer's specifications. We assessed CrAg prevalence for a difference above/below CD4 100/mm3 (primary analysis), and above/below CD4 200/mm3 (secondary analysis).

Results: Among 773 participants, mean age was 34.4 years, and 41% were female. Overall CrAg prevalence was 10.1% (95% CI 8.0-12.2%), and was not significantly associated with age or gender. CD4 count was available for 660 (85%) participants; median CD4 count was 210/mm3 [Interquartile Range (IQR) 80-358/mm3]. Participants with CD4 >100/mm3 had an estimated CrAg prevalence of 9.9% (95% CI 7.2-12.6%), which was not significantly difference from those with CD4 ≤100/mm3 (8.7%; 95% CI 4.7-12.6%). Similarly, participants with CD4 >200/mm3 had an estimated CrAg prevalence of 14.7% (95% CI 10.5-19.0%), which was significantly higher than those with a CD4 ≤200/mm3 (7.5%; 95% CI 4.6-10.4%). Median CD4 count was 249/mm3 (IQR 83-445/mm3) among CrAg-positive participants, and 203/mm3 (IQR 80-352/mm3) among CrAg-negative participants.

Conclusions: Prevalence of cryptococcal infection at the time of HIV diagnosis is high in Durban. Our data suggest there is little difference in those designated as high risk versus low risk for cryptococcal infection using the current CD4 count screening criteria. Therefore, the screening recommendation should be reexamined as it misses many cryptococcus-infected people.

836 Monocyte Dysfunction Is Associated With 14-Day Mortality in Cryptococcal Meninigits

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Background: Cryptococcal meningitis (CM) remains a significant cause of death amongst individuals with HIV-1 infection. Immune correlates of protection are lacking. Animal and in vitro studies suggest macrophage and monocyte activation plays a key role in determining outcome from infection. This study examines the relationship between peripheral blood monocyte activation and clinical outcome in patients with HIV-1-associated CM.

Methodology: Patients with HIV-1-associated CM were recruited from hospitals in Cape Town. Initial anti-fungal therapy was IV amphotericin 1mg/kg and oral fluconazole 800mg per day. Monocyte sub-populations and their activation phenotype were characterized in whole blood at baseline using flow cytometry. Intracellular cytokine responses were assessed following 6-hour stimulation with lipopolysaccharide (LPS) and R848 (TLR7/8 agonist). Comparisons in baseline monocyte activation were made between subjects who survived to 14 days and those who died.

Results: 59 subjects were enrolled, median CD4 count was 34x106/ml and 14-day mortality was 24%. Compared to survivors (S), non-survivors (NS) had significantly lower expression of HLA-DR, and significantly higher expression of CD163, on CD14+CD16+ monocytes at baseline (mean HLA-DR MFI 7272 (S) vs 4197 (NS); mean CD163 MFI 10541 (S) vs 17420 (NS); p=0.007 and p=0.03 respectively). In addition, following LPS stimulation monocyte cytokine responses were impaired in non-survivors, with significantly fewer monocytes producing TNFα (26% (NS) vs 44% (S), p=0.002). However, there was no difference in monocyte responses following TLR7/8 stimulation (see table).

Conclusions: This study suggests impaired monocyte function may be an important factor determining poor outcome in cryptococcal disease. This may reflect overstimulation, and compensatory down-regulation, of inflammatory responses in circulating monocytes. Reversal of this defect may be a potential immune-based therapeutic strategy.

Differences in Baseline Immune Parameters in survivors and non-survivors			
	Survivor	Non-survivor	P value
CD4 (median, IQR)	29[11-85]	33[13-55]	0.72
HLADR MFI CD14+CD16+ Mo (mean, 95%CI)	7272 [6154-8390]	4197 [2340-5653]	0.007
CD163 MFI CD14+CD16+ Mo (mean, 95%CI)	10541 [7846-13237]	17420 [9240-25602]	0.03
%TNFα +ve Mo LPS stimulation (mean, 95%CI)	44%[39-50]	26% [15-37]	0.002
%TNFα +ve Mo R848 stimulation (mean, 95%CI)	68.1[60.0-76.3]	64.7[53.1-76.4]	0.66
CRP (median, IQR)	34.7 (12.73-67.33)	84.9 (39.3-119.8)	0.01

837 Serum Biomarkers Following Induction Therapy for Cryptococcal Meningitis Predict Survival

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Background: In the Cryptococcal Optimal ART Timing (COAT) trial, early ART initiation (7-13 days) after cryptococcal meningitis (CM) was associated with higher mortality compared with deferred (5 weeks) ART initiation. A significant proportion of deaths (70%, 49/70) occurred after completion of 14 days of amphotericin induction therapy. We hypothesized that serum biomarkers may enable risk stratification of short and long term mortality.

Methodology: 177 COAT subjects were randomized in Kampala and Mbarara, Uganda and Cape Town, South Africa. 156 participants survived to the end of amphotericin therapy of which 153 had 22 serum biomarkers profiled using ELISA or Luminex multiplex assay. We compared by logistic regression log2-transformed biomarkers versus 5 week survival (i.e. time of outpatient clinic registration) and 46 week survival, adjusting for randomized arm (early ART vs. deferred ART).

Results: Of 153 persons who survived 14 days after cryptococcal meningitis diagnosis, 121 (81%) survived for 5 weeks until time of outpatient clinic registration and 104 (68%) survived >1 year. Twelve serum biomarkers were associated with increased risk of mortality. Odds Ratio (OR) for mortality for each two-fold increase in serum biomarker is presented in the Table. Serum CRP was a consistent risk factor for short and long term mortality. Additionally, when CRP was measured at 21 days after diagnosis (2 weeks after randomization), CRP was associated with mortality between 3-5 weeks (OR 2.22 per 2-fold increase (95%CI: 1.35, 3.66, P=.0002) as well as mortality through one year (OR 1.45 per 2-fold increase, 95% CI: 1.08, 1.95; P=.01).

Biomarker (Serum)	5-week mortality OR (95% CI)	P-value	1 year mortality OR (95% CI)	P-value
G-CSF	1.31 (0.97, 1.75)	0.07	1.30 (1.02, 1.66)	0.03
GM-CSF	1.37 (1.13, 1.68)	0.002	1.24 (1.05, 1.46)	0.01
IFN-g	1.49 (1.10, 2.02)	0.01	1.18 (0.97, 1.44)	0.11
IL-10	1.29 (1.04, 1.59)	0.02	1.22 (1.02, 1.46)	0.03
IL-13	1.54 (1.09, 2.17)	0.01	1.21 (0.92, 1.58)	0.16
IL-17	1.21 (1.03, 1.43)	0.02	1.16 (1.02, 1.31)	0.02
IL-6	1.27 (1.04, 1.55)	0.02	1.24 (1.04, 1.46)	0.02
IL-8	1.23 (0.90, 1.69)	0.20	1.32 (1.01, 1.71)	0.04
IL-1b	1.60 (1.08, 2.36)	0.02	1.44 (1.05, 1.97)	0.02
MCP-1	1.25 (0.97, 1.60)	0.08	1.25 (1.01, 1.55)	0.04
CD14	2.43 (1.21, 4.85)	0.01	1.71 (0.98, 2.97)	0.06
CRP	1.84 (1.23, 2.77)	0.003	1.53 (1.12, 2.10)	0.008

Conclusions: Serum biomarkers at the end of amphotericin induction therapy may enable risk stratification of short and long term mortality, most notably including CRP, a commonly available routine lab test. Through risk stratification, close clinical follow up may be wise for individuals who have survived their initial cryptococcal meningitis but remain at high risk of death.

838 Cryptococcal Antigenemia in Severely Immunocompromised HIV Patients in Rural Tanzania

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Background: Cryptococcal meningitis is a leading cause of death in people living with HIV/AIDS in sub-Saharan Africa. To decrease cryptococcosis, WHO recommends pre-antiretroviral (ART) targeted cryptococcal antigen (CrAg) screening for persons with CD4 < 100 cells/μL. Aiming to explore the potential impact of this strategy in Tanzania, we assessed the prevalence, natural course, and outcome of cryptococcal antigenemia in a rural region of southern Tanzania.

Methodology: Retrospective study including all patients prospectively enrolled in the Kilombero and Ulanga Antiretroviral Cohort (KIULARCO) with a pre-ART visit between Jan 1, 2007 and Dec 31, 2012. Cryopreserved pre-ART plasma samples of ART-naive patients > 5 years-old and with CD4 < 150 cells/μL were tested for CrAg using lateral flow assay kits. Logistic regression was used to estimate the association between CrAg+ and a composite outcome of death or lost to follow-up (LFU) after one-year follow-up.

Results: Of 801 eligible patients, 29 (3.6%) were CrAg+, corresponding to 6.1% (18/293), 2.3% (6/263), and 2% (5/245) prevalence among patients with CD4 < 50, 51-100, and 101-150 cells/μL, respectively. ART was initiated in 686 (85.6%). Within one year, 72.4% (21/29) of CrAg+ patients died or were LFU compared with 47.2% (364/772) of CrAg-negative patients (p=0.008), with no differences across CD4 strata. After adjusting for age and gender, three independent predictors of death/LFU were identified: CrAg+ (odds ratio (OR) 3.2, 95% confidence interval (CI) 1.4-7.3, p=0.008), CD4 < 100 cells/μL (OR 1.6, 95% CI 1.1-2.2, p=0.006), and not having received ART (OR 7.7, 95% CI 4.5-13.2, p<0.001). The median pre-ART CrAg titre among CrAg+ patients was 1:320 (interquartile range 1:20, 1:2560). Cryptococcal meningitis was diagnosed in 34% (10/29) of CrAg+ patients, and the remainder (19/29) showed no pre-ART neurological symptoms, with similar outcome between both groups (70% vs. 74% death/LFU respectively, p=0.8).

Fluconazole given at physician discretion decreased the proportion of death/LFU among CrAg+ patients (80% without treatment, 60% with 100-200 mg daily, and none with 800 mg daily, p=0.012).

Conclusions: CrAg+ was prevalent and an independent predictor of death/LFU. Targeted pre-ART CrAg screening may decrease early ART-mortality in Tanzania. However, a threshold for CrAg screening at CD4 < 100 cells/μL, according to WHO recommendations, may exclude a substantial number of CrAg+ patients and decrease the potential impact of this strategy.

Session P-R7 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM Exhibit Hall D

OIs Other Than TB and Cryptococcal Disease

839 HSV-2 Serostatus Is Not Associated With Inflammatory or Metabolic Markers in ART-Treated HIV

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Background: Systemic inflammation and immune activation may persist in HIV-infected persons on suppressive antiretroviral therapy (ART) and contribute to adverse health outcomes. A randomized trial recently showed no impact of valacyclovir on inflammatory markers in this population, but the explanation for these negative findings is unclear. We compared markers of immune activation, inflammation, endothelial activation, and abnormal glucose and lipid metabolism in HIV-infected adults according to herpes simplex virus type 2 (HSV-2) serostatus.

Methodology: HIV-infected adults on suppressive (viral load <50 copies/mL) ART were categorized as HSV-2 seropositive or seronegative using the HerpeSelect ELISA (Focus), and underwent study visits at baseline, 3 and 6 months. The primary outcome was the median percentage of activated (CD38+HLADR+) CD8 T-cells. Secondary outcomes included additional immune (activated CD4, regulatory T-cells) and inflammatory (hsCRP, D-dimer, IL-1b, IL-6, MCP-1, TNF, sICAM-1, Ang1/Ang2 ratio) markers. Metabolic outcomes included the proportion with impaired fasting glucose/impaired glucose tolerance/diabetes, insulin sensitivity (Matsuda index), insulin resistance (HOMA-IR), and fasting lipids. The impact of HSV-2 on each outcome was estimated using generalized estimating equation regression models.

Results: Of 82 participants, 38 (45%) were HSV-2 seropositive. The HSV-2+ group included more black (32% vs 9%) and female (26% vs 2%) participants. Median (IQR) age, duration of HIV infection and baseline CD4 count were similar between groups, at 49 (43,53) years, 10 (7, 18) years and 466 (329, 622) cells/mm3, respectively. Most (60.7%) participants were current or former smokers. During the study, CD8 and CD4 T-cell activation declined by 0.16% and 0.08% per month respectively, while regulatory T-cells increased by 0.05% per month. However, HSV-2 serostatus was not associated with a difference in either the primary or secondary immune/inflammatory outcomes (Table; asterisks denote odds ratios of having detectable value), nor in metabolic outcomes, in univariate or multivariable models adjusted for time, sex, duration of HIV infection and baseline CD4 count.

Conclusions: HSV-2 serostatus was not associated with immune activation, inflammatory or lipid and glucose metabolic markers in this cohort of HIV-infected adults on suppressive ART. Whether differences might be seen in sub-populations of patients requires further study.

Associations between HSV2 serostatus and immune / inflammatory markers				
	Univariate HSV2 Estimate (95% CI)	p	Multivariable HSV2 Estimate (95% CI)	p
Immune Outcomes				
CD38 CD8	-0.02 (-1.33,1.29)	0.98	0.26 (-1.20,1.72)	0.72
CD38 CD4	0.00 (-0.47,0.47)	1.00	0.05 (-0.45,0.54)	0.85
CD25	0.09 (-0.41,0.58)	0.73	0.05 (-0.45,0.56)	0.84
Biomarker Outcomes				
hsCRP Log10	0.11 (-0.14,0.36)	0.40	0.06 (-0.17,0.30)	0.59
D-Dimer Log10	0.09 (-0.00,0.19)	0.05	0.08 (-0.01,0.18)	0.09
IL-1β*	1.05 (0.34,3.27)	0.94	0.99 (0.31,3.09)	0.98
IL-6*	1.19 (0.42,3.31)	0.75	1.21 (0.40,3.61)	0.74
MCP-1*	1.80 (0.82,3.95)	0.14	1.81 (0.79,4.13)	0.16
TNF*	1.04 (0.37,2.93)	0.94	1.18 (0.38,3.64)	0.77
sICAM Log10	0.04 (-0.04,0.12)	0.31	0.06 (-0.01,0.13)	0.09
Ang1/Ang2 Log10	0.13 (-0.12,0.37)	0.30	0.15 (-0.11,0.40)	0.26

840 Latent, Acute, or Neuro-Syphilis Does Not Increase HIV-1 Replication in Central Nervous System

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Background: Acute syphilis-infection was associated with blips, i.e. a timely limited HIV-1 virus load (VL)-increase, during otherwise suppressive antiretroviral therapy (ART), and the central nervous system (CNS) inflammation could be a virus reservoir. Purpose of this study was to explore if syphilis-co-infection leads to increased CNS-replication of HIV-1.

Methodology: Retrospective case-control study from a large German HIV-treatment unit, data were collected from 2005-2013; cerebrospinal fluid (CSF) was collected for various reasons in patients with or without neurological symptoms. Patients were eligible, if paired VL-results from simultaneous HIV-1 assessments in CSF and blood plasma were available, in addition to syphilis serology details, ART and clinical/demographic data; VL-ratio for CSF/blood was built for each patient. If TPPA-screening result was positive, further tests (VDRL, IgM, CSF/blood-antibody ratio) allowed patient grouping into latent, acute, or confirmed neuro-syphilis, enabling statistical evaluation of HIV-1 CNS-replication.

Results: 179 HIV-1 infected patients were evaluable: 123 control-patients with negative screening result, and 56 patients with positive TPPA; out of these, 18 had confirmed acute syphilis infection; among these, 10 had neuro-syphilis, as of CSF-evaluation result. In comparisons between syphilis seropositives-subgroups, each versus controls, no significant difference for HIV-1 VL was found in CSF, blood and CSF/blood-ratio.

Positive syphilis serology affected predominantly males (91.1%, vs. controls: 70.7%; p=0.005). Patients were older at first positive HIV-test (p<0.001) and still at time of CSF-collection (p=0.003). Comparing all syphilis seropositives with controls for antiretroviral therapy, the rate receiving it was similar (61.0% vs. 59.3%), but lower for those with acute syphilis infection (35.3%, p<0.05 vs. controls; see Table).

Conclusions: HIV-1 replication in CSF, blood, and CSF/blood VL-ratio was not higher and not significantly different between patient groups with syphilis seropositive status, confirmed acute, or neuro-infection, respectively, and syphilis seronegative controls. This unselected cross-section study from a large treatment cohort could not support the hypothesis of a CNS reservoir for HIV-1 throughout different stages of syphilis infection. Patient characteristics are reflecting a high proportion of HIV-late presenters among those with acute syphilis disease.

Results for HIV-1 infected patients with latent, acute and neuro-syphilis co-infection

	All patients (n=179)	Syphilis negative serology [SNS] (n=123)	Syphilis positive serology [SPS] (n=56)	p-value (SNS vs. SPS)	Acute Syphilis infection [ASI] (n=18)	p-value (SNS vs. ASI)	Neuro-Syphilis infection [NSI] (n=10)	p-vaue (SNS vs. NSI)
Gender: Males (%)	138 (77)	87 (71)	51	0.005	17 (94)	0.033	10 (100)	0.066
Mean age at Lumbal Puncture (LP) in years (y)	44.8	43.1	48.5	0.003	45.3	0.437	47.6	0.206
Patient's CDC-category at LP (A/B/C)	44/27/104	25/17/79	19/10/25	0.052	8/3/5	0.014	4/2/3	0.115
Mean age at 1st HIV+ test (y)	36.7	34.4	42.3	<0.001	36.7	0.545	39.4	0.276
Patients on Antiretroviral Therapy (%)	60.5	61.0	59.3	0.830	35.3	0.044	33.3	0.103
Primary HIV-transmission risk: Men having Sex with Men (%)	31.3	26.0	42.9	0.024	38.9	0.254	40	0.837
Primary HIV-transmission risk: Intravenous Drug User (%)	12.9	16.3	5.4	0.043	5.6	0.233	10	0.602
Median CD4 cell count (/µL) at LP	175	162	209	0.570	239	0.347	218	0.450
Median viral load (copies/mL) in Cerebro-Spinal Fluid	760	1018	340	0.137	585	0.502	650	0.456
Median viral load (copies/mL) in blood	2720	4970	2450	0.335	7620	0.886	7620	0.785
Median viral load-ratio CSF/blood	0.740	0.930	0.375	0.157	0.345	0.246	0.195	0.176

841 Early Impact of cART On the Risk of Herpes Zoster: Results From the FHDH-ANRS CO4

Sophie Grabar[1,2], Pierre Tattevin[3], Hana Selinger-Leneman[1], Arnaud de la Blanchardière[4], Christian Rabaud[5], David Rey[6], Vincent Daneluzzi[7], Samuel Ferret[8], Dominique Costagliola[1], Odile Launay[9]

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Background: Recent studies evidenced a decrease in HZ incidence in the cART era, although HZ has been associated with the emergence of immune reconstitution inflammatory syndrome (IRIS) in patients with late initiation of cART. However evidences are lacking on large longitudinal data on the early impact of cART initiation on the risk of HZ.

Methodology: From the FHDH-Anrs CO4 cohort, we selected patients followed during years 1992-2011, naïve of ART treatment, who either initiated a cART or remained untreated. Risk of HZ according to the duration of cART (0-6, ≥6 months) was studied with Poisson regression with patients untreated during years 1996-2011 as reference. Crude and relative risks (RR) adjusted for demographics and with or without adjustment for CD4 and HIV RNA were computed.

Results: Overall, 48616 patients initially ART-naive were included: 2654 incident HZ occurred at a median CD4 cells count of 366/mm^3 (iqr, 218-530). Of these, 1521 HZ occurred in patients on cART, of whom 379 (25%) during the first 6 months of cART. In cART naive patients, HZ incidence was 1305/10^5 PY prior 1996. After 1996, the incidence was 1617 /10^5 in the first 6 months of cART, was maximal at 3 months of cART (2413/10^5 PY) and declined to 1036/10^5 PY after 6 months of cART. The crude risk of HZ was elevated in the first 6 months of cART with a RRcrude of 1.50 (95%CI, 1.35-1.68), and markedly decreased after 6 months, with a RRcrude of 0.49 (95%CI, 0.45-0.53). Adjustments for current CD4 reduced the risk close to 1 (RR=0.97 95%CI, 0.86-1.09) in the first 6 months, but additional adjustment on HIV RNA showed a persistent moderate increase (RR=1.23 95%CI, 1.07-1.09). Higher risk of HZ was associated with low CD4 and high HIV RNA levels, low CD4/CD8 rate and prior AIDS and age.

Conclusions: The risk of HZ increases in the first months of cART initiation but only moderately while it sharply decreases after 6 months of cART. The overall decrease in incidence after cART is probably related to immune restoration and virological control.

842 Antigen-Presenting Cells Ingest Malaria Parasites and Cause an Increase in HIV-1 Replication

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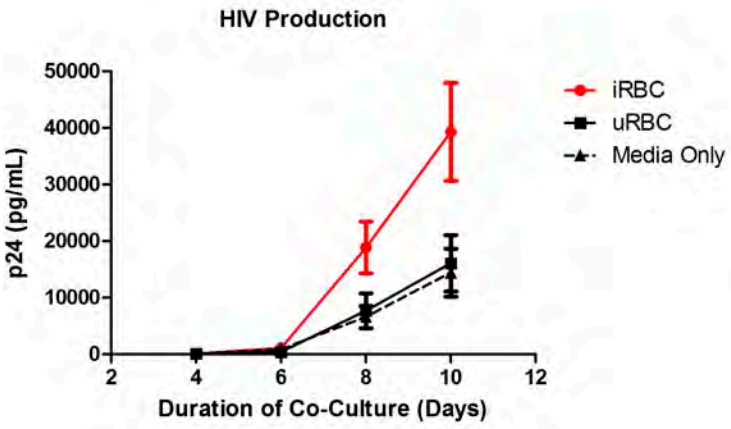
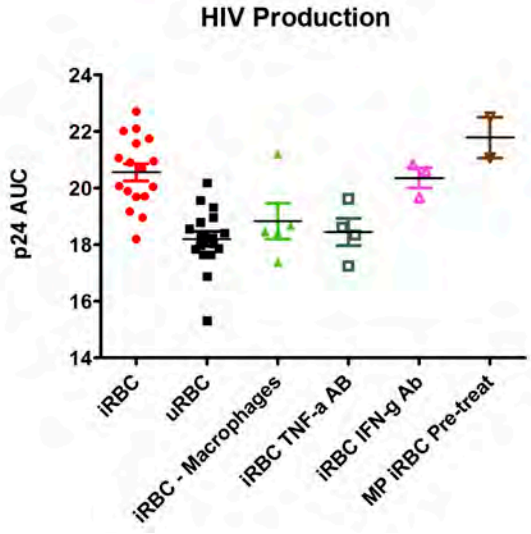
Background: An increasing body of evidence has demonstrated that bidirectional HIV-1/P. falciparum interactions enhance morbidity and mortality where both pathogens are endemic. Repeat bouts of malaria cause an increase in levels of HIV replication and accelerate CD4 cell decline. Increased levels of HIV-1 RNA persist well after parasites are cleared from peripheral blood following antimalarial therapy. The mechanisms contributing to this bi-directional interaction have not been fully elucidated.

Methodology: We developed a tissue culture system in which peripheral blood mononuclear cells (PBMCs) from healthy American donors were infected with HIV in vitro, and co-cultured with P. falciparum infected (iRBCs) or uninfected (uRBCs) red blood cells. HIV-1 production was assessed by quantifying HIV-1 p24 antigen by ELISA in culture supernatants 4, 6, 8 and 10 days after initiation of the co-cultures. In certain experiments T-cell subsets were affinity purified by depletion with antibody-coated magnetic beads. T-cell surface activation markers were assessed by flow cytometry after 24 or 48 hours. Cytokine concentrations were quantified in the supernatants using a multiplex ELISA.

Results: HIV replication increased in the presence of iRBCs compared to uRBCs (area under the curve comparisons 20.6 vs 18.2 respectively, p=0.0045) and was associated with increased CD4 activation as assessed by CD4 HLA-DR/CD38 double positive cells at 48 hours (p=0.001). Supernatants from these co-cultures showed increased production of TNF-α, INF-γ, MIP-1α, but not IL-6. Neutralizing antibodies to TNF-α but not IFN-γ decreased HIV production when TNF-α was neutralized (p=0.04) but not IFN-γ (p=0.37). Depletion of macrophages and dendritic cells reduced HIV production (p=0.0074). In one experiment, macrophages and dendritic cells that had been pre-incubated with iRBCs for 48 hours stimulated HIV production from PBMCs without the addition of iRBCs to the co-cultures. Hemozoin crystals were observed within the dendritic cells after co-cultivation with iRBCs.

Conclusions: iRBCs stimulate replication of HIV-1 by-activated CD4 cells in a TNF-α dependent manner following processing of malarial antigens by macrophages and dendritic cells. These results suggest that the persistent elevation of HIV-1 replication following treatment for acute bouts of P. falciparum malaria may be due, at least in part, to ongoing stimulation of CD4+ T cells by hemozoin loaded macrophages within lymphoid tissues.





843 Incidence of AIDS-Defining Opportunistic Illnesses (ADOIs) Among Patients in North America

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Background: It is not clear if the rates of AIDS-defining opportunistic illnesses (ADOIs) have continued to decline or have stabilized in the recent era of combination antiretroviral therapy (cART) and what ADOIs now occur among HIV-infected North American patients who are in care and have no history of clinical AIDS.

Methodology: We studied 63,088 HIV-infected patients followed in 14 participating cohorts in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) in the U.S. and Canada during 2000-2010. We excluded 13,784 (21.8%) patients who had any pre-existing ADOIs, and analyzed data for the remaining 49,304 patients regardless of their immunologic status. We calculated incidence rates per 100,000 person-years with 95% confidence intervals (CIs) based on Poisson distribution for the first occurrence of any ADOI, and for the first occurrence of select ADOIs thought to be well ascertained in the participating cohorts within three calendar periods: 2000-2003, 2004-2007, and 2008-2010.

Results: Of 49,304 patients analyzed (median [interquartile range] age at baseline = 40 [34-47] years, median CD4 at baseline = 370 [201-569] cells/mm^3), 76% were men, 38% were white, 42% were black, and 19% were injection drug users; 6% were Canadian. The 49,304 patients contributed 196,284 person-years of observation, of whom 7,310 (14.8%) developed at least one ADOI. The incidence rates of ADOIs fell over time (all p<0.001) (Table), coincident with increasing use of cART and improvements in CD4 cell counts and HIV viral load suppression in the population (all p<0.001). During 2008-2010, the leading ADOIs included *Pneumocystis jiroveci* pneumonia, esophageal candidiasis, Kaposi's sarcoma, and disseminated *Mycobacterium avium* complex or *Mycobacterium kansasii*.

Conclusions: We observed persistent reductions in incidence rates of ADOIs among HIV-infected patients in care during 2000-2010, which coincided with the improvements in viral suppression and immune status of the population. On average, among contemporary North American patients with no history of clinical AIDS, fewer than 3 in 100 develop any ADOI per year.

TABLE	Incidence rate per 100,000 person-years [No. of events], (95% CI for incidence rate)		
Calendar period	**2000-2003**	**2004-2007**	**2008-2010**
Total person-years of observation	59,927	77,313	59,044
Any first ADOI*	4515 [2706] (4348-4689)	3608 [2790] (3477-3744)	2752 [1625] (2621-2889)
Pneumocystis jiroveci pneumonia	1000 [602] (924-1083)	861 [668] (798-929)	413 [244] (364-468)
Candidiasis, esophageal	674 [351] (607-749)	692 [484] (633-757)	319 [175] (275-370)
Kaposi's sarcoma	373 [224] (328-426)	239 [185] (207-276)	213 [126] (179-254)
Mycobacterium avium complex or *M kansasii*, disseminated	403 [204] (352-463)	352 [238] (310-400)	211 [111] (176-254)
Non-Hodgkin's lymphoma	268 [161] (230-313)	205 [159] (176-240)	154 [91] (125-189)
Mycobacterium tuberculosis, pulmonary	208 [108] (172-251)	222 [155] (190-260)	86 [47] (64-114)
Cytomegalovirus retinitis	101 [52] (77-133)	51 [35] (37-71)	30 [16] (18-49)
Among all patients at risk			
Percentage of person-years on cART in period	77	80	85
Median CD4 cell count (cells/mm^3), mid-point of period	404	421	464
Percentage with plasma HIV RNA viral load < 500 copies/mL, mid-point of period	50	57	71

*Includes all ADOIs, except for HIV wasting, recurrent pneumonia, and recurrent salmonella septicemia (all poorly ascertained)

Session P-S1 Poster Session
Tuesday March 4, 2014, 2:30 PM–4:00 PM Exhibit Hall D

Reproductive Hormones in Women: Impact On Risk and Barrier Dysfunction

844 Depot-Medroxyprogesterone Acetate Does Not Increase Genital SHIV Shedding in Macaques

Jessica Radzio[1], Krisztina Hanley[2], Debra Hanson[1], James Mitchell[1], Leecresia Jenkins[1], Shanon Ellis[1], Frank Deyounks[1], Walid Heneine[1], J. Gerardo Garcia-Lerma[1]
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Background: Epidemiologic studies in women remain inconclusive on whether the injectable contraceptive DMPA increases mucosal HIV shedding and transmissibility. We recently identified a low 3 mg DMPA dose that suppresses ovulation in pigtail macaques and recapitulates plasma MPA exposure and changes in vaginal epithelial thickness seen in women. Here we used this dose to assess the impact of DMPA on acute SHIV viremia and genital virus shedding.

Methodology: Twelve female pigtail macaques were infected vaginally with $SHIV_{162p3}$ during their normal menstrual cycle (n = 6) or during monthly cycles with 3 mg of DMPA (n=6). Plasma progesterone and medroxyprogesterone acetate (MPA) concentrations were measured weekly. SHIV RNA was quantified in plasma, rectal, and vaginal secretions by RT-PCR. Secretions were collected in sponges and evaluated for hemoglobin content to correct for plasma-derived viruses originating from blood contamination. Peak plasma viral load and RNA area under the curve values ($AUC_{0\text{-}12wk}$) in DMPA-treated and untreated animals were compared using the Wilcoxon rank sum test. Viral shedding was compared using logistic regression with robust variances while controlling for temporal differences among macaques.

Results: Plasma MPA levels peaked 2-3 weeks after each dose, with mean concentrations (2.7 ng/mL; min, max = 1.4-4.8 ng/mL) that fell within the range seen in women receiving 150 mg of DMPA (2.5 ng/mL (range 1.6-3.3)). Progesterone was undetectable in plasma during all 4-week DMPA cycles. Peak plasma viremia was similar in DMPA-treated and untreated macaques ($6.7x10^6$ copies/mL and 1.4×10^6 copies/mL, respectively; p=0.94). RNA $AUC_{0\text{-}12wk}$ values were also similar among treated and untreated macaques (means 1.9×10^6 and 7.0×10^6 RNA copies*day/ml, respectively, p =0.94), although DMPA-treated macaques had higher odds of having virus being detected in plasma relative to controls (OR=6.6, p=0.022). Virus shedding did not differ for treated and untreated macaques in either rectal ($p = 0.72$) or vaginal ($p = 0.53$) secretions.

Conclusions: By using a pigtail macaque model that reproduces the effect of DMPA in women we observed little or no effect of DMPA treatment on acute SHIV viremias, genital, and rectal virus shedding. The lack of effect of DMPA on genital virus shedding does not support increased HIV transmissibility in women using DMPA and suggest non-biological explanations for the differences observed in some clinical and epidemiologic studies.

845 Dysregulation of Estradiol Signaling Contributes To Mucosal Barrier Dysfunction HIV+ Women

Sumathi Sankaran-Walters[1], Anne Fenton[1], Chris Gaulke[1], Lauren Nagy[1], Irina Grishina[1], Jason Flamm[2], Thomas Prindiville[3], Satya Dandekar[1]
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Background: HIV infection is a leading cause of death in women in Africa. HIV disease progression correlates with immune activation which is higher in women compared to men in both the blood and gut. Compromised mucosal integrity allows for increased microbial translocation in women which stimulates systemic immune activation. Estradiol improves epithelial integrity but its effects during HIV infection are unknown. The objective of this study was to identify the effects of HIV infection on estradiol signaling in the gut and its impact on gut epithelial integrity.

Methodology: HIV+ women (n=9) and men (n=12) and HIV- healthy age matched women (n=7) and men (n=7) men were enrolled following IRB approved protocols. Small intestine mucosal samples were obtained by upper GI endoscopy. We compared gene expression profiles in gut epithelium, using laser capture microdissection and gene expression arrays. Plasma levels of microbial products in participants were assayed by real-time PCR. Immunophenotypic analysis was performed using 12 color flow cytometry. The effect of estradiol replacement and HIV infection on epithelial integrity was assayed using 3-D in vitro culture systems.

Results: A greater proportion of HIV+ women on HAART had sustained levels of GALT CD4+T-cell activation (37.4% vs. 6.5%) and CD8+T-cell activation (42.7% vs. 12.52%) than men ($p<.05$) measured by the expression of the surface marker HLA-DR. HIV+ women with and without HAART had lower levels of estrogen receptor β in the jejunum compared to healthy age matched controls. Comparison of gene expression in isolated epithelial cells showed down-regulation of epithelial regeneration pathways and tight junction proteins postmenopausal women associated with an increase in epithelial inflammation compared to premenopausal HIV+ women and men on HAART. Indicators of microbial translocation, such as plasma LPS, and bacterial 16S rRNA, were increased in women compared to men on HAART.

Epithelial cells grown in the presence of βE2 had increased proliferation (up to 40% higher) in a dose-dependent manner. Epithelial integrity measured by the trans-epithelial resistance (TER) also decreased by 25% in the presence of SIV infection. Low basal levels of exogenous βE2 restored the TER and increased expression of the tight junction protein, ZO1

Conclusions: These data suggest that increased inflammation secondary to microbial translocation may explain why women, especially postmenopausal women, have sustained CD4+T-cell activation, despite effective control of viral replication. The decreased expression of ERβ may be a mechanism involved in this effect. Studies investigating the effects of HAART in women should focus on the role of hormones in the maintenance of mucosal integrity and health following menopause.

846 Hormonal Contraceptives Increase Innate Immune Effector Molecules in Cervicovaginal Secretions

Brandon L. Guthrie[1], Robert Y. Choi[2], Alison C. Roxby[2], Rose Bosire[3], Barbara Lohman-Payne[1,2], Taha Hirbod[4], Carey Farquhar[1,2], Kristina Broliden[4]
[1]Department of Global Health, University of Washington, Seattle, WA, United States, [2]Department of Medicine, University of Washington, Seattle, WA, United States, [3]Center for Public Health Research, Kenya Medical Research Institute, Nairobi, Kenya, [4]Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden

Background: Long acting injectable hormonal contraceptives, most commonly in the form of depot medroxyprogesterone acetate (DMPA), are inexpensive and easy to use, but may be linked to increased risk of HIV-1 acquisition. Cationic polypeptides are the principal effector molecules of the innate immune response in the vaginal mucosa, and higher levels of some polypeptides have been associated with increased risk of HIV infection. We hypothesize that DMPA modifies the innate immune response in the vaginal mucosal by increasing cationic polypeptides, contributing to the association between DMPA and HIV risk.

Methodology: We recruited HIV-1-exposed seronegative (HESN) women from HIV-discordant relationships and low-risk control women from concordant negative relationships in Nairobi, Kenya. Cervicovaginal lavage (CVL) samples were collected and enzyme-linked immunosorbent assays (ELISA) were used

to measure cationic polypeptide concentrations. Cervicovaginal IgA was assessed for HIV-1-neutralizing activity by a peripheral blood mononuclear cell-based assay using an HIV-1 clade A primary isolate.

Results: Among 160 HESN women and 73 low-risk control women, 169 (73%) reported not using hormonal contraception at enrollment, 41 (18%) used DMPA, 16 (7%) used an oral contraceptive, and 7 (3%) used an implantable form of hormonal contraception. There were no differences between HESN and control women in their levels of human neutrophil peptides 1-3 (HNP1-3) (p=0.445) or LL-37 (p=0.512). Combining HESN and low-risk control women, compared to women not using hormonal contraception, DMPA users had significantly higher mean levels of HNP1-3 (2.38 vs. 2.05 $\log_{10}$ ng/ml; p=0.024) and LL-37 (0.84 vs. 0.48 $\log_{10}$ ng/ml; p=0.026). These associations did not differ between HESN and control women (p=0.639). DMPA use was not associated with levels of secretory leukocyte protease inhibitor (SLPI) (p=0.776).

Conclusions: We found that HNP1-3 and LL-37 cationic polypeptides were elevated in the CVL fluid of HIV-1 seronegative women using DMPA, regardless of HIV-1 exposure. While these polypeptides have intrinsic antiviral capacity, they are also potent recruiters of target cells for HIV infection. As a result, higher levels of HNP1-3 and LL-37 have been associated with increased HIV infection risk. A potential mechanism for the risk associated with injectable hormonal contraceptive use may be through upregulation of these polypeptides in the vaginal mucosa, resulting in recruitment of dendritic cells that are susceptible to HIV infection. This may provide independent evidence supporting a biological mechanism for increased HIV acquisition seen with DMPA.

847 Injectable Contraception and HIV Acquisition in the VOICE Study (MTN-003)

Lisa M. Noguchi[1,2], Barbra Richardson[3], Z. Mike Chirenje[4], Gita Ramjee[5], Gonasagrie Nair[6], Thesla Palanee[7], Pearl Selepe[8], Ravindre Panchia[9], Kailazarid Gomez[10], Jeanne Marrazzo[11], on behalf of the VOICE Study Team

[1]Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States, [2]Microbicide Trials Network, Pittsburgh, PA, United States, [3]SCHARP, Seattle, WA, United States, [4]UZ-UCSF, Harare, Zimbabwe, [5]MRC, Durban, South Africa, [6]CAPRISA, Durban, South Africa, [7]WITS Reproductive Health and HIV Institute, Johannesburg, South Africa, [8]Aurum Institute, Klerksdorp, South Africa, [9]PHRU, Soweto, South Africa, [10]FHI 360, Durham, NC, United States, [11]University of Washington, Seattle, WA, United States

Background: Injectable contraception constitutes a large proportion of modern contraceptive use globally. Several observational studies have reported an increased risk of HIV acquisition among women using depot medroxyprogesterone acetate (DMPA) compared to women using non-hormonal methods. Previous analyses have used a comparator group not on hormonal contraception (HC), and few have disaggregated use of norethisterone enanthate (NET-EN), another commonly used injectable method in South Africa.

Methodology: MTN-003 was a multi-site, randomized trial of oral and topical tenofovir-based HIV chemoprevention in women. Participants using effective contraception (HC, intrauterine device or sterilization) were eligible for enrollment. Contraceptive use and pregnancy and HIV status were assessed monthly during follow-up. Using a Cox proportional hazards model stratified by study site and censoring for pregnancy, we directly compared rates of HIV acquisition between women using DMPA and those using NET-EN at 11 South African MTN-003 sites.

Results: Among 4,077 participants, 3,167 women used injectable contraception during the study, of which 1,801 (56.9%) exclusively used DMPA, 1,109 (35.0%) exclusively used NET-EN and 257 (8.1%) used both DMPA and NET-EN during follow-up. Although DMPA and NET-EN users had similar rates of sexually transmitted infection at baseline, compared to NET-EN users, DMPA users were more likely to be over 25 (55.7% vs. 48.4%; p<0.001), married (5.7% vs. 3.7%; p<0.04) and have ≥ one child (93.5% vs. 69.8%; p<0.001). Distribution of injectable method types and HIV incidence differed by site (proportion of DMPA, 26.9% to 73.4%; HIV incidence, 1.7 to 9.3/100 person-years [p-yrs]). Among users of injectable contraception, 246 acquired HIV for an overall rate of 6.6 events/100 p-yrs. Rates of HIV-1 acquisition among women currently using DMPA and NET-EN during follow-up were 7.86 and 5.34/100 p-yrs, respectively (unadjusted hazard ratio [HR] 1.31, 95% CI 0.96 to 1.79, p=0.092; adjusted for age and marriage [aHR] 1.44, 95% CI 1.05 to 1.98, p=0.024). Restricting analysis to women under 25 found a similar but non-significant estimate (aHR 1.55, 95% CI 0.99 to 2.32, p=0.055).

Conclusions: Among women willing to use effective contraception while participating in an HIV prevention trial, there was an increased risk of HIV acquisition among women currently using DMPA compared to those using NET-EN. However, lack of a non-HC comparator group prevents estimation of risk associated with either method compared to non-use. Site differences in distribution of methods and HIV incidence may have impacted these results. Our findings support current WHO recommendations that women using injectable progestin contraception should be advised to use condoms.

Session P-S2 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

HIV in Women: Pregnancy, Progression, Pap, and Bones

848 Rapid Disease Progression in HIV-1 Subtype C Infected South African Women

Nigel J. Garrett[1], Lise Werner[1], Koleka Mlisana[1,2], Lyle McKinnon[1], Francois van Loggerenberg[1,3], Thumbi Ndung'u[4], Clive Gray[5], Lynn Morris[6], Carolyn Williamson[5], Salim Abdool Karim[1,7]

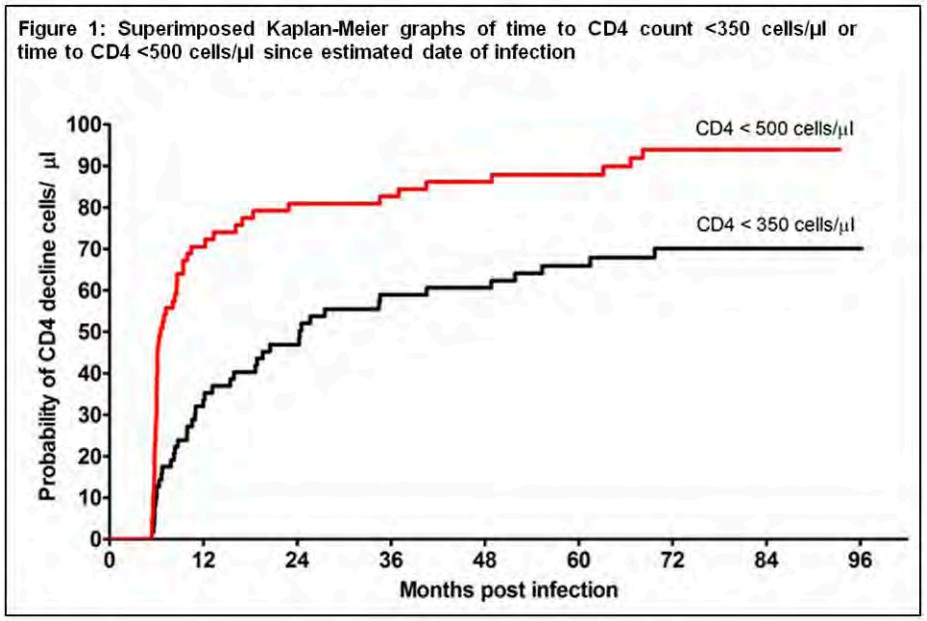
[1]CAPRISA, Durban, South Africa, [2]Department of Medical Microbiology, University of KwaZulu-Natal, South Africa, [3]The Global Health Network, University of Oxford, United Kingdom, [4]HIV Pathogenesis Programme, Durban, South Africa, [5]Institute of Infectious Diseases and Molecular Medicine, Cape Town, South Africa, [6]Centre for HIV and STIs, Johannesburg, South Africa, [7]University of Columbia, New York City, NY, United States

Background: While disease progression to AIDS has been estimated as approximately 10 years in HIV clade B infected cohorts, limited data exists from South Africa. An accurate description of the disease progression spectrum has important policy implications for the provision of antiretroviral therapy (ART). This study examines risk factors for rapid progression in a cohort of women followed from acute clade C infection and establishes proportions of women requiring ART at CD4 thresholds of <350 or <500 cells/µl.

Methodology: HIV uninfected women from seroincidence cohorts (n=839) at two sites in KwaZulu Natal (KZN) were assessed for acute HIV infection monthly (n=245) or 3 monthly (n=594) for up to 4 years. Those diagnosed with acute infection by HIV antibody (Ab) and PCR tests were followed prospectively. Rapid disease progression was defined as reaching a CD4 count of <350 or <500 cells/µl by 2 years post infection. Serial clinical and laboratory assessments were compared using survival analysis and logistic regression.

Results: Sixty-two women, median age 25 (IQR 21-33), were identified at median 42 days post infection (IQR 34-59), and contributed 282 women years of follow up. CD4 decline was rapid, with 31%, 44%, and 55% reaching <350 cells/µl at 1, 2 and 3 years post infection. This decline was even more dramatic using the <500 cells/µl cut-off, with 69%, 79% and 81% reaching this endpoint during the same timeframe (Figure 1). Multivariate predictors of progression to CD4 count <350 at 3 months post infection were CD4 count [adjusted hazard ratio (aHR) 1.96 per 100 cells; 95% CI 1.22-3.15; p=0.006] and viral load (aHR 3.79 per log10 copies; 95% CI 1.38-10.37; p=0.010), prevalent hepatitis B core Ab positivity (aHR 4.58; 95% CI 1.14-18.35; p=0.032) and presence of protective HLA-B type alleles (aHR 0.18; 95% CI 0.05-0.73; p=0.016). Three women with incident hepatitis B infection all progressed rapidly.

Figure 1: Superimposed Kaplan-Meier graphs of time to CD4 count <350 cells/µl or time to CD4 <500 cells/µl since estimated date of infection



Conclusions: Rapid HIV disease progression is common among clade C infected women from KZN, South Africa, and could be predicted in early infection. Based on this study, the majority of women would qualify for ART if the CD4 threshold was increased to 500 cells/µl as per WHO guidelines. Given the high HIV incidence in KZN, the dual benefit of earlier ART to reduce transmission and improve individual health in a setting where rapid progression is the 'norm' provides a strong rationale for achieving greater ART coverage.

849 Pregnancy Intentions Among HIV-Infected Women Seeking Antenatal Care in Cape Town, South Africa

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Background: Unintended pregnancies in HIV-infected women present an ongoing challenge to prevention of mother-to-child HIV transmission efforts, but data are mixed on whether use of antiretroviral therapy (ART) enhances women's pregnancy intentions.

Methodology: We conducted a cross-sectional survey of consecutive HIV-infected women making their first antenatal care visit at a large primary care clinic in Gugulethu, Cape Town (antenatal HIV seroprevalence, 26%). A structured questionnaire was used to collect demographic and medical history; pregnancy intentions were assessed using the London Measure of Unplanned Pregnancy. Analyses compared three groups of women: those newly diagnosed with HIV on the day of the interview, those known to be HIV-infected but not using ART at the time of the interview, and those using ART prior to conception.

Results: Between April and September 2013, 592 HIV-infected women were interviewed (median age, 29 years): 35% of women were newly diagnosed with HIV (n=207), 31% had known HIV-infection but were not on ART (n=182) and 35% were on ART (n=203). Among women on ART, the median duration of ART use was 2.8 years (IQR, 1.4-5.2). Women who were newly diagnosed were younger and had a lower gravidity than women known to be HIV-infected, including those already on ART (p<0.001). The current pregnancy was significantly more likely to be reported as unintended by women who were newly diagnosed (57%) or known HIV-infected but not using ART (61%) compared to women already on ART (43%; global p-value, 0.007); this association was not confounded by demographic or socioeconomic measures (odds ratio from multiple logistic regression, 2.50; 95% CI: 1.61-3.86). Women on ART were also more likely to report discussing pregnancy with their partner and attempting to improve their own health before conception (p=0.003 and 0.024, respectively). In the subset of women on ART, there was no association between duration of ART use and pregnancy intention (p=0.077). Among women who reported an unintended pregnancy, 27% reported use of family planning at the time of conception.

Conclusions: Levels of unintended pregnancy in HIV-infected women are high overall, and there is a clear need for strengthened family planning services for HIV-infected women in this setting. Here, women on ART are more than twice as likely to plan their pregnancies as HIV-infected women not on ART, pointing to the impact of ART initiation on pregnancy intentions in this setting.

Table 1. Socio-demographic characteristics and measures of pregnancy intentions among 592 HIV-infected women making their 1st antenatal clinic visit in Cape Town, South Africa, by knowledge of HIV status / current ART use. All cells are N(%) unless otherwise specified.

	Newly diagnosed with HIV (n=207)	*Known HIV-infected, not on ART* (n=182)	*Known HIV-infected, on ART* (n=203)	p-value	*Overall* (N=592)
Age median (IQR)	26 (23-30)	30 (26-33)	31 (28-34)	0.0001	29 (25-33)
Gravidity median (IQR)	2 (1-3)	3 (2-3)	3 (2-3)	0.0001	2 (2-3)
Married/cohabiting	84 (41)	81 (45)	98 (48)	0.296	263 (44)
Relationship duration in years median (IQR)	3 (1.6-5)	3 (2-7)	4 (2-8)	0.0002	3 (2-6)
Used a family planning method in the month they became pregnant	36 (17)	30 (16)	58 (29)	0.005	124 (21)
Pregnancy timing				0.011	
Right time	75 (36)	69 (38)	105 (52)		249 (42)
Ok, not quite the right time	81 (39)	63 (35)	54 (27)		198 (33)
Wrong time	51 (25)	50 (27)	44 (22)		145 (25)
Pregnancy intention				0.007	
Intended	77 (37)	64 (35)	101 (50)		242 (41)
Changing intentions	12 (6)	7 (4)	14 (7)		33 (6)
Not intended	118 (57)	111 (61)	88 (43)		317(53)
Discussed becoming pregnant with partner	83 (40)	61 (34)	102 (50)	0.003	246 (42)
Attempted to improve own health before becoming pregnant	15 (7)	19 (10)	32 (16)	0.024	66 (11)

850 Effect of Antiretroviral Regimens On Bone Mineral Density of HIV Infected Lactating Ugandan Women

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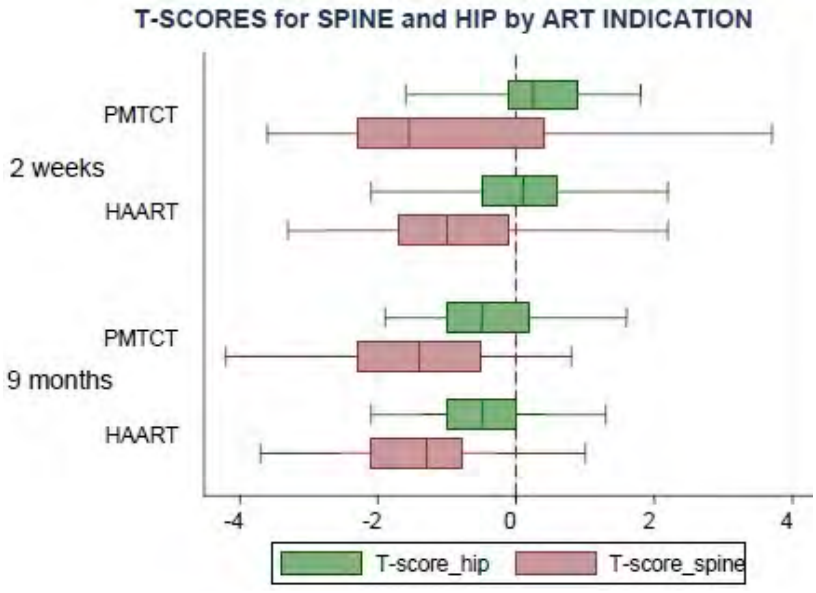
Background: During lactation, bone density (BD) decreases on average about 1% - 3% per month during and returns to prior levels after lactation stops. Among HIV infected individuals, ART may also cause serial decrements in BD over time. Thus, there could be potential synergistic effects among HIV infected women on ART who are also lactating, which could lead to accelerated decreases in BD during the breastfeeding period. Given the dearth of BD data in African populations, we evaluated BD measurements among postpartum HIV infected lactating women receiving ART.

Methodology: From February 2012 - October 2013, we studied BD measurements among lactating HIV infected postpartum women in Kampala, Uganda. Based on evolving prevention of mother-to-child transmission (PMTCT) of HIV/AIDS guidelines in Uganda, women received either zidovudine (ZDV) during pregnancy for PMTCT of HIV/AIDS followed by nevirapine prophylaxis to the infant (Option A) or highly active ART (HAART) for their health. From October 2012, lifelong ART was offered to all pregnant or breastfeeding HIV infected women regardless of CD4 count (Option B+). BD measurements using Dual Energy X-ray Absorptiometry were taken at 2 weeks and 9 months postpartum.



Results: 218 HIV infected lactating women were enrolled at delivery and followed through 9 months post partum: 57 initiated Option A and 161 received Option B+ or HAART. Overall, median T-score for the spine at 2 weeks was -1.05 and at 9 months declined to -1.35 (p=0.0007). Median T-score for the hip at 2 weeks was 0.1 and at 9 months declined to -0.5 (p=0.0001). The median T-score of the spine in women who received Option A at 2 weeks

was -1.55 compared with -1.00 in Option B+/HAART recipients (p=0.42). Median T-score of the hip in Option A recipients at 2 weeks was 0.25 compared with 0.1 in Option B+/HAART recipients (p=0.13). At 9 months, the median T-score of the spine in Option A recipients was -1.4 compared with -1.3 in Option B+/HAART recipients (p=0.84). Median T-score of the hip in Option A recipients at 9 months was -0.5: the same in Option B+/HAART recipients.

Conclusions: Significant decrements in BD were observed over 9 months post delivery in HIV infected and lactating women who received ART either for PMTCT or HAART. However, there were no significant differences in the reduction of BD among women who received antenatal ZDV (Option A) compared to women who received ART (Option B+/HAART).

851 Visual Inspection With Acetic Acid Is Good for Follow-Up After Cryotherapy in HIV-Infected Women

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Background: As See and Treat programs using VIA and cryotherapy gain popularity, knowing the appropriate follow-up is critical. Few studies have addressed the optimal follow-up for HIV-infected women after VIA and immediate cryotherapy. This study seeks to identify the optimal follow-up test to accurately detect persistent moderate/severe cervical dysplasia and cancer in HIV-infected women who participated in a See and Treat program consisting of VIA, digital cervicography and immediate cryotherapy.

Methodology: We present preliminary data from 407 HIV-infected women who were evaluated with repeat VIA, conventional Pap smear, and High Risk HPV testing (hc2HPV DNA test) ≥ 6 months following VIA and immediate cryotherapy. Women who had abnormal testing on VIA, Pap smear (LSIL or worse), or HR HPV were scheduled for colposcopy and biopsy. Accuracy in detecting CIN II or worse was compared among these tests among 165 women with biopsy results.

Results: Median age was 35 yrs, 66% were WHO stage 1-2, median CD4 count was 410, 88% were on combination antiretroviral therapy. VIA agreed perfectly with both Pap and HR HPV tests in 154 women (38%; 95% CI=33-43%), or agreed with at least one of the two tests in 358 women (88%; CI=84-91%). VIA agreed with Pap and HR HPV testing in 73% (CI=69-78%) and 52% (CI=47-57%) of women, respectively. VIA had higher sensitivity (P=0.26) than Pap smear, lower sensitivity than HR HPV (P<0.01). VIA had lower specificity than Pap smear (P=0.23) but much higher specificity than HR HPV (P=<0.01). Positive predictive value was 30.4%, 40.7% and 33.8%, for VIA, Pap smear, HR HPV, respectively (n=165).

We found that the disease negative rate after VIA and cryotherapy (negative VIA, normal Pap smear, negative HR HPV) at ≥ 6 months was 35% (CI=31-40%). Only 2.5% (CI=1.2-4.5%) had persistently abnormal testing on all 3 tests. A significant proportion (65%) continued to have at least one abnormal test.

Conclusions: Follow-up with VIA agrees reasonably well with Pap smear and HR HPV tests. The disease negative rate after VIA and immediate cryotherapy (35%) among HIV-infected women in our study is less than previously reported for non-infected women (85-88%).

Results of VIA, Pap and HR HPV	
VIA/Pap/HR HPV	Number (%)
–/–/–	144 (35%)
–/–/+	142 (35%)
–/+/–	20 (4.9%)
–/+/+	27 (6.6%)
+/–/–	22 (5.4%)
+/–/+	39 (9.6%)
+/+/–	3 (0.7%)
+/+/+	10 (2.5%)
Total	407

Session P-S3 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Immune Mediators and Immune Activation in Women

852 HIV Inhibition and Variation in Anti-Microbial Peptides Associated With Intercourse

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Background: Anti-microbial peptides (AMP) in vaginal fluid play a key role in vaginal mucosal immunity but dynamic effects have not been documented. Since penile-vaginal intercourse (PVI) is an important HIV transmission route, variation in AMP levels could affect HIV inhibition and likelihood of infection. This study documents levels of several AMPs - trappin, human beta-defensin 2 (HBD2), lactoferrin, secretory leukocyte protease inhibitor (SLPI), and lysozyme - at the time of PVI (compared to a neutral control for time levels) and assesses effects on *in-vitro* HIV inhibition.

Methodology: 40 healthy women ages 18-39 years wore a vaginal tampon for 1 hour pre-PVI and again beginning 15 minutes after condom-protected PVI or during 1 hour of quiet time with a partner (without physical contact.) Tampons were frozen in 1 ml of PBS at the subjects' homes until processing. Vaginal AMP levels were assessed by commercially available ELISA assays and normalized to total protein to control for inter-sample dilutional variation. HIV-1 BaL was incubated in 10% vaginal fluid (PVI or quiet time) and used to infect TZM-bl indicator cells. Infectivity was measured by luciferase activity and % HIV inhibition calculated by normalizing to the activity in untreated controls. A random-effects logistic regression model was used to control for multiple within-person comparisons.

Results: Mean trappin levels were significantly greater at the time of PVI (1.99 mg/mg protein) versus quiet time (0.47 mg/mg protein; p=0.01) while mean levels of HBD2 (PVI = 136.36 ng/mg protein; quiet time = 265.16 ng/mg protein; p=0.04) and lactoferrin (PVI = 2.34 mg/mg protein; quiet time = 4.89 mg/mg protein; p=0.02) were significantly lower. Levels of SLPI and lysozyme did not significantly differ during PVI and quiet time. Controlling for PVI and menstrual phase, multivariable logistic regression showed that % HIV inhibition increased significantly with increased levels of HBD2 and lysozyme (p<0.001 and p=0.016, respectively).

Conclusions: PVI is associated with reductions in some vaginal AMP and these changes are associated with decreases in *in-vitro* HIV inhibition. These data describe a potential role for intercourse-associated changes in vaginal mucosal immunity that has implications for understanding of HIV infection as well as topical HIV prevention products such as microbicides.

853 Sex-Related Inflammatory Marker Changes Pre- and Post-ART Initiation

Jyoti S. Mathad[1], Nikhil Gupte[2], Ashwin Balagopal[2], David Asmuth[3], James Hakim[4], Nagalingeswaran Kumarasamy[5], Thomas Campbell[6], Judith S. Currier[7], Susan E. Cohn[8], Amita Gupta[2], for the NWCS319 and ACTG 5175 PEARLS Study Teams

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Background: Immune activation and inflammation are associated with HIV disease progression and death. Women, on average, have lower plasma HIV RNA (VL) early in infection but progress to AIDS at the same rate as men. Sex-specific differences in immune activation/inflammation pre- and post-ART initiation could explain these observed clinical differences, but this has not been well studied.

Methodology: Inflammatory/immune activation markers (IFN-γ, TNF-α, IL-6, IL-18, IP-10, CRP, LPS, sCD14, EndoCAb IgM, activated CD4/CD8) were measured pre-ART and at week 24 and 48 post-ART on a random sub-cohort from ACTG A5175 (PEARLS) comparing 3 ART regimens in 9 countries. Only those virologically suppressed on ART were included. We did a within-sex comparison of median marker levels between week 48 and baseline. Percent detection was used for LPS as many had no detectable LPS. To understand if women had more or less change in markers over time vs men, we performed multivariable longitudinal random effects modeling adjusting for age, country, BMI, baseline CD4, log10 VL, hemoglobin (Hb) and randomized ART arm.

Results: Samples were available for 125 men and 121 women. Women were younger (33 vs 36 years, p=0.01) and included more black subjects (64% vs 43%, p<0.001). At baseline pre-ART, women had higher median CD4 counts (195 vs 165 cells/mm3, p=0.01) and lower median VL (4.9 vs 5.1 log10 copies/mL, p=0.01) and Hb (11 vs 13 g/dL, p<0.001) than men. Women also had lower median CRP (2.1 vs 4.8 mg/L, p=0.002), percent detectable LPS (36% vs 53%, p=0.01), median sCD14 (1.8 vs 2.3 log10 pg/mL, p=0.009), and higher median EndoCAb (52 vs 45 MMU/mL, p=0.04) than men. At week 48, women had higher median IFN-γ (21 vs 13 pg/mL, p=0.04) compared to men.

Compared to baseline, men had lower levels of all inflammatory markers at week 48, except percent detectable LPS. Women also had decreases in TNF-α, IL-18 and IP-10, but had no change in IFN-γ, IL-6, and increased percent detectable LPS. In multivariate longitudinal analyses of changes over 48 weeks, women on average had a greater slope change in CD4 of 40 cells/mm3 (CI: 17-63, p=0.001), TNF-α of 3.3 ng/mL (CI: 0.16-6.5, p=0.04), but less of change in VL (0.31 log copies/mL, CI: 0.11-0.52, p=0.003), CRP (8 mg/L, CI: 2.4-13, p=0.005) and log10 sCD14 (3.8 log10 ng/mL, CI: 1.8-5.8, p<0.001) as compared to men.

Conclusions: Before ART, women had a more favorable immune profile with significantly higher CD4 and lower VL, CRP, detectable LPS and sCD14 than men. With ART, though, men experienced more of a decrease in inflammatory markers than women, erasing women's initial advantage. This difference in response may explain why women progress to AIDS with lower viral loads. Further studies should investigate sex-specific differences in immune activation/inflammation pathways.

854 Influence of RAL vs Boosted ATZ-based Regimens On Cervical Immune Reconstitution and Activation

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Background: A significant amount of HIV-related morbidity has been attributable to genital tract disease in women. It is established that tenofovir (TDF), emtricitabine (FTC), and raltegravir (RAL) have high genital concentrations while atazanavir/ritonavir (ATZ) has more modest levels. We examine if RAL vs ATZ-based regimen is superior with respect to improved cervical immune reconstitution and less immune activation in HIV+ women.

Methodology: Peripheral blood (PB), cervical brush and lavage fluid (CVL), and cervical biopsies were collected from HIV+ women receiving TDF/FTC and either ATZ (n=19) or RAL (n=14). A history of CD4+ T-cells/mm3 (CD4) >= 300, and HIV RNA <48 copies/mL for a minimum of 6 months was required for entry. Cervical cells were analyzed by flow cytometry to determine %HLA-DR+CD38+(DR+38+) on CD4+ and CD8+T-cells. Sections of cervical biopsies were stained by immunohistochemistry and frequencies of CD3+CD4+, and CD3+CD8+cells per mm2 of tissue were determined using quantitative image analysis. RAL and ATZ trough concentrations in plasma and CVL were quantified with validated assays. T-tests, Fisher's exact and linear regressions were used with log transformations as appropriate. Data are expressed as means or geometric means (CI).

Results: RAL and ATZ groups did not differ by age (46 vs 43 years, p=0.5), race (p=1.0), CD4 nadir (309 vs 340, p=0.65), current CD4 (663 vs 758, p=0.4) or PB CD4:CD8 ratio (1.0 (0.84, 1.18) vs 1.03 (0.78, 1.37), p=0.8). Years since HIV diagnosis and years on current ARV was significantly lower in women taking RAL vs ATZ (8 vs 13; p=0.03 and 2 vs 5; p=0.01, respectively). Plasma RAL vs ATZ levels were 121 (44, 335) vs 620 (419, 918) ng/

mL. CVL levels for RAL vs ATZ were 9 (4, 23) vs 4 (2, 8) ng/mL. Genital:plasma (G:P) concentration ratio was significantly higher for RAL (0.078 (0.034, 0.18)) vs ATZ (0.006 (0.004,0.011), p<0.001). Drug concentrations in plasma correlated with those in CVL (RAL ρ=0.63, p=0.02; ATZ ρ=0.54, p=0.03). RAL and ATZ groups did not differ by cervical %DR+38+CD4+T-cells (20 vs 16%, 0=0.4) or %DR+38+CD8+T-cells (23 vs 21%, p=0.7). Cervical CD4:CD8 T-cell ratio in RAL group 0.46 (0.33, 0.63) was not significantly different than ATZ group (0.52 (0.36, 0.74); p=0.6). In HIV- women, the CD4:CD8 T-cell ratio has been reported as 4:1. CD4:CD8 T-cell ratio was significantly higher in PB than cervical tissue in both groups (p<0.001). After adjusting for time on ARV, log(G:P drug ratio) was not a significant predictor of cervical CD4:CD8+ T-cell ratio or immune activation (p>= 0.2).

Conclusions: Low cervical tissue CD4:CD8 ratio persists after years of ARV. Despite higher genital concentrations of RAL compared to ATZ, there was no significant difference in cervical CD4:CD8 ratio or immune activation between women on these regimens.

Session P-S4 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Immune Response To Vaccination in HIV+ Women

855 AMC 054: Safety and Immunogenicity of the Quadrivalent HPV Vaccine in Indian HIV-Infected Women

Joel Palefsky[1], Selvamuthu Poongulali[2], Shelly Lensing[3], Jeannette Lee[3], Maria Da Costa[1], Arumugham Jeeva[2], Syed Iqbal[2], Nagalingeswaran Kumarasamy[2]
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Background: India has a high incidence of cervical cancer. HIV-infected Indian women may be at even higher risk than HIV-uninfected women. Quadrivalent HPV (qHPV) vaccination is effective in prevention of cervical cancer precursors due to HPV 6/11/16/18 in HIV-uninfected women. Little is known about safety and immunogenicity of qHPV in HIV-infected Indian women. Since the qHPV vaccine only prevents initial HPV infection, a high rate of prior exposure would render vaccination less effective. We performed a safety and immunogenicity study of the qHPV vaccine in Indian HIV-infected women. We also measured seropositivity to qHPV types and cervical HPV DNA positivity prior to vaccination.

Methodology: 150 HIV-infected women were enrolled at YRGCare Medical Centre, Chennai, India. At baseline we obtained CD4 level, HIV viral load, cervical cytology, colposcopy, HPV DNA and serology. HPV DNA was detected using MY09/11 primer PCR. Serologic geometric mean titers to HPV 6/11/16/18 were measured using a competitive Luminex immunoassay. Women were enrolled in one of 3 groups: Group 1: CD4 nadir ≤350 cells/mm3, on HAART, Group 2: CD4 nadir >350, current CD4 350-500, not on HAART, and Group 3: CD4 nadir >350, current CD4 >500, not on HAART. The qHPV vaccine was given at 0, 2 and 6 months. Serology was obtained at weeks 0, 28 and 52. Data on adverse events were collected at each visit.

Results: Mean age was 30.8 years (range, 19-44). Baseline DNA data were available for 135 of the 150 (90%) women. There were no high-grade cervical lesions or cervical cancer on cytology or biopsy at baseline. The proportion of women at baseline who were naïve (seronegative and DNA-negative) to HPV 6, 11, 16 and 18 and the percentage that seroconverted at week 28 and 52 are shown in the table. There were no vaccine-related serious adverse events. There were no significant differences among the 3 enrollment groups in terms of the proportion seroconverting. Titers to HPV 6, 16 and 18 did not differ between groups, but did significantly differ for HPV 11 with Group 3 having higher median titers (3035) than Group 1 (2262) or Group 2 (1975) (p=0.025).

Conclusions: The qHPV vaccine was safe and immunogenic in Indian HIV-infected women, regardless of CD4 level and HIV viral load. A high proportion of Indian HIV-infected women were "naïve" to vaccine HPV types. These women should be considered for HPV vaccination to reduce their risk of cervical cancer even though their mean age exceeded 26 years, the upper limit for catch-up vaccination in many countries.

Prior exposure to HPV vaccine types at baseline and seroconversion at week 28 and 52				
	HPV 6	HPV 11	HPV 16	HPV 18
Percent naive (seronegative and HPV DNA-negative) at baseline	71%	87%	73%	81%
Percent seronegative at baseline who seroconverted at week 28	100%	99%	99%	88%
Week 28 seroconverters remaining seropositive at week 52	96%	97%	99%	78%

856 B and T Cell Immune Responses To pH1N1 Monovalent Vaccine in HIV+ Pregnant Women in IMPAACT P1086

Adriana Weinberg[1], Petronella Muresan[2], Kelly Richardson[1], Terrence Fenton[2], Teresa Dominguez[1], Anthony Bloom[3], Mark Abzug[4], Myron Levin[1], Sharon Nachman[5]
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Background: Pregnant women have a high risk of severe influenza disease that can be mitigated by vaccination. Although HIV+ individuals have modest antibody responses to influenza vaccines, vaccination has been effective against disease, suggesting additional mechanisms of protection. We characterize the B and the T cell responses to pH1N1 vaccine and their determinants in HIV+ pregnant women.

Methodology: 57 HIV+ pregnant women received two 30 µg doses of pH1N1 vaccine and had the following studies at entry and post-dose 1 and 2: IgG & IgA B cell ELISPOT; interferon (IFN)γ & granzyme B (GrB) T cell ELISPOT; hemagglutination inhibition (HAI) antibody titers; and B and T cell subsets by flow cytometry.

Results: Participants had mean± S.D. age= 27± 5 years, CD4= 521± 223 cells/μL and plasma $\log_{10}$ HIV RNA= 2.3± 0.9 copies/mL. All women were on antiretroviral treatment, including 51 on HAART.

HAI titers increased from median (interquartile range) of 20 (5, 40) at entry to 160 (40, 320) post-dose 1 and 2 (p=0.0001). ELISPOT-measured IgG antibody-secreting cells (ASC) increased from 6 (2, 28)/10^6 mononuclear cells (MNC) to 15 (4, 6) post-dose 1 (p=0.01) and 14 (6, 70) post-dose 2 (p=0.003). IgA ASC were low at entry [1 (0, 9)] and did not change after vaccination. ELISPOT-measured IFNγ spot-forming cells (SFC) decreased from 166 (38, 324)/ 10^6 MNC to 117 (40, 506) post-dose 1 and 76 (32, 336) post-dose 2 (p=0.06 post-dose 1 vs. 2). Vaccination did not change GrB SFC [entry of 48 (12, 258)].

IFNγ and GrB SFC inversely correlated with plasma HIV RNA at all time points ($\rho \leq$ -0.35, $p \leq 0.02$) and IFNγ SFC positively correlated only with CD4% at entry (ρ= 0.31, p= 0.04). There were no significant correlations of ASC or HAI titers with HIV disease characteristics.

At all time points, IFNγ and GrB SFC were highly correlated with each other ($\rho \geq$ 0.67, p< 0.0001). IFNγ SFC correlated with HAI titers at all time points ($\rho \geq$ 0.29; $p \leq 0.06$). IgG ASC did not correlate with IFNγ or GrB SFC or HAI titers.

The table shows correlations of pH1N1 immune responses with the frequency of B and T cell subsets.

Variable	Subset (% of parent population)	Visit	ρ	P value
HAI Titers	CD8+HLADR+CD38+ activated T cells	Post-dose 1	-0.48	0.002
		Post-dose 2	-0.36	0.02
IFNγ SFC	CD8+HLADR+CD38+	Post-dose 1	-0.40	0.03
	CD4+FOXP3+ regulatory T cells (Treg)	Entry	-0.37	0.04
	CD19+IL10+ regulatory B cells (Breg)	Post-dose 2	-0.35	0.05
	CD8+TGFB+ T reg	Entry	-0.34	0.06
IgG ASC	CD4+IL10+ T reg	Entry	0.45	0.008
	CD4+IL10+ T reg	Post-dose 2	0.61	0.0001
	CD19+IL10+ B reg	Entry	0.47	0.005
	CD19+IL10+ B reg	Post-dose 2	0.39	0.017
	CD8+CD39+ T reg	Post-dose 1	0.42	0.02
	CD19+CD21- CD27+ activated B cells	Post-dose 2	0.35	0.04
	CD4+FOXP3+ Treg	Entry	-0.34	0.050
	CD4+CD25+FOXP3+ T reg	Entry	-0.35	0.046
	CD19+CD21- CD27- transitional B cells	Post-dose 1	-0.36	0.03
	CD19+CD21- CD27-	Post-dose 2	-0.50	0.002
	CD8+FOXP3+ Treg	Entry	-0.39	0.021

Conclusions: HIV+ pregnant women developed pH1N1 IgG, but not IgA, B cell immunologic memory after vaccination. pH1N1 T cell immunity was present at entry, did not increase after vaccination, and IFNγ SFC decreased post-dose 2. High Treg, Breg and activated T cells were associated with low T cell immunity, but high IL10+ Treg and Breg and activated B cells were associated with high B cell memory. High FOXP3+ Treg were associated with low B and T cell immunity.

Session P-T1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Clinical Outcomes of HIV-Exposed Uninfected Infants

857 Maternal CD4 and Infectious Risk for Uninfected Infants Born To HIV+ Mothers in a European Country

Clement Taron-Brocard[1], Jerome Le Chenadec[1], Albert Faye[2, 3], Catherine Dollfus[4], Laurent Mandelbrot[1, 5], Vincent Gajdos[6, 7], Anais Perilhou[1], Jean-Marc Labaune[8], Stephane Blanche[9, 10], Josiane Warszawski[1, 11], and the ANRS French Perinatal Cohort (ANRS CO1/CO11)

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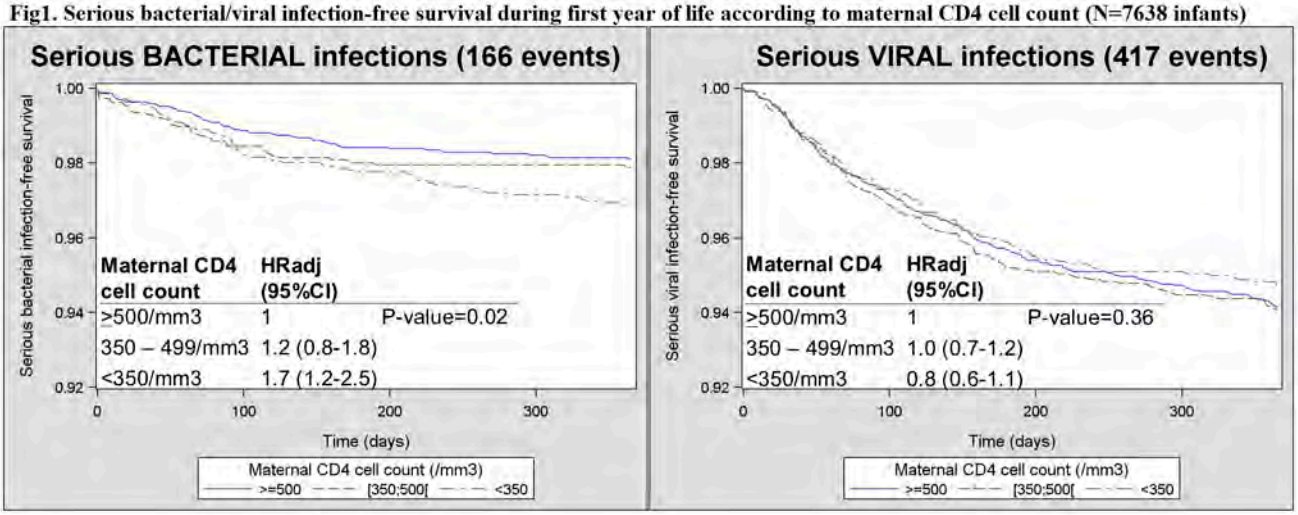
Background: With the dramatic decrease of mother-to-child transmission of HIV since the implementation of HAART and PMTCT, most neonates born to HIV-infected women are now HIV-Exposed-but-Uninfected (HEU). In Africa, morbidity appears to be higher among HEU than in infants born to HIV-non-infected women. Multiple factors, including maternal and care status may be involved. We investigated whether maternal immune depression during pregnancy was associated with a higher risk of infectious morbidity in HEU infants in the national French Perinatal Cohort (EPF).

Methodology: All neonates, born alive at 28 gestational weeks or later, to HIV-1-infected women enrolled in the EPF, between 2002 and 2010 and not breastfed were included. The primary outcome was the first serious (hospitalization or death) infection during the first year of life, classified as bacterial, viral, myco-parasitic or undetermined (validated by a group of clinicians blind to maternal characteristics). The main exposure variable was maternal CD4 cell count near delivery. The Kaplan-Meier (KM) method and multivariate Cox models were applied, with the different types of infections managed as competing events.

Results: Among the 7638 HEU neonates (of which 88.1% were followed up to 365 days), 697 had at least one severe infection (of which 166 were bacterial). The corresponding KM probability was 9.3% at one year, stable throughout the period (P-value=0.33). The mothers of 28% of the neonates were immunosuppressed (<350CD4/mm3). The risk of serious bacterial infection significantly increased with lower maternal CD4 cell count, which was not the case for viral infections, before and after adjustment (Fig 1). The association mainly concerned the postnatal period (after 28 days). The interaction between maternal CD4 cell count and gestational age at birth was not significant (P-value=0.77). The results for term-born neonates were the same (P-value=0.04), and were robust to various ways of classifying infections and to sensitivity analyses.

Conclusions: Maternal CD4 immune deficiency was specifically and significantly associated to an increased risk of serious bacterial infections in HEU infants during the first year of life, especially beyond the neonatal period. This reinforces the need to explore the effects of in-utero exposure to maternal HIV on the infant immune system.

Fig1. Serious bacterial/viral infection-free survival during first year of life according to maternal CD4 cell count (N=7638 infants)



858 Effect of Breastfeeding On Mortality and Morbidity in HIV-Exposed Un-Infected Children in Uganda

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Background: There is a growing population of HIV-exposed un-infected children (HEU), a population with a high risk of mortality. Prior studies examining the association of HIV-exposure and mortality and infectious morbidity have either lacked a comparison to HIV-unexposed un-infected children (HUU) or did not assess the effect of breastfeeding. We leveraged data from a cohort in rural Uganda to assess whether this association persists when controlling for breastfeeding and poverty.

Methodology: We included longitudinal data from 186 HEU (544 person-years) and 389 HUU (264 person-years) children ages 6-24 months enrolled in the PROMOTE cohort and participating in a trial on the effect of antimalarial chemoprevention. Children received medical care at the study clinic per standardized protocols. Outcomes assessed were: all-cause mortality, hospitalization, severe febrile illness (SFI, composite of severe pneumonia or sepsis syndrome), severe diarrhea, malnutrition, and malaria. Generalized estimating equation regression models were used to assess risk, and all models were adjusted for age, breastfeeding, SES, and malaria chemoprevention (trimethoprim sulfamethoxazole, dihydroartemisinin-piperaquine, or sulfadoxine-pyrimethamine). To examine the interaction between HIV-exposure, age, and breastfeeding a sub-analysis was performed for the 6-12 month age strata with three risk categories: HUU non-breastfeeding, HEU breastfeeding, and HEU not-breastfeeding. HUU non-breastfeeding children were excluded from this sub-analysis due to lack of person-time.

Results: There were 7(1.6%) deaths among HEU and 1(0.3%) death among HUU. HEU compared to HUU had a higher relative risk of death (RR 13.5, p=0.04). The risk of malaria was lower in HEU compared to HUU (RR 0.6, p=<0.001). The association of HIV-exposure and hospitalization, SFI, severe malnutrition, and severe diarrhea was not significant for children 6-24 months. However, when we assessed the combination of HIV-exposure and breastfeeding status in the 6-12 month age strata we found non-breastfeeding HEU children were at a significantly high risk of morbidity outcomes compared to the reference group of breastfeeding HUU: hospitalization (RR: 10.3, p<.001), SFI (RR: 3.8, p<0.001), severe diarrhea (RR: 6.5, p<.001), and malnutrition (RR: 18.7, p<.001). Antimalarial chemoprevention did not have a significant effect on health outcomes other than malaria.

Conclusions: HEU had higher risk of mortality compared to HUU, and breastfeeding is a key mediator of the association of HIV-exposure and non-malaria morbidity for children in this cohort.

859 Growth Differences in Infants Born To Perinatally vs. Non-Perinatally HIV-Infected Women

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Background: Pregnancy & infant growth outcomes are not well documented in perinatally HIV+ (PHIV) women & their children. We evaluate growth to 1 year in infants of PHIV vs. non-perinatally HIV+ (NPHIV) women.

Methodology: Using routinely collected weight, length, & head circumference data, we evaluated weight-for-age (WAZ), length-for-age (LAZ), weight-for-length (WFLZ), & head circumference-for-age (HCAZ) *z* scores from birth to 1 year in HIV-exposed uninfected (HEU) infants born to PHIV vs. NPHIV women. HIV+ pregnant women & their infants received care at one of two urban hospitals & delivered from January 2004-March 2012. Twin pregnancies,

those ending in termination or fetal demise, infants ≤28 weeks gestational age (GA), & HIV+ infants were excluded. Demographic, clinical, & antiretroviral therapy (ART) history were collected via chart review. Linear mixed effects models were used to evaluate the effect of PHIV on WAZ, LAZ, & WFLZ.

Results: Of 152 infants, 32 were born to 25 PHIV women. PHIV women were younger (20 vs. 26 years, $p<0.001$) had lower gravidity (1 vs. 3, $p<0.001$), lower pre-pregnancy BMI (24.1 vs. 27.9 kg/m², $p=0.039$), & height (155 vs. 160 cm, $p=0.009$) than NPHIV women. PHIV women were also more likely to harbor lower nadir CD4+ cells in pregnancy (20 vs. 2% with <50 cells/mm³, 16 vs. 11% with 50-200 cells/mm³, $p=0.004$) & receive second line ART (24 vs. 4%, $p=0.005$). They were less likely to attain HIV RNA levels <400 copies/ml by delivery than their NPHIV counterparts (68 vs. 87%, $p=0.036$). Infant GA, race, & APGARS did not differ between groups. Median birth WAZ was lower in infants born to PHIV women (-1.61 vs. -0.81, $p=0.032$); birth LAZ, WFLZ, & HCAZ did not differ significantly between groups. Infants born to PHIV women exhibited lower WAZ & LAZ through 1 year. In multivariate analysis, the relationship between PHIV & LAZ persisted ($\beta=-0.54$, $p=0.026$). Small-for-gestational age (SGA) for birth length (BL) was associated with decreased LAZ ($\beta=-0.48$, $p=0.007$), for birth weight (BW) with decreased WAZ ($\beta=-0.99$, $p<0.001$) & for BW/BL with decreased WLZ ($\beta=-0.36$, $p=0.027$.) A delivery HIV RNA level <400 copies/mL was associated with increased WAZ & WLZ ($\beta=0.43$, $p=0.015$; $\beta=0.38$, $p=0.021$).

Conclusions: HEU infants born to PHIV women may be at risk for decreased length in the first year of life, while maternal viral suppression may be protective for growth. HEU infants born to these women may require close observation & long term follow up of growth.

Figure. Loess Plots of Mean Weight for Age (WAZ) and Length for Age (LAZ) *Z* scores by Maternal HIV Acquisition

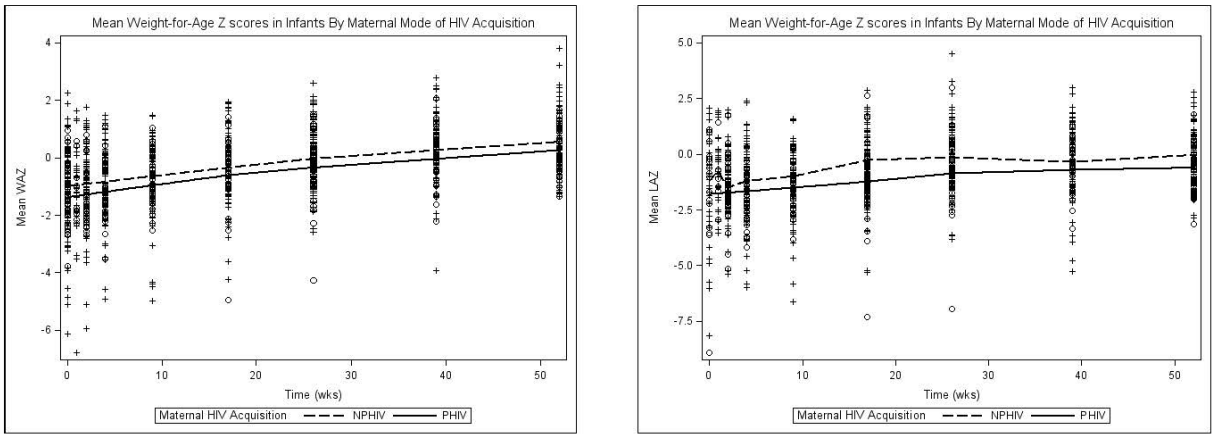

Table. Linear Mixed Effects Model of Maternal/Infant Factors Associated with *Z*-scores of Weight, Length, and Weight-for-Length in HIV-Exposed Uninfected Infants

	Weight		Length		Weight-for-Length	
	Coefficient	*p* value	Coefficient	*p* value	Coefficient	*p* value
Maternal HIV Acquisition						
PHIV	-0.29	*0.137*	-0.54	*0.026*	0.09	*0.597*
NPHIV	0		0		0	
Age of mother, per year	-0.02	*0.090*	-0.01	*0.611*	-0.01	*0.391*
Pre-pregnancy BMI of mother	0.00	*0.913*	0.00	*0.678*	0.00	*0.622*
Nadir CD4 cells in pregnancy						
≤ 200 cells/mm³	0.16	*0.42*	0.44	*0.085*	-0.29	*0.114*
> 200 cells/mm³	0		0		0	
HIV RNA level at delivery						
< 400 copies/mL	0.43	*0.015*	0.17	*0.443*	0.38	*0.021*
≥ 400 copies/mL	0		0		0	
Second line ART use in pregnancy						
Not on second line ART	0.03	*0.912*	0.24	*0.483*	-0.31	*0.216*
On second line ART	0		0		0	
Infant SGA for BW			---	---	----	---
SGA for BW	-0.99	*<0.001*				
Not SGA for BW	0					
Infant SGA for BL	---	---			----	---
SGA for BL			-0.48	*0.007*		
Not SGA for BL			0			
Infant SGA for BW and BL	---	---	---	---		
SGA for BW and BL					-0.36	*0.027*
Not SGA for BW and BL					0	

PHIV=Perinatally HIV-infected, NPHIV=Non-Perinatally HIV-infected, BMI=Body Mass Index, ART=Antiretroviral Therapy, SGA=Small for Gestational Age, BW=Birth Weight, BL=Birth Length

860LB Four Year Cotrimoxazole Prophylaxis Prevents Malaria in HIV-Exposed Children: A Randomized Trial

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Background: WHO recommends cotrimoxazole (CTX) prophylaxis for children born to HIV-infected mothers from 6 weeks of age until breastfeeding cessation and exclusion of HIV infection. We report on the protective efficacy and safety of CTX prophylaxis in these children when continued beyond breastfeeding cessation to age 4.

Methodology: We conducted an open-label randomized controlled trial alongside two observational cohorts in Eastern Uganda, an area of high HIV prevalence, malaria transmission intensity, and antifolate-resistance. 203 HIV-exposed infants enrolled between 6 weeks and 9 months of age were prescribed daily CTX until breastfeeding cessation and HIV status confirmation. After breastfeeding ended, 185 children remained in active follow-up and HIV-uninfected and were randomized 1:1 to discontinue or continue CTX prophylaxis until age 2 years. At that age, the 91 children who continued CTX were randomized 1:1 again to continue or discontinue CTX from age 2 through age 4. For additional comparisons, 48 HIV-infected children on continuous CTX prophylaxis and 100 HIV-unexposed uninfected children who never received CTX prophylaxis were enrolled. All children were followed to age 5. Main outcome measures included malaria incidence, grade 3 and 4 serious adverse events (SAEs), and hospitalizations.

Results: Out of the 185 HIV-exposed children who remained enrolled and HIV-uninfected after the end of breastfeeding, 152 (82.2%) and 146 (78.9%) randomized HIV-exposed children were followed to age 4 and 5 respectively. Continuing CTX prophylaxis to age 4 yielded a 43% reduction in malaria (incidence rate ratio, 0.57; 95% CI, 0.49-0.66; p<0.001). Throughout follow-up, malaria incidence was lowest among HIV-infected children who received continuous CTX prophylaxis and highest among HIV-negative unexposed children who never received CTX prophylaxis. There were no significant differences in incidence of grade 3 or 4 SAEs, hospitalizations, or deaths among HIV-exposed, HIV-unexposed, and HIV-infected children. There was no evidence of malaria incidence rebound in the year following discontinuation of CTX at age 2 or 4, but incidence increased significantly from age 4 to 5 among children who stopped CTX at age 4.

Conclusions: These results indicate that continuing cotrimoxazole prophylaxis beyond the period recommended by WHO is safe and efficacious in protecting HIV-exposed children living in malaria endemic areas even in the presence of high anti-folate resistance.

861 No Evidence of Neurodevelopmental Delay in HEU Infants Exposed To cART In Utero and Breastfeeding

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Background: The 2013 WHO Guidelines on preventing mother-to-child transmission (PMTCT) of HIV recommend maternal cART throughout pregnancy and for 1 year of breastfeeding for HIV infected mothers in many developing countries. Some antiretrovirals (in particular zidovudine and 3TC) are well secreted in breast milk. The neurocognitive impact of prolonged cART exposure on the developing brain of the HIV-exposed uninfected (HEU) infant is currently unknown.

Methodology: Between June 2011 and August 2013, children aged 15-36 months were recruited to a cohort study from the Chelstone Clinic in Lusaka, Zambia. Group A (exposed) children were born to HIV+ women who received ZDV300mg/3TC150mg and Lopinavir400mg/ritonavir100mg all BID starting between 14-30 weeks gestation and through 1 year of breastfeeding postpartum. Group B (control) HIV non-exposed children were recruited from the Chelstone under-5 health clinic. The standardized Capute Scales assessment tool, which consists of the Cognitive Adaptive Test and Clinical Linguistic and Auditory Milestone Scale, was used to assess nonverbal problem-solving and language skills. A score <85 on the Capute Full Scale Developmental Quotient (FSDQ) was considered indicative of developmental delay and the primary outcome compared between the two groups. Additionally, the assessment included a demographic questionnaire, anthropometric measurements, and biological samples to confirm HIV status of the child and mother. HIV positive infants were excluded from enrollment.

Results: Two hundred children completed the neurocognitive assessments (Group A, n=97; Group B, n=103). There were no significant differences in maternal age, gestational age at birth or duration of breastfeeding, between groups. An FSDQ score <85 was found in 8 (8.3%) of Group A participants and 15 (14.6%) of Group B participants. In univariate logistic regressions, lower income (OR=0.93, 95%CI=0.84-0.99, p=0.02), older infant age (OR=1.08, 95%CI=1.01-1.17, p=0.03), and lower birth weight (OR=0.16, 95%CI=0.05-0.44, p=0.0002) were associated with the probability of FSDQ <85, while group (A vs. B) was not (OR=1.88, 95%CI=0.77-4.87, p=0.16). In the multivariable analysis, only lower birth weight (OR=0.17, 95%CI=0.05-0.50, p<0.001) and older age (OR=1.10, 95%CI=1.01-1.21, p=0.03) remained associated with FSDQ <85.

Conclusions: There was no evidence of a higher proportion of delayed infants in the HEU group when compared to a similar HIV unexposed control group. These results suggest that this cART regimen during pregnancy and prolonged breastfeeding does not impact early childhood cognitive development. This finding is reassuring in light of the recent substantial increase in perinatal and postpartum use of cART worldwide.

Session P-T2 Poster Session
Tuesday March 4, 2014, 2:30 PM–4:00 PM Exhibit Hall D

Neonatal Sequelae of In Utero ART Exposure

862 In Utero Exposure To Zidovudine and Neonatal Heart Abnormalities in the ANRS-EPF/PRIMEVA Studies

Jeanne Sibiude[1,2], Jérome Le Chenadec[2], Damien Bonnet[3,4], Roland Tubiana[5,6], Laurent Mandelbrot[1,7], Sandrine Delmas[2], Camille Runel Beliard[8], Babak Khoshnood[9], Josiane Warszawski[10,11], Stéphane Blanche[12,13], for the ANRS-French Perinatal Cohort/PRIMEVA

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Background: Antiretroviral therapy (ART) effectively prevents mother-to-child transmission of HIV. An increased risk of congenital heart defects (CHD) has been reported in infants exposed in utero to zidovudine, the association being strong and specific in a recent large EPF study. Observational studies have also found modification in myocardial mass and contractility in infants, particularly girls, similar to the effects of anthracyclin cardiac toxicity.

We reevaluated these associations with the national ANRS EPF cohort and nested Primeva randomized trial.

Methodology: The EPF-CO1/CO11 has, since 1986, prospectively enrolled nearly 20,000 mother-child pairs from pregnant HIV-infected women delivering in 90 centers throughout France. The relationships between ART and each kind of congenital defect, as routinely collected, have already been studied among 13,124 livebirths between 1994 and 2010. Here, all CHD were reviewed, sites contacted for additional information, and adjudicated by a CHD specialist, blind to in utero exposure.

The phase II/III ANRS-135 PRIMEVA trial was run between 2007 and 2012 in the EPF sites to evaluate a nucleoside-sparing strategy. Women were randomized to receive either LPV/r alone (n=69) or AZT+3TC+LPV/r (n=36) in the last trimester of pregnancy. Infant echocardiogram was planned at 1 and 12 months of age. At least one echocardiogram was performed in 50 infants.

Results: In EPF, zidovudine (vs no zidovudine) in the first gestational trimester was significantly associated with congenital heart defects, before and after adjustment for potential confounding variables and concomitant antiretroviral medication: 1.5% vs. 0.7%, p <0.001; Adjusted Odds Ratio = 2.2 [95% CI 1.3-3.7]. This association mainly involved ventricular septal defects: 1.1% vs. 0.6%, p = 0.001, but not atrial septal defects, both classified as minor CHD. The association was also significant for major CHD: 0.31% vs. 0.11%, p = 0.02, but the numbers of cases was small.

In Primeva, AZT+3TC+LPV/r (versus LPV/r alone) in the last gestational trimester was associated - in girls only - with higher median left ventricle fractional shortening at 1 month (40% vs. 36%; p = 0.008), and with median posterior wall thickness at 1 year (5.4 vs. 4.4 mm, p = 0.01). No differences were observed among boys.

Conclusions: Our results from a large cohort and a randomized trial indicate that zidovudine may affect heart development and/or cardiac function, although its clinical impact is unknown. Potential mechanisms underlying these associations, maybe involving mitochondrial dysfunction, must be investigated. This should be taken into consideration when monitoring the long-term health of children born to HIV+ mothers, given the large number of children exposed to perinatal zidovudine worldwide.

863LB Congenital Anomalies and In Utero Antiretroviral Exposure in HIV-Exposed Uninfected Children

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Background: Most studies examining the association of maternal antiretroviral (ARV) exposures during pregnancy with congenital anomalies (CAs) in their children have been reassuring, but some suggest increased risk with specific ARVs.

Methodology: We evaluated HIV-exposed uninfected children enrolled in the PHACS Surveillance Monitoring of ART Toxicities (SMARTT) study, an ongoing prospective cohort study initiated in 2007 at 22 sites in the US including Puerto Rico. Information on CAs was collected by chart abstraction or from prior studies. Clinicians blinded to ARV exposures reviewed reported anomalies according to the Metropolitan Atlanta Congenital Defects Program (MACDP). Children with ≥1 major or ≥2 conditional CAs were considered cases. Rates of CAs were estimated overall and by birth cohort. Logistic regression models were used to evaluate associations between CAs and 1st trimester exposure to any ARV, specific ARVs, combination ARV regimens (≥3 drugs from ≥2 classes), and ARV classes. Models were adjusted for demographic and maternal characteristics (including CD4, viral load, substance use, other medications, and pregnancy complications).

Results: Among 2580 children born by July 2012 (49% female, 66% black, 33% Hispanic), 162 had a total of 242 confirmed major CAs, and 13 had ≥2 conditional CAs, for a total of 175 cases (6.78%, 95% CI: 5.85-7.82%). The most common anomalies were musculoskeletal (n=72) and cardiovascular (n=56). The prevalence of CAs by birth cohort was 3.8%, 5.2%, 8.0%, 8.3%, and 5.7% for children born ≤2001, 2002-2004, 2005-2007, 2008-2010, and ≥2011, respectively. In unadjusted models, 1st trimester exposures to combination ARV regimens or to protease inhibitors (PIs) were associated with increased risks of CAs [odds ratio (OR)=1.44, p=0.022 and OR=1.51, p=0.010, respectively], but these associations did not persist after adjustment. No individual NNRTI (including efavirenz) or NRTI was associated with an increased risk of CAs, but the combination of ddI+d4T (<1% exposed) was

associated with 8-fold higher odds [adjusted OR (aOR)=8.41, p=0.015]. Among individual PIs, atazanavir and lopinavir were associated with significantly higher odds of CAs in unadjusted models, and the association with atazanavir persisted in adjusted models (aOR=1.93, p=0.004). With 1st trimester atazanavir, risks were highest for skin CAs (aOR=5.24, p=0.020) and musculoskeletal CAs (aOR=2.55, p=0.007).

Conclusions: Few individual ARVs or drug classes were associated with increased risk of CAs after adjustment for child and maternal characteristics, with the exception of the combination of ddI+d4T, now rarely used, and atazanavir, which is increasing in use. As newer ARVs and ARV combinations become more widely used, continued monitoring is essential.

865 Abnormal Fatty-Acid Oxidation in HIV-Exposed Uninfected Neonates in the United States

Brian Kirmse[1], Tzy-Jyun Yao[2], Sean Hofherr[1], Paige Williams[2], Deborah Kacanek[2], Rohan Hazra[3], William Borkowsky[4], Russell Van Dyke[5], Marshall Summar[1]

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Background: Abnormal newborn screens for dysfunctional fatty acid oxidation (FAO) are more common in HIV-exposed uninfected (HEU) neonates than the general population and may be related to in utero exposure to HIV and/or combination antiretroviral therapy (cART). Normal FAO is necessary for normal growth and development. Disordered FAO can result in hypoglycemia, myopathy and liver injury.

Methodology: We analyzed serum acylcarnitine profiles (ACP), as a measure of FAO, in 522 HEU neonates (age 0-7 days) enrolled in the SMARTT study of the Pediatric HIV/AIDS Cohort Study (PHACS). We estimated the prevalence of abnormal ACP and evaluated associations of abnormal ACP with in utero exposure to cART and antiretroviral (ARV) drug classes in logistic regression models, adjusting for maternal demographic characteristics and substance use. We also evaluated associations of abnormal ACP with clinical laboratory parameters (lactate, glucose, creatine kinase (CK) and alanine aminotransferase (ALT)) and measures of neurodevelopment and growth through 3 years of age.

Results: Of 522 neonates, 84 (17%) had abnormal ACP, with most abnormal profiles characterized by generalized or long-chain specific acylcarnitine elevations. Maternal alcohol exposure (adjusted odds ratio (aOR)=2.55, 95% confidence interval (CI): 1.21, 5.37, p=0.01) and, as expected, lower gestational age at birth (aOR=1.21 per week lower, 95% CI: 1.07, 1.36, p<0.01) were associated with higher odds of having an abnormal ACP. In analyses adjusted for alcohol exposure and gestational age, in utero exposure to a protease inhibitor (PI) was associated with higher odds of having an abnormal ACP (aOR= 2.35, 95% CI: 0.96, 5.76, p=0.06) while exposure to a non-nucleoside reverse transcriptase inhibitor (NNRTI) (aOR=0.23, 95% CI: 0.07, 0.80, p=0.02) was associated with lower odds. ALT levels were higher in those with abnormal vs. normal ACP (geometric mean 18.7 U/L vs. 14.9 U/L, p<0.01,), but no differences in lactate, glucose or CK were observed. ACP status was not associated with MacArthur-Bates Index and Bayley Score at 1 year or anthropometric measurements at 2 and 3 years of age.

Conclusions: Abnormal ACP, indicating dysfunctional FAO, are relatively common in HEU neonates and are associated with PI use and maternal alcohol exposure during pregnancy as well as higher neonatal ALT levels. Taken together, these observations suggest the possibility of subclinical hepatic dysfunction in HEU newborns. Abnormal ACP is not associated with levels of CK, glucose, lactate or significant delays in growth or development. Further studies are needed to determine the long-term clinical implications of abnormal FAO in HEU neonates.

866 Comparative Genotoxic Signatures in Cord Blood Cells From Neonates Exposed To AZT or TDF In Utero

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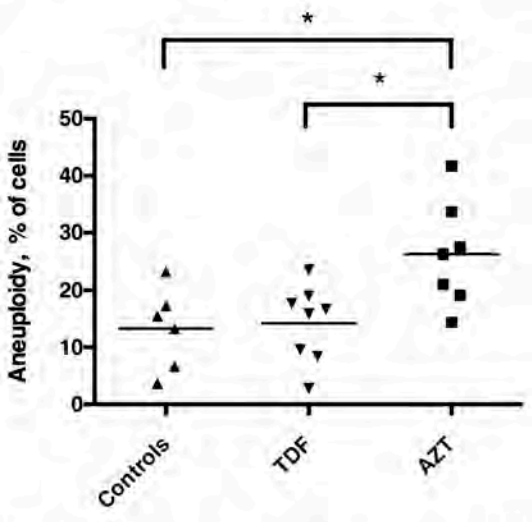
Background: Zidovudine (AZT) and tenofovir (TDF) are the most frequently used nucleoside analogues for reducing perinatal HIV transmission during pregnancy. Various genotoxicity biomarkers have been identified in neonates and animal models exposed to AZT in utero. In contrast, there are no data on TDF exposure - even though the compound is now considered by the WHO as a benchmark drug in this setting. We have previously shown that cord blood cells from neonates exposed to AZT in utero present a higher proportion of aneuploid cells and have a transcriptome profile that is suggestive of increased DNA alteration and repair. The aim of the present study was to compare the genotoxic signatures in neonates exposed to either AZT or TDF in utero.

Methodology: Cord blood cells from neonates exposed to either AZT or TDF in utero were used to enrich CD34+ hematopoietic stem/progenitor cells (HSPCs) or CD3+ T lymphocytes. The cells were then subjected to blinded karyotyping and a transcriptome analysis.

Figure. Aneuploidy Rates in Cord Blood Cells of *In Utero* Exposed Newborns to AZT or TDF Based Antiretroviral Combinations or Controls



The aneuploidy rates were determined as the percentage of all scored cells that were aneuploid for each antiretroviral–exposed and control samples. Bars represent means. * : p < .05.

Results: Karyotyping revealed a higher proportion of aneuploid cells in the AZT-exposed group (n=7, mean ± SD: 26.3% ± 9.2) than in the TDF-exposed group (n=8, 14.2% ± 6.7; p<0.05) and a control group (n=6, 13.3% ± 7.2; p<0.05) (figure). All chromosomes were involved and the alterations were randomly distributed. Our overall analysis of transcriptome profiles revealed a distinct molecular profile in patients exposed to AZT or TDF. This signature was found both in CD34+ HSPCs and CD3+ T lymphocytes. Gene Set Enrichment Analysis revealed significant changes in the activity of genes involved in DNA repair in both the AZT and TDF groups. However, in HSPC experiments, double-strand break repair, Fanconi anaemia pathway and G2/M checkpoint gene sets were enriched in the AZT group but not in the TDF group.

Conclusions: Based on our cytogenetic analysis, antiretroviral (ARV) combination
treatments that include TDF may be less clastogenic than those including AZT. However, hematopoietic cord blood cells present transcriptional abnormalities that are suggestive of DNA damage in neonates exposed to AZT- or TDF-based ARV combination treatments in utero. Given the wide use of these ARV drugs during pregnancy, it is critical to further investigate their genotoxicity and potential impact on health.

867 Risk Factors for Preterm Birth in Pregnant Women Randomized To Lopinavir- or Efavirenz-Based ART

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Background: Preterm birth (PTB) is a major cause of perinatal morbidity and mortality. HIV-infected pregnant women, particularly those with advanced disease, may have higher rates of PTB than HIV-uninfected women. As countries adopt WHO Option B+ and more women start combination antiretroviral therapy (cART), it is critical to understand risk factors for PTB among HIV-infected pregnant women on cART.

Methodology: This is a planned secondary analysis of PTB in the PROMOTE-Pregnant Women and Infants Study (NCT00993031). This was an open-label, randomized controlled trial comparing the risk of placental malaria among HIV-infected, ART-naïve pregnant Ugandan women at 12-28 weeks gestation who were randomized at study enrollment to receive lopinavir/ritonavir (LPV/r)- or efavirenz (EFV)-based cART. All women received daily trimethoprim-sulfamethoxazole and bednets. All eligible, randomized women were included in this analysis with censoring at time of study withdrawal or live birth after 37 weeks gestation. Gestational age at enrollment was calculated by last menstrual period and ultrasound biometry. PTB was defined as less than 37 weeks and very PTB as less than 32 weeks gestation. We excluded stillbirths and spontaneous abortions. Placental malaria was examined by blood smear, rapid diagnostic test, and PCR. Multivariate Cox proportional-hazards modeling was used to evaluate risk factors for PTB.

Results: A total of 389 eligible women were enrolled; mean gestational age was 20.8 weeks and median CD4 cell count was 369 cells per microliter (IQR 272-493). Among 356 live-born singleton deliveries, the prevalence of PTB was 15.4% and the prevalence of very PTB was 1.7%. Univariate risk factors for PTB were gestational age at study enrollment (and hence cART start) of 24-28 weeks vs. 12-23 weeks (HR = 1.85, 95% CI: 1.09-3.14, p = 0.03) and study period weight gain of less than 0.1 kg/week vs. 0.1 kg/week or more (HR = 2.32, 95% CI: 1.37-3.94, p = 0.002). Placental malaria was not a risk factor for PTB (HR = 0.95, 95% CI: 0.34-2.66, p = 0.93), nor was antiretroviral regimen of LPV/r vs. EFV (HR = 1.10, 95% CI: 0.65-1.88, p = 0.70). In multivariate analysis controlling for time since HIV diagnosis, gestational age at cART start greater than 24 weeks was significantly associated with PTB (aHR = 1.80, 95% CI: 1.06-3.07, p = 0.03), whereas antiretroviral regimen was not (aHR = 1.15, 95% CI: 0.60-1.97, p = 0.60).

Conclusions: In this cohort of HIV-infected pregnant women presenting at 12-28 weeks gestation, starting cART at an earlier gestational age was associated with a reduced risk of preterm birth. There was no difference in the risk of preterm birth among women randomized to LPV/r- or EFV-based cART.

Session P-T3 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Pregnancy Incidence and Outcomes Among Women in ART Programs

868 Incidence and Predicting Factors of Pregnancy Post-ART Initiation in 9 West African Countries

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Background: In sub-Saharan Africa, women of reproductive age constitute the most HIV-affected population. Since antiretroviral therapy (ART) has become widely available, HIV-infected women health status has improved and the pregnancy rate post-ART has risen. In order to correctly respond to reproductive health needs of HIV-infected women in reproductive age, estimating incidence and predicting factors of pregnancy after ART initiation is crucial. This study estimated these outcomes among HIV-infected women after ART initiation at 15 clinical sites in nine West-African countries over a 10-year period.

Methodology: This retrospective cohort analysis was conducted within the International epidemiologic Databases to Evaluate AIDS (IeDEA) West Africa collaboration. All HIV-infected women aged <50 years, starting ART for their own health according to country-specific protocols between 2002-2011, and not reported pregnant at ART initiation were eligible for analysis. Ever becoming pregnant as reported in the database after ART initiation was the main outcome. Poisson regression analysis accounting for countries heterogeneity was used to estimate pregnancy incidence post-ART and to identify its

predicting factors. Incidence rate ratios were adjusted on baseline CD4 count; age, Body Mass Index & hemoglobin at ART initiation; first ART regimen; calendar year of ART start; time following ART initiation and country.

Results: Overall 27,489 HIV-infected women contributed for 75,403 women-year of follow-up to this analysis. At baseline, median age was 33 years old [IQR: 28.5-38.8] and median CD4 cell count was 170 cells/µl [IQR: 84-266]. During follow-up, 2,337 pregnancies were reported after ART initiation: 1,961 women reported one pregnancy, 167 and 14 women reported two and three pregnancies, respectively. Median time to first pregnancy after ART initiation was 24.2 months [IQR: 11.9-42.6]. The crude incidence rate of pregnancy was 3.1 per 100/women-year [95%CI: 3.0-3.2]. Pregnancy incidence rate was highest among women aged 16-24 years (4.7 per 100/women-year; 95%CI: 4.2-5.2); adjusted incidence rate ratio was 14.4 (95%CI: 10.6-19.5) when compared to women aged 40-49 years. Incidence of first pregnancy was higher during the first year post-ART initiation (15.5 per 100/women-year; 95%CI: 14.1-16.9); adjusted incidence rate ratio was 27.7 (95%CI: 24.1-31.9) when compared to women in at least their fourth year on ART.

Conclusions: In the West-African region, although probably underestimated, the incidence rate of pregnancy post-ART initiation was high. Importantly, this incidence was higher during the first year following ART initiation. Family planning services should be delivered to all women initiating ART accordingly to their desire of procreation.

869 Pregnancy and Retention or Progression To AIDS/Death Post-ART in 9 West African Countries

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Background: We hypothesized that pregnancy after antiretroviral therapy (ART) initiation may impact health outcomes among HIV-infected women. The objectives of this west-African multi-country study were to assess whether pregnancy post-ART initiation had an effect on the risk of loss to follow-up (LTFU), AIDS progression or death and on CD4 cells gain.

Methodology: This retrospective cohort analysis was conducted within the IeDEA West Africa collaboration. All HIV-infected women aged <50 years, starting ART for their own health at 13 clinical sites in 9 West-African countries over a 10-year period were eligible. First, the effect of pregnancy (time dependent variable) on LTFU, progression to AIDS/death 48 months after ART initiation was estimated by adjusted Cox regression models. Second, the mean gain of CD4 cells in the first 24 months following ART initiation was estimated in multivariable linear mixed models accounting for countries heterogeneity and according to the occurrence or not of pregnancy.

Results: The first analysis accounted for 12,851 HIV-infected women not pregnant and/or with no AIDS diagnosis at ART initiation, of which 864 (6.7%) reported at least one pregnancy at M48 post-ART initiation. Among women with pregnancy and no pregnancy, 15.2% and 12.7% progressed to AIDS or death and 8.3% and 24.8% were LTFU at M48, respectively. After adjustment on CD4 count, age, Body Mass Index,hemoglobin and regimen at ART initiation; calendar year at ART start and country, pregnancy reduced the risk of AIDS or death (aHR=0.61; 95%CI: 0.40-0.92) and the risk of becoming LTFU at M48 (aHR=0.71; 95%CI: 0.55-0.92). Overall 20,408 HIV-infected women accounted for the CD4 analysis, of which 1,561 (6.2%) reported at least one pregnancy at M24 post-ART. The mean gain of CD4 cells between ART initiation and M24 was significantly higher among women who experienced a pregnancy in the first six months following ART initiation, compared to those with no pregnancy (Table 1).

Conclusions: In West-Africa, pregnancy during early post-ART initiation is a common event and reduces by roughly one third both the risk of AIDS disease progression or death and the risk of LTFU at 48 months after ART initiation. Moreover, pregnancy post-ART initiation had no deleterious impact on immune response. However, we suspect an underreported pregnancy rate and that a significant proportion of LTFU might be dead. More complex sensitivity analyses are underway to address these two issues.

Table 1. Post-ART pregnancy and CD4 count cells gain in the first 24 months following ART initiation

	Mean CD4 count slope between ART initiation and M6 (cells/µl gained per month)		Mean CD4 count slope between M6 and M24 (cells/µl gained per month)		Mean CD4 count gain between ART initiation and M24 (cells/µl)*	
Variables	Adjusted estimate** (95%CI)	p-value	Adjusted estimate** (95%CI)	p-value	Adjusted estimate** (95%CI)	p-value
No pregnancy	+29.9 (26.6;33.3)	Ref	+5.6 (2.5;8.7)	Ref	+280 (227;333)	Ref
Pregnancy in the first 6 months after ART initiation	+35.5 (31.6;39.4)	<0.0001	+5.7 (2.5;8.8)	0.7839	+315 (260;370)	<0.0001
Pregnancy beyond 6 months after ART initiation			+5.7 (2.5;8.8)	0.7839	+281 (227;335)	0.7839

* Linear mixed models adjusted for CD4 count at baseline; age, Body Mass Index (BMI) and hemoglobin at ART initiation; initial ART regimen; calendar year of starting ART and country.

** For the reference group: baseline CD4 count <50 cells/µl, 16-24 years old women treated with nevirapine, starting ART in 2011, with BMI=18.5;25kg/m², baseline hemoglobin<7.5g/dl and followed-up in Ivory Cost.

Session P-T4 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Cellular and Immune Correlates of MTCT

870 Maternal HIV Envelope V3-Specific IgG Responses Are a Correlate of Risk of Perinatal Transmission

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Background: More than 300,000 infants become vertically-infected with HIV-1 annually, despite the availability of effective antiretroviral prophylaxis regimens. Immunologic interventions, such as a maternal or infant vaccine, will likely be required to eliminate pediatric HIV-1. Immune correlates of risk of HIV-1 acquisition were identified in the moderately-successful RV144 HIV-1 vaccine trial, including the potentially-protective Envelope (Env) variable regions 1 and 2 (V1V2) IgGresponse. In this study, we aimed to define whether the potentially-protective responses identified in the RV144 vaccine trial or other Env-specific antibody responses would also predict the risk of mother to child HIV-1 transmission (MTCT).

Methodology: Utilizing the Women and Infants Transmission Study (WITS) cohort of U.S., nonbreastfeeding HIV-infected mothers, which began enrolling prior to the availability of antiretroviral prophylaxis, we selected untreated, HIV-transmitting mothers (n = 83; 52% peripartum, 13% in utero and 35% unknown transmission mode) and a clinically-matched group of nontransmitting mothers (n = 165) with plasma samples available between 25 weeks of gestation and 2 months postpartum. A pilot study revealed no significant differences in the Env-specific humoral responses during this peripartum period. We utilized a multivariable logistic regression model to determine whether plasma IgG and IgA Env binding responses (including V1V2 and V3 regions), neutralizing antibody score, avidity, and antibody-dependent cell cytoxicity predicted the risk of MTCT.

Results: Application of a primary immune variable model adapted from that applied to the RV144 trial revealed that neither the maternal Env V1V2 IgG response nor the Env breadth IgA score correlated with the risk of MTCT. However, assessment of additional binding antibody responses revealed that IgG responses against Env V3 correlated with the risk of MTCT (OR: 0.76, p = 0.04, q = 0.15). On secondary analysis, neutralizing antibody responses against tier 1 clade B variants MN and SF162 significantly correlated with the risk of peripartum transmission (OR: 0.54, p = 0.005, q = 0.1 for both). Finally, avidity of the IgG response against gp140 directly interacted with IgG responses against gp41, gp120, and V3 to predict the risk of MTCT (p = 0.01, q = 0.17-0.19).

Conclusions: Maternal Env V3 IgG and neutralizing responses inversely correlated with transmission risk of MTCT, revealing distinctions between humoral immune correlates of risk of MTCT and vaccine-elicited humoral immune correlates of risk of sexual HIV-1 transmission identified in the RV144 trial.

871 Ontogeny of HIV-Targeted CD4+ T Cells During Exclusive and Non-Exclusive Breastfeeding

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Background: Mixed breastfeeding (BF) is associated with a higher risk of mother-to-child transmission than exclusive BF (EBF), however the mechanisms of increased risk are unclear. We determined whether feeding practices alter the expression of $CD4^+$ T cell phenotypes with increased susceptibility to HIV.

Methodology: We prospectively evaluated 99 HIV-exposed, but uninfected, breastfed Ugandan infants at birth, 2, 6, 12, 18, 24, and 48 wks. T cells in fresh blood were characterized by flow cytometry for naïve, central (CM), effector (EM), and effector RA^+ (EMRA) memory phenotypes by differential expression of CD45RA/CCR7, for markers of gut homing (β7), and for activation ($HLA\text{-}DR^+/CD38^+$) on $CD4^+$ and $CD8^+$ T cells and for HIV susceptibility by expression of surface coreceptor CCR5 on $CD4^+$ cells. FMO tubes were used to define gating. Mothers were counseled to practice EBF but made a study-independent choice of feeding practice. EBF infants (n=49) were reported to have received only breast milk at all visits through 24 wk. Non-exclusively breastfed infants (NX, n=19) received non-breast milk liquids or solids, ±continued BF, at $\geq$2 visits between 2-24 wk. There was one HIV-infected infant who was excluded from the analysis. Values are expressed as medians; p values determined by paired t test for changes over time and Wilcoxon Rank-Sum test for comparisons between EBF and NX.

Results: In the whole cohort at birth, although most $CD4^+$ T cells were naïve (91.7%), memory cells were already detected, particularly CM (6.9%). $CD4^+$ CM T cells expressing CCR5 were present at birth and increased 2.6-fold from birth to 2 wk (3.0% vs. 7.9%, $p<0.001$). Memory $CD4^+$ cells with gut-homing β7hi expression were rare at birth but increased progressively from birth to 48 weeks among CM (1.3% vs 14.4%, $p=<0.001$) and EM (1.6% vs 7.0%, $p<0.001$). We identified specific differences between EBF and non-exclusive BF (NX) by 24 weeks, when feeding practices had diverged. NX had a higher frequency of HIV-targeted β7hi/$CCR5^+$ $CD4^+$ T cells than EBF in both CM and EM subsets ($p\leq0.05$). Within the β7hi EM subset, NX had higher frequency of activated cells ($p=0.03$). In the $CD8^+$ T cell population, β7hi CM cells were also higher frequency in NX compared to EBF, as were activated cells in each memory phenotype ($p\leq0.01$).

Conclusions: Non-exclusively breastfed infants had altered frequencies of CD4 and CD8 T cell subsets compared to EBF infants. The higher frequencies of $CCR5^+$, gut-homing, memory CD4+ T cells, thought to be prime targets for HIV, might contribute to the higher transmission rate associated with mixed breastfeeding.

872 Infant Variants Require More CD4 for Entry Than Maternal Variants Regardless of Transmission Route

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Background: Despite high level, persistent exposure to virus, the majority of children born to chronically HIV-infected women escape infection. Most infections that do occur are initiated by a single genetic variant selected from a diverse quasi-species swarm. Given the relative paucity of activated, HIV-susceptible CD4+ target cells, particularly in the fetus, we sought to determine the minimum level of CD4 expression required for cell entry by early-transmitted isolates, and whether we could find evidence for selective transmission of variants particularly adept at utilizing low levels of CD4 (such as is present on macrophages) for productive infection.

Methodology: Pseudotype viruses were produced in 293T/17 cells using standard techniques. Affinofile cells, a 293 variant with independently inducible CD4 and CCR5 expression systems and an HIV-inducible secreted luciferase reporter, were treated to maximize expression of CCR5 while CD4 was varied across an ~2 log10 gradient. Infection was normalized as a percentage of entry under saturating CD4 conditions. Percent entry was then plotted by absolute number of CD4 molecules per cell to generate an infection curve. Infection curves were used to back-calculate the number of CD4 molecules/cell necessary to achieve 20% of maximal entry (EC20) for each viral variant. EC20s for epidemiologically linked mother-infant transmission pairs were then analyzed using the GEE model.

Results: EC20 values were generated for 160 unique envelope clones from 7 in utero and 11 breast milk transmission pairs. Regardless of transmission route, infant variants required more CD4 molecules/cell to achieve entry as measured by EC20 ($p<0.0001$). There were no differences in EC20 between variants from infants infected in utero or by breastfeeding ($p=0.7228$), or between variants from the transmitting mothers in each group ($p=0.7340$).

Conclusions: Our data indicate that vertical transmission of HIV does not select for highly efficient usage of CD4, and in fact may require the presence of susceptible target cells with relatively high CD4 expression for either initiation or propagation of infection. Given the lack of route specificity, the described selection is likely not occurring at the site of initial barrier breach (e.g. placenta or gut epithelium), and may represent a common pathway of amplification/outgrowth required for efficient dissemination following the initial seeding event. Our data also support a role for transient inflammation in enhancing fetal/infant susceptibility to infection.

Session P-T5 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Characteristics of Pregnant Women in PMTCT

873 HIV Viral Load and CD4 Cell Count in Untreated Pregnant Women Entering Care in Cape Town, South Africa

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Background: In many parts of sub-Saharan Africa, CD4+ cell counts are used to determine eligibility for triple-drug antiretroviral therapy (ART) regimens in HIV-infected pregnant women. There is widespread interest in policies for the universal use of ART in pregnancy, regardless of CD4+ count, to reduce viraemia and the subsequent risks of both vertical and horizontal HIV transmission. Yet there are few data on the distribution of HIV viral loads in untreated HIV-infected pregnant women before antiretroviral exposure, and the correlation between viraemia and CD4+ cell counts that may be used to define ART eligibility.

Methodology: We measured HIV viral loads (VL) in consecutive HIV-infected pregnant women, not already on ART or antiretroviral prophylaxis, making their first visit to services for the prevention of mother-to-child HIV transmission (PMTCT) at a large urban antenatal clinic in Cape Town, South Africa. Specimens for VL (Abbott RealTime HIV-1 assay) and CD4+ cell count via flow cytometry (Beckman Coulter) were taken before initiating antiretrovirals. Socio-demographic characteristics and medical history were taken from structured interviews and clinical/laboratory record reviews.

Results: Among 398 women initiating PMTCT between April and September 2013, the median age and gestational age were 28 years (IQR, 24-32) and 21 weeks (IQR, 16-26), respectively; 52% of women were newly diagnosed with HIV in the current pregnancy. The median VL was 3.9 log10 copies/mL (IQR, 3.4-4.5); 8% of women (n=33) had >100,000 copies/mL, 15% (n=62) had 500 cells/μL, respectively (Table).

Conclusions: A substantial proportion of HIV-infected pregnant women in this setting have high viral loads and are at high risk of both mother-to-child and sexual HIV transmission, but also have raised CD4+ cell counts that would make them ineligible for triple-drug antiretroviral regimens under many policies. As efforts to optimize PMTCT services and eliminate paediatric HIV infection expand across Africa, these data point to potential limitations of strategies that use CD4-based criteria to define ART eligibility for pregnant women.

Table. Distribution of HIV viral load by CD4 cell count categories among untreated HIV-infected pregnant women before ART initiation.

CD4 cell count (cells/μL)	*HIV viral load (copies/mL)*			
	<1000	*1000 – 10,000*	*10 000 – 100,000*	*>100,000*
<350	8 (14%)	38 (27%)	82 (59%)	24 (79%)
350-500	14 (25%)	44 (31%)	35 (25%)	2 (7%)
>500	34 (61%)	61 (43%)	23 (16%)	4 (14%)

874 Detectable Viraemia Among Pregnant Women On Antiretroviral Therapy Initiating Antenatal Care

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Background: Services for preventing mother-to-child transmission (PMTCT) of HIV in sub-Saharan Africa typically focus on identifying HIV infection and initiating antiretroviral regimens in pregnant women who are not already in care. However significant increases in antiretroviral therapy (ART) uptake across the region mean that a growing number of HIV-infected women conceive and initiate antenatal care already on ART. Women conceiving on ART are presumed to be virally suppressed throughout pregnancy, and thus at minimal risk of vertical HIV transmission, but there are few data on viraemia in pregnancy in women conceiving on ART in African settings.

Methodology: Working in a large primary care antenatal clinic (ANC) in Cape Town, South Africa, we conducted a cross-sectional study of consecutive HIV-infected pregnant women who had started ART before conception. We examined the prevalence and correlates of viraemia, defined in separate analyses as >50 copies/mL (Abbott RealTime HIV-1) and >1000 copies/mL (as vertical transmission risk increases above this level).

Results: Between April and September 2013, 210 women reported current use of ART at their first ANC/PMTCT visit, representing 35% of all HIV-infected pregnant women attending the service. The median duration of ART use before pregnancy was 2.7 years (IQR, 1.4-5.2). The majority of ART regimens (69%) were tenofovir, lamivudine and either efavirenz (50%) or nevirapine (19%); and additional 13% of women were on a second-line regimen based on protease inhibitors (PI). Twenty percent reported missing ART doses on at least 2 days during the preceding month. Overall 167 (81%) of women had 10,000 copies/mL, respectively. In logistic regression models, there were no significant demographic or clinical predictors of viraemia at either >50 or >1000 copies/mL, including age, gravidity, gestation, regimen or duration of ART use. However women with viral loads >1000 copies/mL were more than twice as likely to report missing 2 or more doses in the preceding 30 days, compared to women who were suppressed (p=0.025).

Conclusions: These data demonstrate a surprisingly high prevalence of detectable viraemia among pregnant women entering PMTCT services already on ART, representing a vertical transmission risk that is not well understood in African ART programmes. With increasing numbers of HIV-infected women of reproductive age receiving lifelong ART (more than one-third in this setting) there is an urgent need to investigate the causes of viraemia in this group of patients and in turn develop strategies to intervene to reduce viral load rapidly in these women.

875 Steady Decline: Temporal Changes in Substance Use by HIV-Positive Pregnant Women in the US

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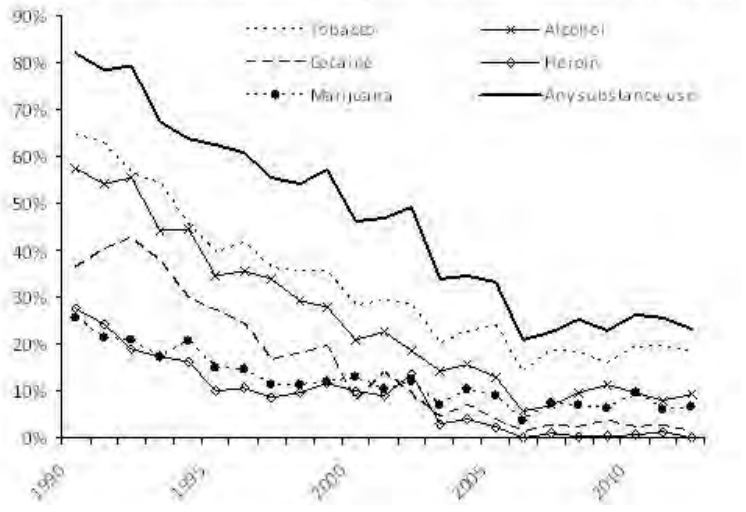
Background: Substance use during pregnancy has implications for HIV transmission, infant outcomes, and maternal outcomes. This study describes changes in and correlates of substance use during pregnancy from 1990-2012 in two US-based cohorts of HIV-infected women.

Methodology: All women enrolled in the Women and Infants Transmission Study (WITS) and the Pediatric HIV/AIDS Cohort Study's Surveillance Monitoring for ART Toxicities Study (SMARTT) who gave birth from 1990-2012 and had available substance use information were included. Women were classified as using a substance during pregnancy if they self-reported or had a positive biological sample (urine in WITS or meconium in SMARTT) for alcohol, tobacco, marijuana, cocaine, or heroin use. Log binomial generalized estimating equations (GEE) were used to test for temporal trends and account for correlation between repeated pregnancies by the same woman. Predictors of substance use were evaluated using a multivariable logistic GEE.

Results: Over the duration of the study, substance use among the 5,451 enrolled women sharply declined; 82% of women reported substance use during pregnancy in 1990, compared to 23% in 2012 (Figure 1). During the 22-year period, use of each substance decreased significantly (p<.001 for each substance) in an approximately linear fashion, until reaching a plateau in 2006. In the subset of 824 women with multiple pregnancies under study observation, substance use did not significantly decrease with successive pregnancies. Women who used a substance during the previous pregnancy were 5.45 times more likely (95% Confidence Interval: 4.46, 6.67) to use a substance during their next pregnancy. In the HAART era (1996 - 2012), White race, older age, less education, being unmarried, and not taking antiretroviral medications were associated with an increased risk of using substances during pregnancy.

Figure 1. Substance use during pregnancy by year of delivery (N = 5,451)



Conclusions: A substantial decrease in substance use during pregnancy was observed between 1990 and 2012 in two large US cohorts of HIV-infected women. The observed decrease may largely be due to the HIV/AIDS epidemic becoming more generalized in the US population in recent years. Our data also suggest that HIV-infected women who used substances during previous pregnancies are at an increased risk of using substances in future pregnancies, and may be a target for future interventions.

Session P-T6 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Early Infant HIV Diagnosis

876 Modeling the Performance and Cost of Early Infant HIV Diagnosis at Birth

Intira J. Collins[1], Martina Penazzato[2], Dick Chamla[3], Anisa Ghadrshenas[4], Teri Roberts[5], Jennifer Cohn[5], Nicole Ngo-Giang-Huong[6], Nathan Shaffer[2], Meg Doherty[2], Lisa J. Nelson[2]

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Background: Untreated HIV-infected infants are at high risk of death in the first year of life. WHO recommends early infant diagnosis (EID) using virological testing (VT) from 6 weeks, but coverage is poor. Testing at birth (BT) was hypothesized to improve EID coverage and reduce mortality by earlier initiation of ART, although VT has poorer sensitivity at birth. We modelled the performance and cost of BT against the current WHO algorithm. We present preliminary results of the model applied to South Africa.

Methodology: A decision tree cohort simulation model was developed and applied to infants born in a prevention of mother to child transmission of HIV (PMTCT) program setting. Infants enter the model at birth with a risk of in-utero, intra- and post-partum transmission. In the BT algorithm, children are tested at birth (0-3 days), 12 wks, 9 and 18 months vs. testing at 6 wks, 9 and 18 months in the WHO algorithm. Both algorithms include testing at end of breastfeeding. The model runs up to 24 months of age. HIV-infected children have a probability of diagnosis, referral for HIV care, ART initiation or pre-ART death (Table 1). Outcomes of interest were positive predictive value (PPV), negative predictive value (NPV) of VT, cost per diagnosis, proportion of HIV-infected children correctly diagnosed, initiated on ART and pre-ART deaths.

Results: PPV and NPV was 88.5% and 97.6% in BT and 90.8% and 97.6% in the WHO algorithm, respectively. Cost per HIV-infected diagnosis was $1,379 and $458, respectively. The proportion of HIV-infected children diagnosed by 24 months was 69.2% in BT vs 54.9% in WHO algorithm. However, the proportion of HIV-infected children starting ART was more comparable at 37.0% vs 32.4%; and pre-ART deaths was 24.9% vs 26.7% respectively. In scenario analyses, assuming improved EID coverage, retention and referral for ART (90%) the proportion starting ART rose to 70.2% vs. 68.5%, and pre-ART deaths fell to 17.1% and 18.1% respectively. In contrast, if we assumed current coverage/referral rates but higher sensitivity of BT (98%), the proportion of HIV-infected diagnosed rose to 75.2%, but with modest improvements in proportions starting ART(40.7%) and pre-ART death (23.1%).

Conclusions: EID at birth would potentially increase the proportion of HIV-infected children diagnosed, but has lower PPV; if not accompanied by improved retention and referral for ART, it offers limited improvements in proportion starting ART or in reducing pre-ART mortality.

Table 1. Key model parameters and assumptions

Parameter	Estimate	Source/Comment
No. HIV-exposed infants born per year	258,000	S.African EID report 2012
Coverage of PMTCT (excluding single dose nevirapine)	95%	UNAIDS 2012
Risk of transmission in the PMTCT setting (assuming access to ART, include late presenters/defaulters)	3% in-utero, 1.3% intra partum, 0.2% per month breastfeeding	Guided by Sherman & Lilian 2012 (cumulative MTCT 7.9% If breastfeed for 18 months)
Infant diagnosis coverage	88% at birth (facility birth); 54.7% at <2 months;50% at 9months / end breastfeeding, 30% at 18 months	SA UNDP Maternal health 2009;South Africa EID report 2012; Assumption
Sensitivity of DNA PCR	67% at birth; 98.8% at 6 weeks; 99.2% >90 days	Shapiro et al. IAS 2011; S. Africa EID report 2012; WHO 2010.
Specificity of DNA PCR	99.09% at birth; 99.4% ≥ 6 weeks	Shapiro et al. IAS 2011; WHO 2010.
Rate of return for EID results	60%	Rollins et al. 2009
Referral to / initiate ART	67% if diagnosed <2mo;60% in older children	Hsiao et al. 2013

877 Access To Early Infant Diagnosis and Antiretroviral Therapy in Abidjan, Côte d'Ivoire, 2011-2013

Divine Avit[1], Madeleine Folquet-Amorissani[2], Clarisse Amani-Bosse[1], Jeanne Eliam-Kouakou[1], Véronique Méa-Assandé[3], Edmond Aka[4], Irma Ahoba[5], Didier K. Ekouévi[6], Marguerite Timité-Konan[7], **Valériane Leroy[8,9]**, for the MONOD ANRS 12206 Study Group

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Background: Since 2010, the routine initiation of early antiretroviral therapy (ART) is recommended by WHO for all HIV-infected children younger than two years old. The national Ivoirian program decided to scale-up the early infant diagnosis (EID) of HIV using Dried Blood Spot (DBS) in 2011. We described the access to pediatric HIV EID results and pediatric ART in Abidjan, Côte d'Ivoire.

Methodology: In the context of the recruitment in the MONOD ANRS 12206 trial, a survey of the tools and timing used for EID, and the access to ART for all the children identified as HIV-infected before the age of two, was conducted in 29 health centers in Abidjan from September 2011 to January 2013. The rate of announcement of EID results, and the subsequent access to ART before the age of two for those HIV-infected were studied; barriers were described and the correlates of early access to ART analyzed using a logistic regression model.

Results: A total of 2397 HIV-exposed infants under 12 months had access to an EID based on "Dried Blood Spot". Their test results were returned to the sites in 77.2% of cases and announced to their family in 58.7% of cases. Out of the 226 children confirmed as HIV-infected<2 years of age, 80.3% were identified by PCR DNA on DBS before 12 months of age, 4.8% by PCR DNA at 12-18 months and 14.9% by serology after 18 months. Before the age of two, 148 children were initiated on ART: the ART coverage was 64.6% (95% CI [59.3%-71.7%]) of which 70.0% via the inclusion in the Monod trial. The missed opportunities of access to ART (34.4%) were due to the early death of the child (57.7%), the parental refusal of ART (30.8%) and the loss to follow-up of children (11.5%). The age of the child>12 months at diagnosis (adjusted odds ratio [aOR]:4.2;95% CI:1.6-11.0), a maternal age>30 years (aOR:2.4;95% CI:1.2-4.9), the parental access to ART for their own health (aOR:2.6;95% CI:1.2-5.6) were independently significantly associated with a higher access to early initiation of pediatric ART, while "an unknown HIV status for himself or his child" declared by the father was associated with a lower access to pediatric ART (aOR:0.2;95% CI:0.1-0.5).

Conclusions: Although pediatric access to ART is feasible, there are still remaining too many missed opportunities to cover the access to ART needs before 2 years of age in 2011-2013. Challenges still remain to improve early diagnosis of HIV-infected infants at the earliest convenience, and to promote a continuum of care for HIV-infected children before they die. With the commitment of the National Program, it is crucial to identify sustainable mechanisms to promote an early access to infant HIV care services within a family approach in Côte d'Ivoire.

Session P-T7 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Risk Factors for MTCT

878 Impact of Maternal Incident HIV Infection On Early HIV Vertical Transmission, South Africa in 2011

Thu-Ha Dinh[1], Kevin Delaney[1], Debra Jackson[2], Selam Woldesenbet[3], Yogan Pillay[4], Ameena Goga[5]

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Background: We used data from a nationally representative evaluation of the South African prevention of MTCT program to estimate the risk of maternal incident HIV infection during pregnancy on early MTCT risk in South Africa (SA) in 2011-2012

Methodology: We recruited mothers and their 4-8 week old infants from 578 primary health facilities using a stratified multi-stage sampling design from August 2011 to March 2012. Mothers were interviewed and infant dried blood spot samples (iDBS) were collected and tested for presence of HIV antibody and HIV DNA. Maternal incident HIV infection during pregnancy was defined as an HIV antibody positive result on DBS of an infant whose mother reported having a negative HIV test result and had no evidence of receiving antiretroviral (ARV) drugs when pregnant with the infant. We used a uniform distribution of the time between delivery and last reported negative HIV test result during the pregnancy to estimate gestational age at infection. Estimates are adjusted for nonresponses and weighted by 2011's live births in SA

Results: Of 9802 mother-infant pairs included in the current analysis, 7064 infants tested HIV antibody negative and 2738 HIV antibody positive on iDBS indicating the mother was HIV infected when pregnant with the infant. The latter includes 212 maternal incident HIV infections. This results in a weighted national estimate of 3.1% maternal incident HIV infection. Median time of incident infection was at 32.1 weeks gestation (95% confidence interval (CI) 31.4-33.4wks) with 23.6% occurring between 32-36 weeks and 27.4% after 36 weeks gestation. Mother to Child Transmission of HIV (MTCT) risk was 10.7% (95% CI: 6.2% - 16.8%) for mothers with incident infection compared to 2.2% (95% CI: 1.6% - 2.8%) for mothers already HIV infected. Although they represent only 2.2% of all mothers (n=9802), and 6.7% of HIV-infected mothers, mothers with incident infection accounted for 26% of early MTCT risk. Multivariable analysis indicates incident infection was highest for women who reported the baby's father was HIV infected (Adjusted Odd Ratio (AOR) =6.2, p< 0.05) compared to those that knew the baby's father was uninfected), while each additional follow-up antenatal care visit reduced incident infection (AOR=0.92, p<0.05)

Conclusions: Maternal incident HIV infection during pregnancy is high and contributes to a significant burden of newly HIV infected infants in SA. Repeat-testing at 32 weeks gestation, during labor and 6 weeks postpartum will identify mothers with incident infection who should receive ARV therapy (ART) to reduce MTCT risk. Couple counseling and providing ART to HIV positive male partners of HIV-negative women seeking to become pregnant could also reduce maternal incident HIV infection and MTCT

879 Syphilis in HIV-Infected Mothers and Infants: Results From the NICHD/HPTN 040 Study

Nava Yeganeh[1], Heather Watts[2], Margaret Camarca[3], Esau Joao[4], Jose Henrique Pilotto[5], Glenda Gray[6], Gerhard Theron[7], Valdilea G. Veloso[8], Lynne M. Mofenson[2], Karin Nielsen-Saines[1], NICHD HPTN 040/ P1043 Study Team

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Background: The HIV and syphilis epidemics overlap, particularly in low and middle-income countries. Over 1 million pregnancies are complicated by congenital syphilis annually. Untreated maternal syphilis is associated with spontaneous abortion, stillbirth, prematurity, and neonatal and infant mortality.

Methodology: We evaluated data available from 1664 mothers and 1684 infants enrolled in NICHD/HPTN 040 (P1043), a study focused on prevention of *intrapartum* HIV transmission to infants born to HIV-infected mothers who did not receive antiretrovirals prior to labor. Univariate and multivariate logistic regression were performed to determine predictors of maternal syphilis and the occurrence of congenital syphilis in their newborns.

Results: One hundred seventy-one HIV-infected women enrolled in NICHD/HPTN 040 (~10% of the cohort) had serological evidence of syphilis without adequate documentation of treatment during pregnancy. One hundred thirty two women had reactive non-treponemal serologies with confirmatory treponemal tests while 39 women had a positive non-treponemal test with no confirmatory testing performed. One hundred and twenty infants were treated for congenital syphilis during the study, with 24 infants treated for both HIV and syphilis. Multivariate analysis demonstrated that dually-infected women were significantly more likely to self-identify as non-white (AOR 2.5, 95% CI 1.5-4.2) and to drink alcohol during pregnancy (AOR 1.5, 95% CI 1.1-2.1). Dually-infected women were also twice as likely to transmit HIV to their infants (AOR 2.1, 95% CI 1.3-3.4), with 88% of HIV infections in these children acquired *in-utero*. Co-infected infants were significantly more likely to be born to mothers with VDRL titers $\geq$1:16 (AOR 3, 95% CI 1.1-8.2) and higher HIV viral loads (AOR 1.5 95% CI 1.1-1.9). Of 6 newborns with symptomatic syphilis, 2 expired shortly after birth, and 2 were HIV-infected.

Conclusions: Syphilis continues to be a common co-infection in HIV-infected women and is associated with a higher likelihood of *in utero HIV* transmission. Prompt recognition of syphilis infection in HIV-infected women is necessary to avoid adverse pregnancy outcomes, including HIV *in utero* transmission or fetal/neonatal death. While most neonates with congenital syphilis are asymptomatic at birth, symptomatic disease is associated with high morbidity and mortality.

880 Antiretroviral Adherence Associated With Reduced Breastmilk HIV-1 Transmission: The BAN Study

Nicole L. Davis[1], William C. Miller[2], Michael G. Hudgens[3], Charles S. Chasela[4], Dorothy S. Sichali[4], Dumbani Kayira[4], Athena P. Kourtis[5], Sascha R. Ellington[5], Denise J. Jamieson[5], Charles M. van der Horst[6]

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Background: Postnatal HIV-1 transmission occurred in the Breastfeeding, Antiretrovirals and Nutrition (BAN) study despite well-controlled implementation of either maternal antiretrovirals (ARV) or daily infant nevirapine (NVP) throughout 28 weeks of breastfeeding. One possible explanation for transmission is suboptimal adherence to prescribed antiretrovirals. Quantifying the association between adherence and breastmilk HIV-1 transmission will have significant practical implications for elimination of mother-to-child HIV transmission efforts.

Methodology: We included mother-infant pairs randomized to receive 28 weeks of either maternal ARV (Zidovudine, lamivudine, and either nevirapine, nelfinavir, or Kaletra©) or daily infant NVP as part of the BAN study. Using extended Cox models, we estimated associations between postpartum ARV adherence and breastmilk HIV-1 transmission between 5-38 weeks of age. We measured adherence over four time intervals between 2-28 weeks postpartum using pill count, suspension bottle weight, and maternal self-report. We used multiple imputation to account for missing adherence measures. Infant HIV infection was determined by polymerase chain reaction every 2-6 weeks using the Roche Amplicor 1.5 DNA assay. The primary endpoint was infant HIV infection by 38 weeks of age among infants alive and uninfected at 5 weeks, with censoring at loss to follow-up.

Results: 1477 mother-infant pairs were included in analyses. Using pill count and bottle weight information, 22-40% of mother-infant pairs at any given interval were < 90% adherent. Between 5-10% of mothers at any given interval self-reported missing at least one dose of maternal or infant ARV medication over the last three days. Having ≥ 90% pill count or bottle weight adherence was associated with a 56% (95% CI 12-78%) relative reduction in the rate of HIV-1 transmission by 38 weeks of age, compared with having < 90% adherence when controlling for study arm, time-dependent reported breastfeeding status, and maternal baseline characteristics, including age, CD4+ count, and hemoglobin level. Reporting missing no pills in the prior 3 days (100% self-reported adherence) was associated with a 66% (95% CI 14-86%) relative reduction in the adjusted rate of HIV-1 transmission, compared with those self-reporting < 100% adherence during the prior 3 days. Complete case analyses rendered similar results (pill count or bottle weight: n=500, adjusted HR 0.41, 95% CI 0.18-0.93; self-report: n=540, adjusted HR 0.26, 95% CI 0.09-0.72).

Conclusions: Maintaining adherence to postpartum ARVs throughout breastfeeding is important for elimination of mother-to-child transmission. More work is needed to identify patients likely to be non-adherent, and to intervene before HIV transmission occurs.

881 Cytomegalovirus and Possibly Epstein-Barr Virus in Breast Milk May Facilitate HIV-1 Transmission

Johannes Viljoen[1], Edouard Tuaillon[2], Nicolas Nagot[2], Siva Danaviah[1], Marianne Peries[2], Prevashinee Padayachee[1], Vincent Foulongne[2], Ruth Bland[1], Nigel Rollins[3], Marie-Louise Newell[1], **Philippe Van de Perre[2]**

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Background: HIV-1 mother-to-child transmission (MTCT) occurs despite antiretroviral treatment (ART), including through breastfeeding, although the exact mechanisms remain largely unknown. Since the vast majority of breastfed infants of HIV-1 infected mothers escape infection even in the absence of ART, some factors must drive HIV-1 transmission by breastfeeding. Co-infections including Cytomegalovirus (CMV) and Epstein-Barr virus (EBV), may be associated with increased risk of HIV-1 MTCT through mechanisms enhancing reciprocal viral replication. Here we report the findings of a case-control study that investigated the relationship between CMV DNA levels and EBV DNA detection in breast milk (BM) and the risk of MTCT of HIV-1 via breastfeeding.

Methodology: Active subjects were 62 mothers with established HIV-1 infection and proven postnatal transmission of HIV-1 via breastfeeding (transmitters), matched by non-transmitter controls. Cell-free HIV-1 RNA, cell-associated HIV-1 DNA, CMV and EBV DNA were quantified in breast-milk (BM) and their association with MTCT of HIV-1 determined. Samples immediately prior to the estimated timing of transmission of HIV-1 were used.

Results: Maternal HIV-1 RNA plasma viral load was significantly higher in transmitters (4.5 log10 copies/ml) [IQR 3.9-4.8] than in controls (3.8 log10 copies/ml) [IQR 3.1-4.4] (p=0.003) and there was a trend towards lower CD4 counts; median (IQR) BM HIV-1 DNA level was similarly higher in transmitters, 5002 (1993-14890) than in controls, 280 (280-461.5) copies/106 BM cells. Median CMV DNA viral load was significantly higher in transmitters (median 88044 DNA copies/106 BM cells; IQR 18586-233904) than controls (median 11167; IQR 3221-31152) (p&lt0.001). Breast milk CMV DNA load was associated with maternal CD4 depletion in blood (p&lt0.001) CMV DNA viral load in BM was significantly associated with post-natal MTCT of HIV-1 with a &gt2-fold risk of MTCT with every 1 log increase in CMV DNA level. This risk was independent of HIV-1 RNA levels in milk. EBV DNA detection in BM may also facilitate MTCT of HIV-1, but only marginally.

Conclusions: This study provides evidence of an independent association between CMV DNA in BM, and additionally a marginal association between EBV DNA in BM, and postnatal MTCT of HIV-1, while confirming previous findings that HIV-1 RNA and DNA levels in breast-milk are strongly predictive of postnatal transmission of HIV-1. The demonstrated association between CMV and EBV DNA and HIV-1 levels in BM in this study may explain persistent shedding of HIV-1 in BM in women receiving ART. Valacyclovir as a potential adjuvant to ART to reduce MTCT of HIV-1 during the period of breastfeeding is an interesting concept that would require further study.

Session P-T8 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

PMTCT Approaches: Implementation and Outcome

882 Programmatic Implementation of WHO Option B in Botswana Associated With Increased Projected MTCT

Scott Dryden-Peterson[1,2], Sajini Souda[3], Rebecca Zash[2,4], Jennifer Chen[5], Chipo Petlo[6], Eldah N. Dintwa[6], Refeltetswe Lebelonyane[6], Mompati Mmalane[2], Shahin Lockman[1,2], Roger L. Shapiro[2,4]

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Background: The 2013 WHO guidelines for prevention of mother-to-child transmission (PMTCT) recommend that countries offering antenatal zidovudine (Option A) transition to 3-drug antiretroviral treatment (ART) for all pregnant women, regardless of CD4 count (Option B or B+). In 2009, Botswana became one of the first African countries to transition from WHO Option A to Option B. Although midwives at antenatal clinics administered Option A, women were referred to ART clinics to start ART under Option B. We evaluated the impact of this transition on projected MTCT.

Methodology: From May 2009 to October 2012, covering both the initial pilot in selected regions and the general roll-out of Option B, we abstracted all obstetric records at 6 of the busiest maternity wards in Botswana to determine the PMTCT interventions received in pregnancy and at the time of delivery. We used published estimates for MTCT rates by maternal CD4 strata and interventions received to assign an MTCT prevention score (MPS) to each delivery. Multivariable regression accounting for clustering was used to estimate the impact of Option B on the MPS while adjusting for maternal and facility characteristics.

Results: Of 36597 Botswana citizens delivering, 29.7% were HIV infected, 69.1% were HIV-uninfected, and 1.2% had undocumented HIV status. Among 10867 HIV-infected women, 27.2% started ART prior to pregnancy and 72.8% were ART-naïve. Of ART-naïve women, 65.2% entered antenatal care at a clinic offering Option A and 34.8% at a clinic offering referral for Option B (an onsite ART clinic was available to provide Option B for 65.3% of women). Trends in antiretroviral use and MPS are shown in Figures 1 and 2. In adjusted analyses, registering at a clinic offering referral for Option B was associated with increased ART use (adjusted odds ratio [aOR] 2.68, 95% confidence interval [CI] 2.32 to 3.10), but also an increased likelihood of no antenatal antiretroviral use by the time of delivery (aOR 2.05, 95%CI 1.69 to 2.47). Overall, in the first 3 years of the program, Option B implementation was significantly associated with higher projected MTCT rate, MPS +0.14 (P<0.001).

Conclusions: Implementation of Option B in Botswana was associated with an overall increased projected MTCT rate, due to increased numbers of women receiving no antenatal antiretrovirals. Programs starting Option B or B+ should ensure that ART is initiated at antenatal clinics and that zidovudine monotherapy remains an available option in the event of delayed ART initiation.

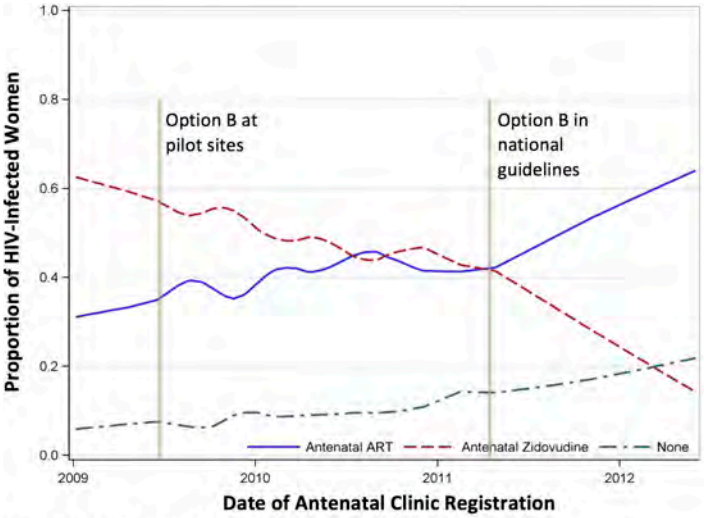

Figure 1: Antenatal antiretroviral use by women delivering at surveillance sites, 2009 to mid-2012.

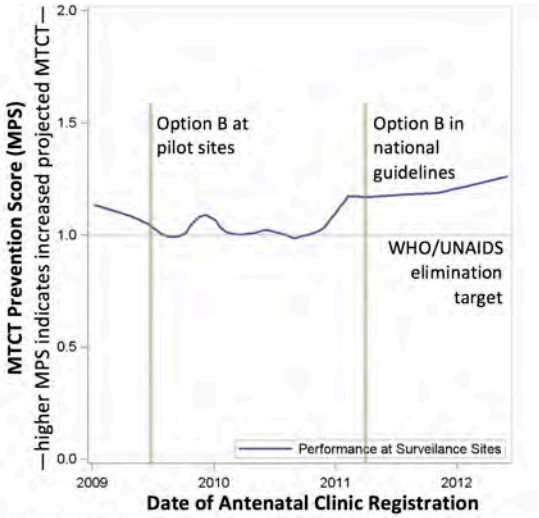

Figure 2: MTCT Prevention Score (MPS) for women delivering at surveillance sites, 2009 to mid-2012.
* MPS indexes projected risk of transmission to the WHO/UNAIDS elimination target (<5% transmission). MPS above 1.0 indicates projected transmission above target.

883 Impact of Option B+ On Uptake, Retention, and Transmission: A Pre/Post Study in Lilongwe, Malawi

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Background: In September 2011, Malawi implemented Option B+ (B+), lifelong antiretroviral therapy (ART) for pregnant and breast feeding women. The Tingathe program, started in 2009, two years prior to B+, is a service program utilizing dedicated community health workers (CHWs) as case managers to improve uptake and retention along the PMTCT cascade. The service is offered as part of routine care at participating government health centers. We assessed the impact of B+ on service uptake, retention, and vertical HIV transmission by comparing outcomes pre and post B+ implementation at 2 health centers in Lilongwe.

Methodology: PMTCT service utilization, program retention, and transmission outcomes at 1st DNA PCR (4-20 wks of age) were compared for HIV-infected (HIV+) pregnant women and their exposed infants followed in Tingathe 18 months pre (Oct 2009-Mar 2011) and post (Oct 2011-Mar 2013) B+. Chi-square and Fisher's exact test as well as two-sample t-test were used to compare proportions of events and continuous variables, respectively.

Results: A total of 13,926 (pre) and 14,022 (post) women presented to antenatal care. Post B+ a smaller proportion of women were HIV tested (98.9% pre vs 83.4% post; p<0.001); attributed to test kit stock-outs. There were 1654 (pre) and 1535 (post) HIV+ women identified, with a larger proportion already known to be HIV+ (18.1% vs 41.2%; p<0.001) and an increase in the proportion of women already on ART post B+ (22.8% vs 31.1%; p<0.001). Of those starting ART, mean time to ART initiation (38 ± 32 vs 19.7 ± 47 days; p<0.001) and duration on ART prior to delivery (69 ± 43 vs 93 ± 46.5 days; p<0.001) improved significantly. Amongst recorded live births there was no change in proportion of women (95.6% vs 96.3%; p=0.45) and infants receiving antiretrovirals for PMTCT (96.3% vs 95.3%; p=0.11) nor infants receiving 1st DNA PCR (80.9% vs 82%; p=0.55). However, other outcomes suggest improvements in infant care post B+: mean age at 1st DNA PCR (70 ± 45 pre vs 57 ± 31 days post; p<0.001) and transmission at 1st DNA PCR was lower (4.6% pre vs 2.6% post; p=0.046); proportion of HIV+ infants starting ART was greater (78.1% vs 90%; p=0.45); mean age at initiation was lower (171 ± 88 vs 118 ± 76 days; p=0.046).

Conclusions: Patient level data from a CHW supported program in Lilongwe, Malawi demonstrate that B+'s simplified PMTCT approach has resulted in several improvements including improved ART use during pregnancy and more rapid initiation with longer duration of coverage for those newly initiating. Early findings suggest concomitant improvements in infant care along the cascade. Health systems issues like timely and reliable HIV testing for women and infants, continue to greatly impact implementation and will need to be addressed to ensure an AIDS-free generation.

884 Home, Antenatal Clinic or VCT: Preferences of Pregnant Women and Their Partners for Male HIV Testing

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Background: Male partner HIV testing and counseling (HTC) enhances prevention of mother to child HIV transmission (PMTCT), yet male HTC during pregnancy remains low. Identifying male HTC models preferred by pregnant women and their male partners might improve male partner uptake of HIV testing and involvement in maternal and child health.

Methodology: In a randomized clinical trial of home-based versus clinic-based male partner HTC to improve male partner testing during pregnancy, pregnant women and their male partners were interviewed to determine the preferred location for male partner testing as either home-based, at a voluntary counseling and testing center (VCT) or antenatal care (ANC) clinic. Proportions of women and their partners who preferred each testing model were determined at baseline and then compared 6 weeks after the intervention using McNemar's tests.

Results: Three hundred women were randomized, 150 to home-based and 150 to ANC clinic based male partner HTC. At enrolment, the majority (54%) stated they would prefer home-based to ANC clinic based (34%) or VCT based (12%) male partner HTC. Overall, post-intervention, the proportion of women preferring home-based HTC increased (65% vs 54%; odds ratio [OR] 1.90 95% confidence interval [CI] 1.26-2.89, p=0.001), while the proportion preferring male partner testing at the ANC clinic (25% vs 34%; OR 0.60 CI 0.35-0.87; p=0.007) or VCT (9% vs 12%; p=0.258) decreased.

At enrollment, 95 (71%) of 133 male partners reached at home compared to 33 (60%) of 55 male partners who came to the clinic preferred home-based HTC. Following the intervention, majority of men 116 (87%) reached at home were significantly more likely to recommend home-based HTC (OR 3.33 95% CI 1.54-7.98; p=0.001), while more men 36 (65%) tested at the ANC clinic had a non-significant trend towards home-based male partner HTC (OR 1.27 CI 0.54-3.10; p= 0.548). Post intervention, significantly fewer men reached at home recommended male partner testing at the ANC clinic (7% vs 14%; OR 0.41 CI 0.144-1.04, p= 0.041) or VCT (6% vs 14%; OR 0.35 CI 0.11-0.94; p=0.035). Male partners reached at the clinic post-intervention were less likely to prefer ANC clinic based HTC (24% vs 31%; p=0.394) but slightly more likely to prefer VCT center HTC (11% vs 9%; p= 0.706), however these changes were not statistically significant.

Conclusions: Home-based male partner testing was preferred over VCT based or ANC clinic based testing by both pregnant women and their male partners. Home-based male partner HTC during pregnancy may increase the number of male partners who undergo HTC, and identify HIV negative women in HIV discordant relationships who are at high risk of HIV acquisition and mother-to-child HIV transmission.

885 Early Infection Among Ugandan HIV-Exposed Infants Whose Mothers Received Option B+ vs Option A

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Background: Interventions with combination antiretroviral (ARV) treatment during pregnancy and breastfeeding have shown significant progress in prevention of mother to child transmission (PMTCT) of HIV. At Mulago Hospital, Uganda, Option A(antenatal zidovudine plus peripartum single dose nevirapine/zidovudine/3TC tail and infant nevirapine throughout breastfeeding) were used from December 2010 for PMTCT. Option B+ (lifetime ART for PMTCT) with Tenofovir/3TC/Efavirenz was rolled out in October 2012

Methodology: We compared early (6-12 week) infection rates among infants of HIV+ mothers at Mulago Hospital who received either Option A from Dec.2010 to Oct. 2012 or maternal ART if they met HIV treatment criteria; with infant infection rates among HIV+ women who received option B+ (Oct. 2012_Aug. 2013) HIV positive mothers received option B+ (lifelong ART for PMTCT), and HIV exposed newborns received daily Nevirapine for 6 weeks. Infant DNA PCR testing using Roche Taqman on DBS was done from 6-12 weeks

Results: Out of 1015 mothers who received option A for PMTCT, 29 (2.9%) infants tested PCR positive at age 6-12 weeks, compared to 11/586 (1.9%) infants born to mothers who received Option B+. The lowest infection rates were observed for infants whose mothers received ART for their own health; 21/1948(1.1%) during both time periods.

Conclusions: There were no significant differences in early HIV infection rates among HIV exposed infants whose mothers received option B+ compared to those who earlier received option A. Further follow up is needed to ascertain long term adherence, emergence of resistance, and late transmission rates for Option A versus B+ regimens; particularly among asymptomatic HIV + women with higher CD4 counts.

Table1: Infant PCR Status at 6-12 weeks

ARV Regimen	HIV PCR Positive	Total
Option A	29 (2.9%, 95% CI 1.9-4.1)	1015
Option B+	11 (1.9%, 95% CI 0.9-3.3)	586
ART	21 (1.1%, 95% CI 0.7-1.6)	1948
Total	61	3549

**ART: met adult treatment criteria for own health during roll out of option A and option B+*

886 Lay Health Worker Support To Strengthen PMTCT: A Randomised Controlled Trial in South Africa

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Background: In South Africa, PMTCT services need to be strengthened to eliminate pediatric HIV by 2015. Lay health workers (LHWs) can play an important role in supporting the continuity of care in primary health care services in developing countries.

Methodology: This pragmatic cluster randomised controlled trial assessed the effectiveness of LHWs in reducing missed opportunities at PMTCT services. The study was conducted in the Free State province, South Africa where HIV antenatal prevalence was estimated at 30% in 2011.

LHWs at 16 intervention clinics supported pregnant women individually; presented health promotion messages, and assisted with clinic tasks. Sixteen control clinics offered standard PMTCT services. Routine data on PMTCT cascade indicators were collected and verified against paper-based registers and clinical records at all sites, from April 2011 to March 2013. Time series analysis was used to analyse overall trends in the indicators over time, and mulitvariate logistic regression was used to model the effect of the intervention for each indicator. The main outcome was PMTCT coverage, defined as the proportion of HIV-infected women who received prophylaxis or ART at delivery.

Results: Over 24 months, there was a significant increase in early antenatal presentation; follow-up HIV re-testing rates at 32 weeks and PMTCT coverage across all 32 sites. HIV-negative women who tested were more likely to retest for HIV at 32 weeks at the intervention sites (OR: 1.32, 95% CI: 1.03-1.69, p<0.05). The odds of PMTCT coverage were greater in the intervention sites, however, this outcome was not statistically significant (OR: 1.12, 95% CI: 0.86-1.46). Other PMTCT indicators did not show significant differences between intervention and control arms.

Conclusions: LHWs played a crucial role in supporting, informing and ultimately enabling continuity of care during pregnancy. The increased 32-week re-testing rate in intervention sites suggests LHWs positively influenced continuity of care. The increasing trend in performance across all sites may have been due to external factors, including the prioritization of national PMTCT policy at the time.

Session P-T9 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

ART Pharmacokinetics During Pregnancy and Breast-Feeding

887 Low Darunavir Exposure During Pregnancy With 800/100 mg Darunavir/r QD Dosing

Angela Colbers[1], José Moltó[2], Jelena Ivanovic[3], David Hawkins[4], Tariq Sadiq[5], Kabamba Kabeya[6], Andrea Gingelmaier[7], Katharina Weizsäcker[8], Graham Taylor[9], David Burger[1]

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Background: Perinatal guidelines include ritonavir-boosted darunavir (DRV/r) as an alternative protease inhibitor for use in antiretroviral (ARV)-naive pregnant women. The dosing recommendation for ARV-naive patients is DRV/r 800/100mg QD but pharmacokinetic data on this dose in pregnant women are limited.

Methodology: Patients treated with DRV/r (800/100mg QD) during pregnancy had intensive steady-state 24-hour PK profiles in the 3rd trimester and at least 2 weeks postpartum. Geometric mean ratios (GMR) and 90% confidence intervals (CI) were calculated for PK parameters 3rd trimester/postpartum. Unbound concentrations were determined using an ultracentrifugation method.

Results: 15 patients were included in the analysis, 11 were treatment experienced at conception. 7 patients were Black and 8 Caucasian. Seven paired PK curves (3rd trimester and postpartum) were available.

Median gestational age at delivery was 38 (36-41) weeks. Approaching delivery 73% had an HIV viral load <50 cps/mL, 93% <1000 cps/mL. Two weeks prior to delivery one patient still had a significant viraemia: (28,711 copies/mL). This patient was thought to be non-adherent and had directly observed therapy until delivery. All children were born uninfected. No congenital abnormalities were reported.GMR (90% CI) of DRV PK parameters 3rd trimester/postpartum were: 0.63 (0.51-0.77) for AUC; 0.72 (0.57-0.93) for C_{max}; 0.36 (0.22-0.58) for C_{24h}. Mean free fraction (95%CI) was 12% (11-14%) in the 3rd trimester and 10% (7-13%) postpartum. 2/15 of the patients showed DRV concentrations <0.55 mg/L (EC50 for resistant virus) in the 3rd trimester, versus none postpartum. The median (min-max) cord blood/maternal ratios (n=6) were 0.12 (0.08-0.35).

Conclusions: Third trimester darunavir exposure when administered as 800/100mg QD was significantly lower than postpartum. Trough concentrations were approaching the C_{trough} target minimum, indicating that this dose is likely to lead to sub-therapeutic concentrations during pregnancy, especially for treatment experienced patients. This decrease seems not to be compensated by a higher free fraction during pregnancy. DRV/r 600/100mg BID is suggested to be the preferred dose during pregnancy for treatment experienced patients.

888 Pharmacogenetics of Efavirenz Excretion Into Human Breast Milk and Transfer To Breastfed Infants

Adeniyi Olagunju[1,2], Marco Siccardi[1], Ogechi Okafor[3], Oluseye Bolaji[2], 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

Background: The influence of drug metabolizing enzyme, transporter and nuclear receptor single nucleotide polymorphisms (SNPs) on efavirenz (EFV) concentrations in human breast milk and infants exposed through breast milk is understudied. SNPs in maternal CYP2B6, NR1I3, ABCG2 and ABCB5 were investigated here.

Methodology: HIV positive nursing mothers (n = 51) receiving once daily regimens containing 600 mg EFV and their exclusively breastfed infants were recruited from 3 Nigerian hospitals. Paired dried blood spots (DBS; maternal and infant) and dried breast milk spots (DMS) were collected 12 - 14 hours post maternal dose. EFV was quantified by validated LC-MS/MS. Plasma EFV concentration was estimated using [DBS[EFV]/(1-HCTf)]*fbpp, where HCT is average haematocrit and fbpp is fraction bound to plasma protein. Genotyping for CYP2B6 rs3745274, NR1I3 rs2307424, NR1I3 rs3003596, ABCB5 rs6461515, ABCB5 rs2301641, ABCG2 rs2231164 and ABCG2 rs2622604 was conducted. Associations of EFV concentrations with SNPs and demographic factors were investigated by univariate (Mann-Whitney U test) and multivariate analyses (multiple linear regression). P < 0.05 was considered statistically significant.

Results: Median (IQR) EFV breast milk concentration was 2280 (1180, 3270) ng/ml. Using 150ml/kg/day as average milk intake, this equates to a ~340 (177, 491) µg/kg/day infant dose and resulted in 178 (87.7, 340) ng/ml in infant plasma. Maternal plasma EFV was 2310 (1580, 4460) ng/ml and median (IQR) milk-to-maternal plasma ratio was 0.82 (0.51, 1.1). There were significant correlations between maternal plasma and breast milk EFV concentrations (p = 1.3 x 10-12; rho = 0.80) and between breast milk and infant plasma (p = 7.9 x 10-5; rho = 0.52). Significant differences in maternal, infant and breast milk EFV concentrations were observed based on CYP2B6 rs3745274 genotypes (Figure). Only CYP2B6 rs3745274 was independently associated with breast milk [β = 0.22 (0.10, 0.35), p = 0.001], maternal [β = 0.23 (95% CI: 0.13, 0.32), p=1.5 x 10-5] and infant [β = 0.23 (0.09, 0.37), p = 0.002] EFV concentrations in multivariate analyses. Other statistically significant SNP associations were observed in univariate but not multivariate analysis.

Conclusions: CYP2B6 rs3745274 was independently associated with EFV concentrations in human breast milk and infants exposed through breast milk. Further study is warranted to define clinical significance and implications for stratified medicine in these patients.

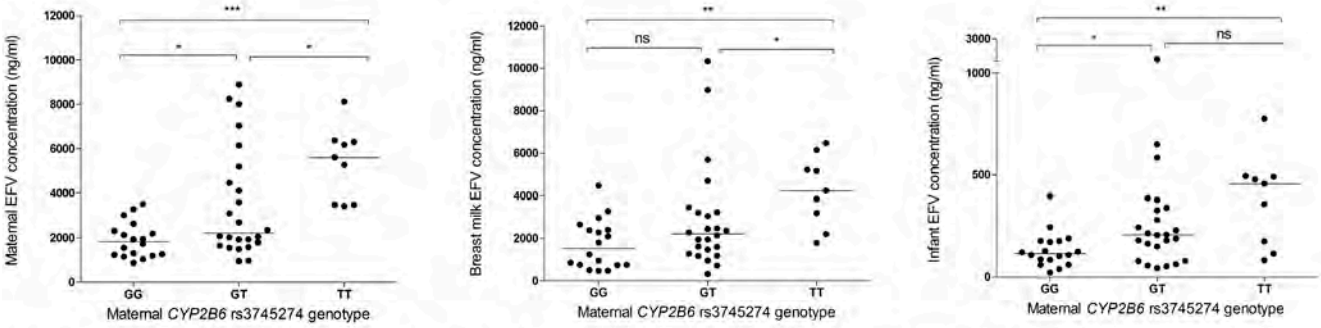

Figure 1. Maternal plasma, breast milk and infant plasma efavirenz concentrations based on CYP2B6 rs3745274 genotypes. ***, ** and *: statistically significant differences observed at 0.1, 1.0, 5.0% levels; ns: no significant differences.

889 Safety, Efficacy, and PK of Atazanavir/Ritonavir (300/100 mg QD) in HIV+ Pregnant Women Cohort

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Background: Atazanavir/ritonavir (ATV/r) is one of the most popular protease inhibitor recommended to minimize the risk of mother to child transmission. The objectives of this study were to assess steady state ATV plasma concentrations at 24 hours post-dose (C24h) and the impact of several cofactors on its PK then to describe the efficacy of ATV/r containing regimen in HIV+ pregnant women.

Methodology: A multicenter, cross-sectional, non-interventional cohort was conducted from 2006 to 2013. HIV-1 adult pregnant women, receiving ATV/r (300/100 mg qd) containing regimen, with available demographics characteristics, plasma HIV-RNA (pVL) and CD4 count were enrolled. ARV C24h were determined using UPLC-MS/MS at the three trimesters (Tn) of pregnancy, at delivery and at post-partum (PP). ATV C24h were interpreted according to the 150 ng/mL efficacy cut-off. Safety assessments including ATV/r jaundice were notified. Newborn data was also collected: weight, gestational age, APGAR score. Virological failure was defined by two successive pVL>50c/mL at delivery. Results were presented as median (IQR).

Results: Characteristics of the 103 included pregnant women were: 34 (31-37) years, 88% from sub-Saharan Africa, 7 (3-9) years since HIV diagnosis, 5 (2-8) years of ARV treatment duration, 1 (0-1) year of ATV/r duration, 13% of ARV naïve, 24% started ATV/r in the year of their pregnancy, 41% received TDF, 6%, 4% and 2% of HBV-, HCV- and HBV/HCV co-infected, respectively. BMI was 25 (21-28) kg/m² and CD4 nadir 197 (101-290)/mm3. In the present study, 16 premature newborns (<37 weeks of gestation), 3 deaths in utero and 1 current pregnancy were reported. ATV C24h (ng/ml) were: 624 (243-1,018; n=31) at T1, 630 (254-1,136; n=105) at T2, 676 (460-1,027; n=130) at T3, 774 (496-1,339; n=42) at delivery, 902 (554-1,102; n=52) at PP, 9% of ATV C24h were < 150 ng/mL; ATV C24h did not significantly differ between T3 and PP (p=0.50). Bilirubinemia was 22 µmol/L (15-35; n=194). Ratio of cord blood/maternal ATV concentration was 0.20 (0.11-0.38, n= 28). Baby's characteristics were: gestational age 38 (37-39) weeks, weight 2,970 gr (2,755-3,358), APGAR score 10. Among available data at delivery, 92 (97%) women had pVL<50c/ml and 3 women presented 50<pVL<400c/ml. No instance of mother-to-child transmission was found.

Conclusions: In this population of mostly African HIV+ pregnant women, ATV/r (300/100 mg qd) containing regimen demonstrated a good virological efficacy and safety profile. No significant impact of the gestation trimesters on ATV C24h was found. No dose adjustment was required in the present study. ATV/r might be a treatment of choice in NNRTI resistant strains infected migrant population and also in pregnant late presenter's women with favourable PK interaction with integrase inhibitors

890 A Comparison of the Pharmacokinetics of Raltegravir During Pregnancy and Postpartum

Maren Blonk[1], Angela Colbers[1], Carmen Hidalgo-Tenorio[2], Katharina Weizsäcker[3], José Moltó[4], David Hawkins[5], Marchina van der Ende[6], Andrea Gingelmaier[7], Graham Taylor[8], David Burger[1], PANNA Network

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Background: During pregnancy physiological changes take place which can influence the pharmacokinetics (PK) of antiretroviral agents and lead to decreased drug exposure. Effective plasma concentrations are important to prevent treatment failure, development of resistance and mother-to-child transmission. According to perinatal guidelines raltegravir (RAL) can be used in pregnant HIV infected women in special circumstances, because safety and PK information is limited. The use of RAL in late pregnancy for women who have a high viral load (VL) has been suggested because of its ability to rapidly suppress VL. More data on the PK behaviour and safety of RAL during pregnancy are needed to be able to recommend its use in this setting.

Methodology: An open-label, multi-centre phase IV study in HIV infected pregnant women recruited in HIV treatment centers in Europe (PANNA Network). Patients treated with RAL 400 mg BID during pregnancy had intensive steady-state12-hour PK profiles in the 3rd trimester and at least 2 weeks postpartum. Where possible a cord blood (CB) and matching maternal blood samples were taken at delivery to asses placental transfer. Safety and virological efficacy were evaluated.

Results: Fourteen patients (8 Black, 6 Caucasian) were included in the analysis of which 5 patients were treatment naive at conception. Paired PK curves (3rd trimester and postpartum) were available for 12 and 3rd trimester only for two patients. Treatment with RAL was started during pregnancy in 11/14 women, of which 5 were in the 3rd trimester. RAL was combined with a PI-based regimen in 9/14 patients. Median (range) gestational age at delivery was 38 weeks (36-41); birth weight was 3115 (2300-3730) gm. Approaching delivery 10/14 patients had a VL <50 cps/mL, all were <1,000 cps/mL. No SAEs were reported. None of the children were HIV infected and no birth defects were reported. Geometric mean ratios (90% CI) of RAL PK parameters 3rd trimester/postpartum were: 0.77 (0.59-1.00) for AUC_{0-12h}; 0.83 (0.55-1.25) for C_{max}; 0.54 (0.28-1.05) for C_{12h}. Geometric mean (95% CI) for AUC_{0-12h}, C_{max} and C_{12h} in the 3rd trimester were: 4.95 (3.01-8.13) mg*h/L, 1.40 (0.74-2.65) mg/L and 0.054 mg/L (0.032-0.091) mg/L respectively. One patient in the 3rd trimester (and none postpartum) had a C_{12h} level below the suggested threshold of 0.020 mg/L which was associated with failure to achieve an undetectable VL in QDMRK. The median (range) ratio of CB/maternal RAL concentrations (n=8), was 1.24 (0.13-4.53).

Conclusions: The slight decrease observed in exposure to RAL during 3rd trimester compared to postpartum is not considered to be of clinical importance. RAL was well tolerated during pregnancy without causing congenital abnormalities. RAL efficiently crosses the placenta.

891 Intensive Etravirine PK and HIV-1 Viral Load in Breast Milk and Plasma in HIV+ Women Receiving HAART

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Background: MTCT of HIV can occur at different time periods perinatally: in utero, at time of delivery or during breast feeding. Breast feeding accounts for 6.5%- 25.9% of infections worldwide, with the majority of transmissions occurring in the first 6 weeks of life. ARVs with good penetration into breast milk (BM) have the greatest impact on decreasing MTCT transmission through breastfeeding.

Methodology: Nine HIV+ postpartum women on stable HAART with an undetectable viral load added Etravirine (ETR) to their current regimen on postpartum Day 1 and continued for 14 days. Intensive PK sampling of BM and plasma was done on postpartum days 5 (D5) and 14 (D14) at times 0, 2, 5, 8 and 24 hours after the dose of ETR. BM and plasma HIV-1 RNA viral load (VL) were quantified. ETR drug concentrations were measured by a validated LC/MS/MS assay. Non-compartmental analysis was used to estimate PK parameters.

Results: The median BM concentration of ETR on D5 was 241.46 ng/ml (160.76-890.8) and on D14 was 797.7 ng/ml (161.02-2714.2) p=0.046. The median plasma concentrations were 299.9 ng/ml (52.76-563.8) and 196.9 ng/ml (131.88-706.4) on D5 and D14 respectively. The median BM:plasma ratio were 1.09 ng/ml (0.59-3.04) on D5 and 3.27 ng/ml on D14 (1.25-4.55) P=0.01. BM concentrations exceeded the upper limit of the ETR IC 50 range (0.39-2.4 ng/ml) in all patients. HIV RNA levels were detectable in the BM of two patients despite undetectable plasma HIV RNA. ETR AUC_{0-24} and BM:plasma ratios did not differ in the detectable vs. the undetectable women.

Conclusions: ETR penetration into BM is largely driven by plasma PK and exceeds the plasma HIV inhibitory concentration at all time points. This study suggests that unbound ETR readily diffuses from blood to the breast compartment likely because of its lipophilicity. However, differences in concomitant ARVs and individual pharmcodynamics may allow for compartmental viral replication. HAART combinations that include ETR may prove useful for prevention of BM MTCT in resource limited countries where exclusive breastfeeding is recommended.

892 Effective Exposure To Atazanavir During Pregnancy, Regardless of Tenofovir Use

Angela Colbers[1], David Hawkins[2], Carmen Hidalgo-Tenorio[3], Marchina van der Ende[4], Kabamba Kabeya[5], Andrea Gingelmaier[6], Katharina Weizsäcker[7], John Lambert[8], Jürgen Rockstroh[9], David Burger[10]

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Background: Atazanavir with low-dose ritonavir boosting moved from an alternative protease inhibitor to a preferred protease inhibitor for use in antiretroviral-naive pregnant women. The package insert recommends an atazanavir (ATV) dose increase in the 2nd and 3rd trimester of pregnancy if

tenofovir (TDF) or an H2 receptor antagonist is used concomitantly. Conflicting data exist about the influence of TDF on ATV concentrations, and therefore also for the necessity to increase the ATV dose in the 2nd and 3rd trimester of pregnancy if used with TDF.

Methodology: Patients treated with ATV/r (300/100mg QD) during pregnancy had intensive steady-state 24-hour PK profiles in the 3rd trimester and at least 2 weeks postpartum. Geometric mean ratios (GMR) and 90% confidence intervals (CI) were calculated for PK parameters 3rd trimester/postpartum. PK parameters with and without TDF co-treatment were compared by an independent t-test.

Results: 29 patients were included in the analysis, 11 were treatment naive at conception. 15 patients were black and 14 Caucasian. Paired PK curves (3rd trimester and postpartum) were available for 25 patients. 19/29 patients used TDF as part of the combination antiretroviral therapy.

Median gestational age at delivery was 39 (36-42) weeks. Approaching delivery 76% had an HIV viral load <50 cps/mL, all <1000 cps/mL.GMR (90% CI) of ATV PK parameters 3rd trimester/postpartum were: 0.65 (0.56-0.74) for AUC; 0.69 (0.60-0.79) for C_{max}; 0.58 (0.47-0.71) for C_{24h}. No statistical difference in AUC was found between patients using TDF vs no TDF: GM (95%CI) 3rd trimester 28.9 mg*h/L (22.2-37.4) vs 32.1 mg*h/L (21.1-48.7); postpartum 46.1 (36.2-58.7) vs 49.2 mg*h/L (34.7-69.8). None of the patients showed ATV concentrations <0.15 mg/L (target for treatment naive patients). One baby had a congenital diaphragmatic hernia resulting in respiratory failure, septic shock and death. A relationship with ATV/r is not likely, because ATV/r was started in week 21 of pregnancy, whereas the closure of the pleuroperitoneal canal occurs around week 8 of pregnancy. None of the children were HIV infected.

Conclusions: Despite 35% lower ATV exposure during pregnancy, 300/100mg ATV/r seems to generate effective concentrations for PI naive patients, even if co-administered with TDF. For experienced patients therapeutic drug monitoring of ATV should be considered to adapt the ATV/r dose on an individual basis.

Session P-U1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

ART in Children and Adolescents

893 P1073: Immune Reconstitution Inflammatory Syndrome - Wide Spectrum and Severity in Children

Mark F. Cotton[1], Hilda Mujuru[2], Raziya Bobat[3], Boniface Njau[4], Avy Violari[5], Vidya Mave[6], Charles Mitchell[7], James Oleske[8], Bonnie Zimmer[9], Savita Pahwa[10]

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Background: The Immune Reconstitution Inflammatory Syndrome (IRIS) is well described after initiating antiretroviral therapy (ART) in severely immunocompromised patients. It is classified as "paradoxical" when symptoms or signs of a known co-morbidity increase or re-appear and "unmasking" with recognition of a previously unsuspected condition.

There are few prospective studies of IRIS in children.

Methodology: P1073 was a prospective multi-center observational study of children below 6 years of age initiating ART from 5 sites in sub-Saharan Africa and one in India. Children were recruited from public ART programs.

Results: 203 children (median age 1.14y: IQR 0.48 to 2.12) were enrolled from December 2010 through June 2013. Of 9 deaths (case fatality 4.4%), 6 occurred within 12 weeks of ART initiation. Of these, 3 had IRIS: 1) vasculitis and pneumonia in a child with disseminated TB, 2) esophageal candidiasis and 3) Bacille Calmette Guerin (BCG) IRIS in a child who later died of gastroenteritis.

Thirty-eight children (18.7%) developed 46 episodes of IRIS, 6 had 2 types of IRIS and 1 had 3 discrete IRIS episodes. Case fatality rate in IRIS cases was 7.9%. BCG IRIS was most common (21/46 - 45.6%); 33% only having increased inflammation at the injection site, the remainder having regional adenopathy. 11 children had TB IRIS (23.9%) and 10 had dermatological IRIS (papular pruritic eruption - 4, dermatitis - 2, molluscum contagiosum - 1, tinea capitis - 1, TB vasculitis - 1 and zoster- 1). Median time to IRIS was 3.4 (2 to 8) weeks. The earliest was on day 8 and the latest at 13.9 weeks. Those with IRIS were younger (median 0.7y vs 1.25y: $p = 0.024$) with lower CD4%.(16.7% vs 20%: $p = 0.017$). Both unmasking and paradoxical IRIS had severe, unexpected morbidity. Two with CMV colitis (1 unmasking and 1 paradoxical) required ICU admission; a child with newly diagnosed pulmonary TB developed prolonged seizures due to unsuspected intra-cerebral TB granulomas. Another, with unsuspected intracerebral granulomas developed focal seizures and raised intracranial pressure requiring ICU (unmasking IRIS; treated for TB). Unmasking candida esophagitis was associated with death in 1 child and unmasking TB IRIS due to unsuspected abdominal TB led to biliary obstruction, surgery and hospitalization for 5 months in another.

Conclusions: Although many cases of IRIS were benign, some were unexpectedly severe (especially the unmasking type) with morbidity and mortality. Children initiating ART in public programs require careful monitoring for IRIS in the initial 3 months of ART.

894 sdNVP Exposure and ART Response in Children <3 Years Initiating ART in the ARROW Trial

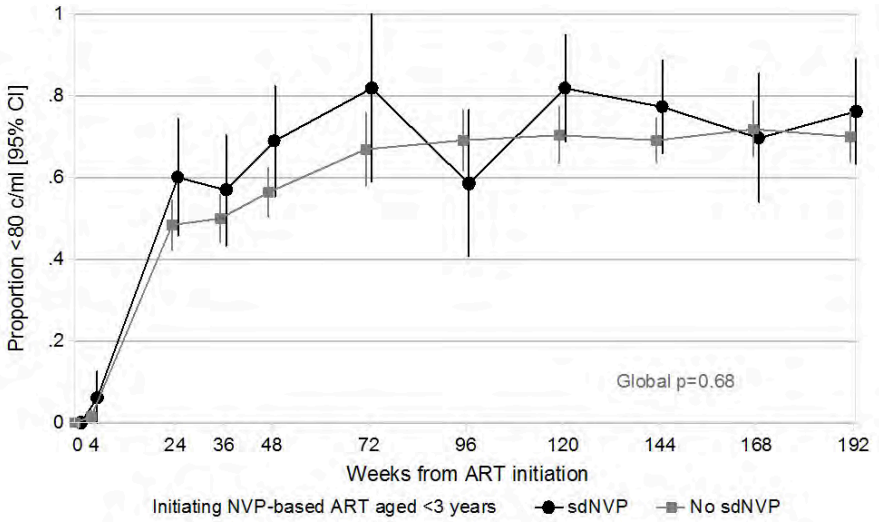
Philippa Musoke[1], Victor Musiime[2], Kusum Nathoo[3], Patricia Nahirya-Ntege[4], Alexander J. Szubert[5], Kuda Mutasa[6], David E. Williams[2], Moira Spyer[5], Ann Sarah Walker[5], **Diana M. Gibb[5]**, and the ARROW Trial Team

[1]Baylor-Uganda, Kampala, Uganda, [2]Joint Clinical Research Center, Kampala, Uganda, [3]University of Zimbabwe, Harare, Zimbabwe, [4]MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda, [5]MRC Clinical Trials Unit, London, United Kingdom, [6]Zvitambo Institute for Maternal Child Health Research, Harare, Zimbabwe

Background: Poorer virologic response to NNRTI-containing regimens has been reported in children with prior sdNVP exposure. Despite WHO guidelines now recommending all children <5 years initiate LPV-containing ART, availability is limited and formulations challenging. We therefore compared VL response in children initiating ART aged <3 years in the ARROW trial according to previous sdNVP exposure.

Methodology: In 2007-2008, 370 ART-naïve children aged <3 years were enrolled from Uganda/Zimbabwe, and randomized to standard 3-drug NNRTI+3TC+ABC (Arm A) vs 4-drug NNRTI+3TC+ABC+ZDV induction, decreasing at 36 weeks to 3-drug NNRTI+3TC+ABC (Arm B) or to 3TC+ABC+ZDV (Arm C). VL was assayed using Abbott Taqman or Roche Amplicor, with lower detection limit 80 c/ml. Predictors of suppression <80 c/ml 48 and 144 weeks after ART initiation were identified using backwards elimination (p=0.1) from pre-ART CD4%, weight/height-for-age, CD4%, VL, sex, centre, ART randomisation, CD4 monitoring (yes/no), current ART as all syrups, and reported missed ART doses in the last 4 weeks, forcing sdNVP and age at ART initiation into the model.

Results: Three children initiated ART with EFV and were excluded. In the remaining 367 initiating NVP-based ART aged <3 years, median age was 20 months (IQR 12-27).57(16%) children had received sdNVP. Children receiving sdNVP were younger (median 15 vs 20 months in those without sdNVP, p=0.003) and therefore had slightly higher CD4 counts (median 902 vs 724 cells/ul, p=0.02) and lower weight (median 7.8 vs 8.4 kg, p=0.05), but did not differ significantly in pre-ART CD4% (median 14%), VL (508314 c/ml), weight-for-age Z-score (-2.7) WHO stage (71% 3/4), sex (48% boys), centre/country or initial ART (p>0.15).There was no evidence that suppression<80 c/ml was any worse with sdNVP vs no sdNVP exposure(Figure; wk48 adjusted (a)OR=1.84 [95% CI 0.83-4.05] p=0.13, wk144 aOR=1.39 [0.66-2.95] p=0.38). At week 48/144, suppression was lower in boys (aOR=0.45/0.56 p=0.004/0.03) and those with higher pre-ART VL (aOR=0.49/0.59 per log10 higher p=0.001/0.01).At week 48, it was also lower in those on syrups (aOR=0.50 p=0.04) or missing ART doses (aOR=0.34 p=0.07); and at week 144 in those on triple NRTI maintenance (aOR=0.58 p=0.04). There was no independent effect of age (p=0.42/0.14).



Conclusions: In this cohort of African children <3 years of age starting ART with advanced HIV disease, there was no evidence of poorer VL response to NVP-containing ART in children exposed to sdNVP.

895 Virologic Response To Efavirenz vs Nevirapine-Containing ART in the ARROW Trial

Adeodata Kekitiinwa[1], Moira Spyer[2], Richard Katuramu[3], Victor Musiime[4], Tawanda Mhute[5], Sabrina Kitaka[1], Oscar Senfuma[4], Marshall Munjoma[5], Ann Sarah Walker[2], Diana M. Gibb[2], and the ARROW Trial Team

[1]Baylor-Uganda, Kampala, Uganda, [2]MRC Clinical Trials Unit, London, United Kingdom, [3]MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda, [4]Joint Clinical Research Center, Kampala, Uganda, [5]University of Zimbabwe, Harare, Zimbabwe

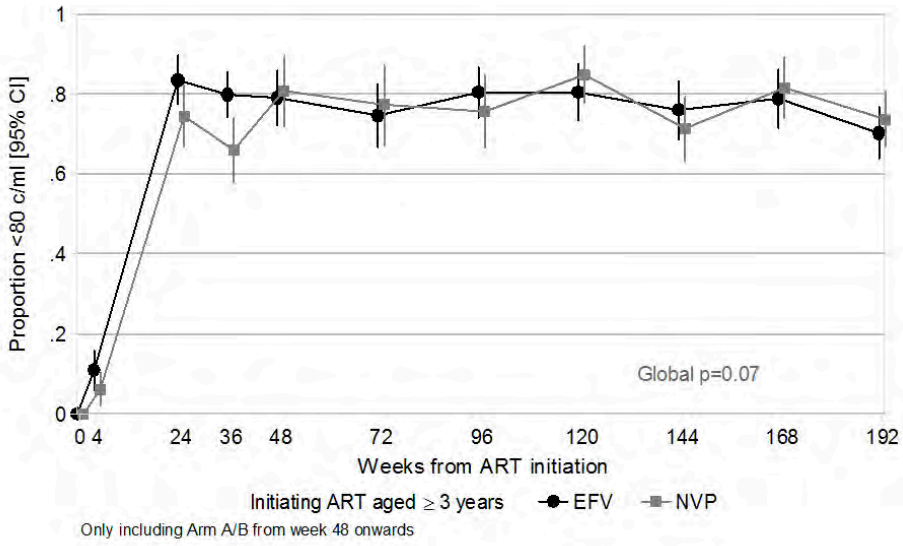
Background: Poorer virologic response to NVP vs EFV-based ART has recently been reported. We compared VL response in ARROW trial children aged ≥3 years initiating ART with NVP vs EFV.

Methodology: 836 ART-naïve children age ≥3 years from Uganda/Zimbabwe were randomized to 3-drug NNRTI+3TC+ABC (Arm A) vs 4-drug NNRTI+3TC+ABC+ZDV induction, decreasing at week 36 to 3-drug NNRTI+3TC+ABC (Arm B) or 3TC+ABC+ZDV (Arm C). NNRTI was chosen by clinicians. VL was assayed using Abbott Taqman or Roche Amplicor, with lower detection limit 80 c/ml. Predictors of suppression <80 c/ml at 36wk (all children) and 144wk (Arm A/B only) after ART initiation were identified using backwards elimination (p=0.1) from pre-ART CD4%, weight/height-for-age, CD4%, VL, sex, centre, ART randomization, CD4 monitoring, and reported missed ART doses in the last 4wk, forcing EFV vs NVP and age at ART initiation into the model, and categorizing age to reflect non-linear effects.

Results: 445 (53%) children received EFV and 391 (47%) NVP. Children on EFV were more likely to be male (58%, p=0.007), older (median 8.6 year EFV vs 7.5 NVP, p<0.001), less underweight (weight-for-age -1.7 vs -2.4, p<0.001) and had higher CD4% (12% vs 10%, p=0.05) and lower pre-ART VL (160011 vs 203882c/ml, p=0.07), but similar pre-ART CD4 (p=0.9). 631 (75%) had ≥1 post-baseline VL. Overall there was a trend to better suppression <80 c/ml with EFV (Figure; global unadjusted p=0.08, particularly ≤36wk). After adjustment, at wk 36 (n=274 to date), EFV was superior to NVP in

those with pre-ART VL>75000 (p=0.001; interaction p=0.003); suppression <80 c/ml was poorer in the youngest and oldest children (aOR(3-4 vs 5-9yr olds)=0.57 p=0.14; aOR(10+ vs 5-9yr olds)=0.33 p=0.007). Differences at wk144 were smaller (75% EFV vs 70% NVP <80 c/ml (n=196)) but still significant (p=0.03), with a strong relationship between older age and poorer VL suppression in those on EFV (aOR per year older=0.78 [0.68-0.89] p<0.001) but no relationship in NVP (aOR =0.97 [0.80-1.17] p=0.74) (age interaction p=0.06).

Conclusions: In a non-randomized NNRTI comparison, although short-term VL suppression favoured EFV, long-term suppression depended on age: children <10 years at ART initiation had better long-term VL suppression with EFV than NVP; whereas those >10 years had better long-term suppression with NVP than EFV. The relative performance of EFV vs NVP therefore varies over time on ART, by baseline VL and by age at ART initiation, the latter possibly due to CNS side-effects of EFV.



896 Growth Recovery Among HIV+ Children Randomized To Lopinavir/Ritonavir or NNRTI-Based Therapy

Theodore Ruel[1], Abel Kakuru[2], Gloria Ikilezi[2], Florence Mwangwa[2], Albert Plenty[3], Edwin Charlebois[3], Diane Havlir[3], Moses Kamya[4], Jane Achan[5]

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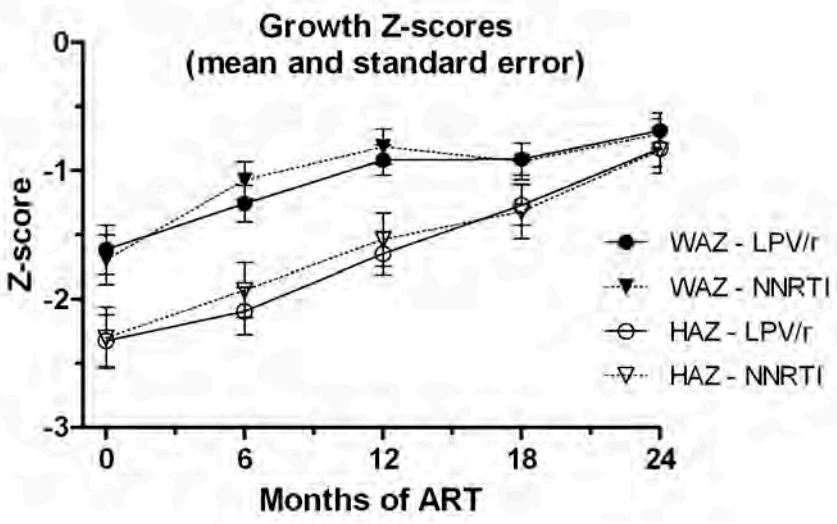
Background: HIV-infected African children suffer high rates of wasting and short stature. Growth generally improves with the initiation of antiretroviral therapy (ART), but some studies have suggested poorer outcomes with the use of lopinavir/ritonavir (LPV/r). We compared the recovery of weight and height in a rural cohort of HIV-infected children randomized to initiate LPV/r- or non-nucleoside-reverse-transcription-inhibitor(NNRTI)-based ART.

Methodology: In the PROMOTE-pediatrics trial, HIV-infected children aged 2 months to 6 years were enrolled in Tororo, Uganda, and randomized to NNRTI- or LPV/r -based ART. Children were seen monthly and received food supplementation if malnourished. This analysis included data from the 24 months following ART-initiation among ART-naive enrollees on a per-protocol basis. Changes in gender specific World Health Organization Z-scores for weight-for-age (WAZ) and height-for-age (HAZ) compared to enrollment were compared by arm using generalized linear repeated-measure models that adjusted for baseline Z-score score, socioeconomic status and confirmed virologic failure (consecutive HIV RNA > 400 copies/ml).

Results: At enrollment, 129 children had median (IQR) age of 3.2 years (2.2, 4.5), CD4 count of 588 cells/mm3 (389, 913), CD4 percentage of 16 (12, 23), HIV RNA level of 5.4 log10(copies/ml) (4.8, 5.9), WAZ of -1.3 (-2.4, -0.61) and HAZ of -2.38 (-3.28, -1.41). Median (IQR) follow-up times were 23.9 months (18.4, 23.9) for the LPV/r arm (n=64) and 23.8 months (17.5, 23.9) for the NNRTI arm (Nevirapine: n=36, Efavirenz: n=29). The height and weight of HIV-infected Ugandan children in both arms improved steadily over 24 months following ART-initiation (figure). The median (IQR) change in Z-scores among children who reached 24 months of follow-up on LPV/r (n= 45) vs NNRTI (n=40) were, respectively, WAZ: 0.47 (0.10, 1.62) vs 0.53 (0.03, 1.14) (p=0.59) and HAZ: median 1.55 (0.78, 1.86) vs 1.19 (0.62, 1.65) (p=0.23). In multivariate modeling, study arm (LPV/r vs. NNRTI) was not predictive of change in WAZ (beta: -0.02, 95%CI:-0.25, 0.20) or HAZ (beta: 0.05, 95%CI: -0.10, 0.19).

Conclusions: Our results suggest that as the use of LPV/r expands throughout Africa, HIV-infected children receiving LPV/r in similar settings can be expected to have comparable growth to children receiving NNRTI-based ART. However, that Z-scores remained below zero underscores the need for additional strategies to improve growth in HIV-infected African children.



Session P-U2 Poster Session
Tuesday March 4, 2014, 2:30 PM–4:00 PM Exhibit Hall D
HIV Drug Resistance and Tropism in Children and Youth

897 Prevalence and Predictors of HIV Drug Resistance Among US Children and Youth With Perinatal HIV

Russell B. Van Dyke[1], Kunjal Patel[2], Ron M. Kagan[3], Shirley Traite[4], William A. Meyer[5], Katherine Tassiopoulos[2], George R. Seage[2], Lorna M. Seybolt[6], Sandra Burchette[7], Rohan Hazra[8], and the Pediatric HIV/AIDS Cohort Study

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Background: With extensive antiretroviral (ARV) exposure and the challenge of maintaining adherence, children and youth with perinatal HIV are at high risk for acquired drug resistance.

Methodology: The Adolescent Master Protocol of the Pediatric HIV/AIDS Cohort Study is a prospective study being conducted at 14 U.S. sites. From 2007 to 2009, we enrolled 451 subjects with perinatal HIV who were 7-16 years of age at entry. We abstracted results from genotypic resistance testing performed for clinical care. For subjects without these results and with a viral load (VL) ≥400 copies/mL, their most recent plasma sample was sent for genotypic resistance testing at a reference laboratory (Quest Diagnostics). Results were compared to the overall results from the reference laboratory for 2006 and 2012. Correlates of resistance were assessed using the Wilcoxon Test for continuous and Chi-square Test for categorical variables.

Results: Of the 446 subjects with at least one VL performed on study, 284 (64%) had at least one VL ≥400 copies/mL and 230 had resistance testing results from 2007-2013 (median 2010). Their median age at testing was 14.8 years; 57% were female, 70% black and 25% Hispanic. 74% had any ARV resistance; 61%, 40%, and 34%, respectively, had resistance to anv NRTI. anv NNRTI. or anv PI. substantiallv higher than that of the reference laboratory population (Table). The prevalence of resistance was highest for: zidovudine, nevirapine, and efavirenz (40%); stavudine (39%); lamivudine (37%); and didanosine and nelfinavir (32%). The prevalence of resistance was lowest for lopinavir (18%), etravirine (15%), tipranavir (10%), and darunavir (4%). Resistance to all ARVs in a class was uncommon (Table). Univariable correlates of any resistance included more cumulative years of HAART (p=0.03), more HAART regimens (p=0.005), a lower pre-HAART nadir CD4% (p=0.001), a higher pre-HAART peak VL (p<0.001), and a lower current VL (p=0.02). Factors not significantly associated with resistance included use of ART prior to HAART, current CD4 count, current CDC class, and current ARV adherence. At their most recent visit, 67% of AMP subjects had a VL < 400 copies/mL.

Prevalence of HIV resistance by drug class and combination of classes

Resistance	PHACS Subjects (N=230)			Reference Lab (N >>10,000)	
				2006	2012
	N	Prevalence	95% CI	Prevalence	
Any ARV	170	74%	68%, 79%	44%	36%
At least 1 class					
NRTI					
Any	140	61%	54%, 67%	33%	21%
All	19	8%	5%, 13%	6%	2%
NNRTI					
Any	93	40%	34%, 47%	28%	26%
All	35	15%	11%, 21%	0.9%	1%
PI					
Any	78	34%	28%, 40%	17%	7%
All	7	3%	1%, 6%	1%	0.4%
At least 2 classes					
NRTI + NNRTI					
Any	68	30%	24%, 36%	18%	12%
All	5	2%	1%, 5%	0.4%	0.2%
NRTI + PI					
Any	70	30%	25%, 37%	15%	5%
All	3	1%	0.3%, 4%	0.6%	0.2%
All 3 classes					
Any	41	18%	13%, 23%	8%	3%
All	1	0.4%	0%, 2%	0%	0.1%

Any: any drug in class or classes; All: all drugs in class or classes; ARV: antiretroviral; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor.

Conclusions: Viral resistance is common among U.S. youth with perinatal HIV, including resistance to multiple ARV classes, with a prevalence of resistance substantially higher than that of the general U.S. HIV-infected population. Resistance to newer ARVs is less common and effective regimens are available for most youth with viral resistance.

898 HIV-1 Resistance After Randomized Virologic Switch at 1000 or 30,000 c/ml in Children

Linda Harrison[1], Diana Gibb[2], Susan Fiscus[3], Yacine Saidi[4], Eleni Nastouli[5], Lynda Harper[2], Alexandra Compagnucci[4], Abdel Babiker[2], Ann Melvin[6], Gareth Tudor-Williams[7], and the PENPACT 1 (PENTA 9/PACTG 390) Study Team

[1]Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, MA, United States, [2]Medical Research Council, Clinical Trials Unit, London, United Kingdom, [3]UNC-Chapel Hill Virology Laboratory, University of North Carolina School of Medicine, Chapel Hill, NC, United States, [4]INSERM, SC10, Paris, France, [5]University College Hospital, University College London, London, United Kingdom, [6]Seattle Children's Hospital, Seattle, WA, United States, [7]Imperial College London, London, United Kingdom

Background: There are no comparisons of resistance after randomized virologic switch criteria.

Methodology: PENPACT 1 was an international open label 2 by 2 factorial trial randomizing HIV infected children to start antiretrovirals with a protease inhibitor (PI) vs non nucleoside reverse transcriptase inhibitor (NNRTI) based regimen, and switch at RNA threshold of 1000 vs 30000 c/ml. Switch criteria were: not achieving the threshold by week 24, confirmed rebound above the threshold after week 24 (RNA tested 12 weekly), or CDC C event. Resistance testing was on the last sample ≥1000 c/ml before switch, or confirmed ≥1000 c/ml before re-suppression; to ensure fair comparison by 1000 and 30000 arms. Additional testing was on samples ≥1000 c/ml at 4 years and trial end. This secondary analysis tested differences in number of major IAS mutations by Poisson models.

Results: Of 263 children, 67 started PIs and were assigned the 1000 threshold (PI 1000), 64 PI 30000, 67 NNRTI 1000 and 65 NNRTI 30000. Half on PIs started lopinavir/ritonavir, 62% on NNRTIs efavirenz (**Table**). The 1000 criteria were reached by 94 (36%) children during median 5.0 (IQR 4.2-6.0)

years follow-up. Time to reaching the 1000 criteria was similar by class (log rank P 0.26). Most in the 1000 arm reaching the criteria switched soon after (PI vs NNRTI median 12 vs 8 wks, log rank P 0.60). Median weeks from 1000 to 30000 criteria was 80 for the 30000 arm; PI vs NNRTI 58 vs 80, log rank P 0.81, and 25% of children had switched by 44 weeks; PI vs NNRTI 63 vs 17, log rank P 0.16. 87/107 (81%) children with last sample ≥1000 c/ml had resistance test results. Median weeks from entry to last test was 96; 1000 vs 30000 72 vs 124, rank sum P<0.01. More NRTI resistance mutations were accumulated in NNRTI 30000 than the other arms (**Table**). More NNRTI than PI mutations were accumulated; NNRTI mutations were frequent in 1000 and 30000, and PI resistance was less common in both arms. For non-randomized NRTIs, 62 started ABC+3TC, 166 3TC+ZDV/d4T, and 35 other (25 ZDV+ddI). The ABC+3TC group had fewer mutations than the others. The 5 with mutations on ABC+3TC were on NNRTIs; all had M184V/I and 1 K65R, L74V, Y115F, while 22/39 3TC+ZDV/d4T were on NNRTIs; all had M184V/I and 10 had TAMs.

Conclusions: Children starting PIs tended to switch later spending longer above 1000 but accumulated fewer mutations. Children starting NNRTIs switched soon after the 30000 criteria and accumulated more mutations, particular to NRTIs. An ABC+3TC backbone seemed most protective against NRTI resistance.

Major IAS resistance mutations accumulated on first-line					
	PI 1000c/ml	PI 30000c/ml	NNRTI 1000c/ml	NNRTI 30000c/ml	Poisson P-value*
Total children	**67**	**64**	**67**	**65**	
Lopinavir/ritonavir Nelfinavir Other** Efavirenz Nevirapine	29 (43%) 37 (55%) 1 (1%) 0 (0%) 0 (0%)	36 (56%) 27 (42%) 1 (2%) 0 (0%) 0 (0%)	0 (0%) 0 (0%) 0 (0%) 43 (64%) 24 (36%)	0 (0%) 0 (0%) 0 (0%) 39 (60%) 26 (40%)	
Number requiring tests Number with test results	34 28	22 17	26 20	25 22	
NRTI resistance 1 or 2 mutations ≥3 mutations	 11 (18%) 0 (0%)	 7 (12%) 1 (2%)	 12 (20%) 0 (0%)	 12 (19%) 7 (11%)	 any difference <0.001
PI or NNRTI resistance 1 or 2 mutations ≥3 mutations	 10 (16%) 0 (0%)	 4 (7%) 0 (0%)	 13 (21%) 1 (2%)	 12 (19%) 5 (8%)	 PI vs NNRTI <0.001
	ABC+3TC	**3TC+ZDV/d4T**	**Other (mainly ZDV+ ddI)**		
Total children Number requiring tests Number with test results	**62** 15 9	**166** 67 59	**35** 25 19		
NRTI resistance 1 or 2 mutations ≥3 mutations	 4 (7%) 1 (2%)	 32 (20%) 7 (4%)	 6 (21%) 0 (0%)		 any difference <0.01
Thymidine analogue mutations (TAMs) 1 or 2 TAMs ≥3 TAMs	 0 (0%) 0 (0%)	 6 (4%) 4 (3%)	 6 (21%) 0 (0%)		
K65R L74R Y115F M184V/I	1 (2%) 1 (2%) 1 (2%) 5 (9%)	0 (0%) 1 (1%) 0 (0%) 39 (25%)	0 (0%) 0 (0%) 0 (0%) 0 (0%)		
*Analysis assumes those not requiring tests were not resistant, and excludes those with unavailable resistance results. ** 1 fosamprenavir/ritonavir, 1 high-dose ritonavir					

899 Longitudinal Evolution of Tropism in Perinatal HIV-1 Infection: The HICCUP Study

Caroline Foster[1], Steve Kaye[2], Colette Smith[3], Nicola Mackie[4]

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Background: Data on changes over time in HIV tropism and association with disease progression in perinatal HIV-1 infection (PaHIV) is sparse. Optimal sequencing of antiretrovirals (ART) including CCR5 antagonists is a priority for a young population currently requiring life long ART and requires a clear understanding of the natural history of coreceptor usage in PaHIV.

Methodology: Eligible patients with PaHIV were CCR5 antagonist naïve and were defined as (1) slow (ART from 10+ yrs) or (2) rapid (ART pre 5 yrs) progressors and (3) long term non-progressors (LTNP). RNA was extracted from stored plasma samples at baseline and at yearly time points or virological

failure to latest follow up. The V3 region of gp120 was sequenced and tropism determined using the Geno2pheno algorithm (FPR 5.75%). Logistic regression with generalised estimating equations was used to assess factors associated with the presence of R5 virus. Time to tropism change was assessed using standard survival methods.

Results: At baseline (n=48) median age was 12 yrs, 52% female, 79% black African, 96% non-B subtype, group 1(n=20), 2(n=17) and 3(n=11). 81% (39/48) had R5 and 19% (9) had X4/dual-mixed (DM) viruses. Median follow-up was 7.7 yrs (308.6 person-yrs) with a median of 5 (range 1-14) samples per subject (252 samples total). Analysing all samples, the presence of R5 virus was associated with higher current CD4 count (median 520 cells/μL for R5 virus vs 202 for X4; p=0.0005), LTNP (35% vs 11% p=0.05), non Black African ethnicity (74% vs. 89%; p=0.05) and female (55% vs 28%; p=0.005).

Of 38 patients with R5 virus at baseline and at least one follow-up sample, switch to X4/DM occurred in 12 (30.8%). Estimated 5 yr risk of tropism switch to X4/DM was 24.4% (95% CI 9.7-39.2%). Lower current CD4 predicted coreceptor switch (unadjusted HR=0.62 per 50 cells higher; 95% CI 0.47-0.81; p=0.0006) but not viral load (p=0.81), age (p=0.85) or clinical group (p=0.56). Of 19 patients who ever had X4/DM virus and at least one further sample, 11 (58%) had R5 virus at one or more subsequent time points. 5/11 had three or more switches between R5 and X4/DM over time, 3 of whom were R5 at last follow up.

Conclusions: As seen in adult studies, lower CD4 count was predictive of coreceptor switching in PaHIV. CCR5 antagonists were a treatment option for 81% at 12 yrs, falling to 56% over 7.7 yrs of follow up. Globally 30% of children with PaHIV are triple class experienced and currently are expected to remain on ART for life. Paediatric studies of CCR5 antagonists should be expedited to ensure they are a treatment option before tropism switching occurs in children. The frequent reversion from X4 to R5 may result in CCR5 antagonists being prescribed to patients harbouring undetected X4 virus and careful monitoring of individuals commencing such therapy is indicated.

Session P-U3 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

ARV Pharmacokinetics, Pharmacogenetics, and Safety in Children and Adolescents

900 Rilpivirine Pharmacokinetics in HIV-1-Infected Adolescents: A Substudy of PAINT (Phase II Trial)

Herta Crauwels[1], Annemie Hoogstoel[1], Simon Vanveggel[1], Wayne Yarnall[2], Marita Stevens[1], Katia Boven[2]
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Background: Rilpivirine (RPV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) approved in combination with other antiretrovirals for the treatment of HIV-1-infected, treatment-naïve adults. RPV pediatric dosing has not been established. PAINT (Pediatric study in Adolescents Investigating a New NNRTI TMC278, NCT00799864) is an ongoing, open label, 48-week Phase II trial to evaluate RPV pharmacokinetics (PK), safety/tolerability and antiviral activity in adolescents. Part 1 of PAINT aimed to establish, in a subset of adolescents, a well-tolerated RPV dose providing comparable exposure to adults. Steady-state PK data from Part 1 are presented.

Methodology: Antiretroviral treatment-naïve HIV-1-infected adolescents (>12-≤18y) were recruited from investigational sites (India, Thailand, Uganda, South Africa). All patients were treated with RPV 25mg once daily (qd), taken with a meal, and two nucleoside/nucleotide reverse transcriptase inhibitors. A steady-state 24h PK profile was determined using blood samples collected predose, 2, 4, 5, 6, 9, 12 and 24h after an observed RPV dose, at the Week 2 or Week 4 visit. RPV plasma concentrations were determined by liquid chromatography-tandem mass spectrometry (1.0 ng/mL lower limit of quantification), and RPV PK parameters with non-compartmental analyses.

Results: Twenty-five adolescents were enrolled in Part 1, 12 were >12-≤15y and 13 were >15-≤18y old. There were 11 males and 14 females; 4 were Asian and 21 Black. Intensive PK data were available for 23 adolescents. The geometric mean (SD) AUC_{24h}, C_{0h} and C_{max} were 1750 (718) ng•h/mL, 70.6 (40.4) ng/mL and 102 (38.0) ng/mL, respectively. These values are comparable to those observed in adult HIV-1-infected patients. Geometric mean PK parameter ratios (adolescents/adults) were 0.98, 1.21 and 0.88 for AUC_{24h}, C_{0h} and C_{max}, respectively. There was no apparent relationship between RPV PK parameters and bodyweight, and no apparent difference in RPV PK parameters between age categories or between genders. At Week 4, the mean (SE) observed decrease from baseline in viral load was 2.3 (0.17) log_{10} copies/mL, and the mean (SE) observed increase in $CD4^+$ cell count was 104.6 (27.20) cells/mm^3. Up to week 4, 16/25 (64%) patients experienced at least one adverse event (AE), none serious or grade 4, considered related to RPV in 8/25 (32%). The observed AEs were similar (type and severity) to those reported in adults (53% up to Week 4).

Conclusions: The RPV dose selected for further evaluation in adolescents >12-≤18y old is 25mg qd with a meal. This dose provides comparable RPV exposure in adolescents and adults, and was generally safe and well tolerated. Long-term safety/tolerability, antiviral activity and further PK of RPV in adolescents are being investigated in Part 2 of PAINT.

901 Safety, Pharmacokinetics and Efficacy of Dolutegravir in Treatment-Experienced HIV+ Children

Rolando M. Viani[1], Carmelita Alvero[2], Terry Fenton[2], Edward Acosta[3], Rohan Hazra[4], Ellen O'Gara[5], Barbara Heckman[6], Debra Steimers[7], Sherene Min[7], Andrew Wiznia[8]
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Background: IMPAACT P1093 is an ongoing Phase I/II multicenter open-label PK, safety, dose finding study of dolutegravir (DTG) plus optimized background regimen (OBR) in children and adolescents in age defined cohorts. Adequate pharmacokinetics (PK), safety and virologic efficacy have been described in children aged 12 to 18 years, leading to the recent FDA approval. Here we report the PK, safety and virologic efficacy of DTG in children ≥ 6 to < 12 years old.

Methodology: HIV infected treatment experienced children ≥6 to <12 yrs on a failing antiretroviral (ARV) regimen with an HIV RNA of ≥1000 copies/mL (c/mL) were enrolled in an intensive PK stage as part of the study. DTG tablets (10, 25, 50mg) at ≈1 mg/kg once a day (based on defined weight bands) were added to a stable, failing ARV regimen, with an OBR added after intensive PK (~Day5-10). Target PK exposures were $AUC_{(0-24)}$ range of 37-67 µg*h/mL (primary) and C_{24} range 0.77 - 2.26 µg/ml (secondary). Safety, tolerability, CD4 cell count and HIV-1 RNA were evaluated at Week 24. Virologic success was defined as achieving an HIV-1 RNA < 400 c/mL or ≥ 1 Log_{10} decline in HIV RNA by Week 24 based on the FDA snapshot algorithm, with an additional secondary endpoint of HIV-1 RNA <50 c/mL.

Results: Eleven children were enrolled and completed the 24 week study visit. Demographics were as follows: 64% (7/11) male, 36% (4/11) African American, 27% (3/11) Caucasian, 18% (2/11) Asian, 36% (4/11) were of Hispanic ethnicity. Mean (SD) age was 9.5 yrs (±1.8); weight was 34.9 kg (±11.9). Median (IQR) baseline CD4+ cell count and % were 645 cells/µL (325, 732) and 19% (14, 26) respectively. Median (IQR) baseline HIV-1 RNA log_{10} was 5.0 log_{10} c/mL (3.5, 5.3). Five subjects (≥ 40 kg of weight) received DTG 50 mg, 2 subjects (30-< 40 kg) received DTG 35 mg and 4 subjects (20-<30 kg) received DTG 25 mg once daily. DTG geometric mean (CV%) $AUC_{(0-24)}$ and C_{24} were 50.46 (63%) µg*h/mL and 0.92 (89%) µg/mL respectively. Virologic success was achieved in 81.8 % (9/11; 95% CI: 48.2 % to 97.7%) at Week 24. Additionally, 63.6% (7/11; 95% CI: 30.8% to 89.1%) had an HIV RNA load < 50 c/mL at Week 24. Median (IQR) gain in CD4 cell count and % at Week 24 was 209 cells/µL (14, 403) and 8% (6, 11) respectively. DTG was well tolerated, with 3 subjects experiencing Grade 3 laboratory abnormalities; two developed unconjugated bilirubin elevation while on atazanavir as part of the OBR, and another subject developed neutropenia, which was deemed unrelated to treatment. There were no Grade 4 AEs, SAEs or study discontinuations due to AEs.

Conclusions: DTG plus OBR had a favorable safety profile and achieved adequate mean AUC_{24} and C_{24} in HIV infected children ≥ 6 to < 12 years. DTG plus OBR provided good virologic efficacy through Week 24 in this pediatric population.

902 Bioequivalence of Two Pediatric Formulations vs Adult Tablet Formulation of Elvitegravir

Joseph M. Custodio[1], Xiang Yin[2], Hiba Graham[3], Mischa Hepner[4], Lauren Wiser[5], Erin Quirk[3], Brian P. Kearney[1], Srinivasan Ramanathan[1]

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Background: Safe and effective pediatric antiretroviral therapies are needed. Elvitegravir (EVG) is a once-daily integrase inhibitor in regulatory review for treatment of HIV-1 infection when coadministered with a pharmacoenhancer. This study evaluated the pharmacokinetics (PK) of ritonavir (RTV)-boosted EVG administered as the pediatric EVG tablet or suspension formulation (test) vs the adult EVG 150 mg tablet formulation (reference).

Methodology: This was a prospective, open-label, crossover, randomized, multiple cohort study in healthy adult subjects. Cohort 1 (n=30) evaluated the single dose PK of the pediatric tablets (3 X 50 mg) vs reference. Cohort 2 (n=26) evaluated the single dose PK of the pediatric suspension (30 mL; 5 mg/mL) vs reference. Cohort 3 (n=18) evaluated the multiple dose PK of both pediatric formulations. . All treatments included 100 mg of RTV as a pharmacoenhancer and were administered under fed conditions with 240 mL of water. Intensive PK sampling was conducted over 48 hours post dose and PK parameters were calculated using noncompartmental methods. BE was assessed in Cohorts 1 and 2 using geometric mean ratios (GMR) and associated 90% confidence interval (CI) bounds of 80%-125% (>85% power to conclude BE). In Cohort 3, only descriptive PK was assessed. Safety assessments were performed throughout study and during follow-up.

Results: Study treatments were generally well tolerated. All enrolled subjects (n=74) completed the study. No Grade 2, 3 or 4

Table 1: Results of Pharmacokinetic Analysis

EVG Single Dose PK				
	Mean (%CV)		GMR (%)	90% CI
	Test	Reference		
Cohort 1: 3 × 50 mg Pediatric Tablets (Test) vs 150 mg Adult Tablet (Reference)	n = 30	n = 30		
AUC_{last} (ng*h/mL)	21100 (32)	21000 (29)	99.6	(93.2, 106)
AUC_{inf} (ng*h/mL)	22200 (34)	22100 (36)	100	(93.8, 107)
C_{max} (ng/mL)	1650 (30)	1640 (28)	100	(93.1, 107)
Cohort 2: 30 mL of 5 mg/mL Pediatric Suspension (Test) vs 150 mg Adult Tablet (Reference)	n = 26	n = 26		
AUC_{last} (ng*h/mL)	24200 (36)	21800 (37)	111	(103, 120)
AUC_{inf} (ng*h/mL)	25000 (36)	22800 (36)	109	(102, 118)
C_{max} (ng/mL)	1800 (40)	1650 (38)	108	(98.7, 118)

EVG Multiple Dose PK		
Cohort 3	**Pediatric Tablets (3 × 50 mg) n=9**	**Pediatric Suspension (30 mL of 5 mg/mL) n=9**
AUC_{tau} (ng*h/mL) Mean (%CV)	24100 (16)	20600 (24)
C_{max} (ng/mL) Mean (%CV)	2470 (22)	1940 (30)
C_{tau} (ng/mL) Mean (%CV)	411 (18)	377 (30)
T_{max} (h) Median (Q1, Q3)	4.00 (3.50, 4.00)	4.00 (3.52, 4.00)
$t_{1/2}$ (h) Median (Q1, Q3)	7.64 (7.21, 8.35)	7.44 (5.87, 8.47)

adverse events were observed. Mean (%CV) and the GMR (90%CI) of EVG PK parameters are presented in Table 1. In Cohorts 1 and 2, EVG exposure (AUClast, AUCinf, and Cmax) were within the protocol-defined BE bounds for both the pediatric tablet and suspension formulations vs the reference (adult) tablet formulation. In Cohort 3, EVG PK following multiple doses of EVG with RTV was comparable between pediatric tablet and suspension formulations and consistent with historical steady state data of boosted EVG, including achievement of mean trough concentrations (EVG Ctau) ~8.5 and 9.2-fold, respectively, above the IC95 (44.5 ng/mL).

Conclusions: EVG pediatric tablet and suspension formulations were each bioequivalent to adult tablets, when coadministered with RTV. The EVG formulations were well tolerated, and the multiple dose PK of both formulations were consistent with historical data of boosted EVG. As such, these study findings support evaluation of these pediatric formulations in HIV infected children.

903 CYP2B6 Polymorphisms Challenge Generalized FDA Efavirenz Dosing Guidelines in Children < 3 Yrs

Carolyn Bolton Moore[1], Edmund Capparelli[2], Pearl Samson[3], Mutsa Bwakura-Dangarembizi[4], Patrick Jean-Philippe[5], Carol Worrell[6], Barbara Heckman[7], Lynette Purdue[6], Stephen A. Spector[2], Ellen G. Chadwick[8], IMPAACT P1070 team

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Background: The FDA has published dosing recommendations for Efavirenz (EFV) in children less than 3 yrs of age based on safety, pharmacokinetic (PK), virologic and immunologic data from 3 open-label clinical trials. However, IMPAACT P1070 has found significant EFV PK variability in this age group due to a single genetic polymorphism in CYP2B6 516 (rs3745274); TT [Poor Metabolizers, PM] and GG or GT [Extensive Metabolizers EM]. P1070 preliminary data suggest that FDA recommended dosages will result in a high proportion of EFV exposures outside of the therapeutic range.

Methodology: IMPAACT P1070 is an ongoing, prospective, phase I/II open-label 24 wk trial of EFV as opened capsules in HIV-infected children (Cohort 1) and HIV/TB co-infected children (Cohort 2, not reported), ages 3 to <36 months. In Version (V) 1, a high initial dose of EFV [~1600 mg x (weight in Kg/70)0.7 rounded for weight band dosing] was used to produce a target AUC of 35-180 mcg*hr/mL, a systemic exposure similar to that shown to be effective and safe in older children and adults. Genotypic testing was performed in real-time from dried blood spots using a TaqMan probe assay and genotypic profile determined using allelic discrimination plots. 24 hour plasma PK data at week 2 were grouped by CYP2B6 516 genotype. Based on excessive exposures found in PMs in V1, dosages for PMs were reduced by 75% (~400 mg x (wt in Kg/70)0.7) for V2. Expected AUC and C24 for FDA dosing were estimated from P1070 data: observed AUC or C24 X (FDA dose/study dose).

Results: 38 subjects have had 24 hr PK evaluation; 29 CYP2B6 EM and 9 CYP2B6 PM. Median apparent clearance (CL/F) was 0.45 L/h/kg in the EM subjects but only 0.087 L/h/kg in the PM subjects. The median C24 for EM/PM was 1.8/4.2 mcg/mL for P1070 dosing and 0.9/8.5 mcg/mL for FDA dosing (target 1-4 mcg/mL). The AUC data for P1070 and FDA dosing are presented below:

Conclusions: Based on PK results from P1070, it appears that the FDA recommended doses of EFV will produce sub-therapeutic EFV AUCs in 38% of children <3 yrs who are extensive metabolizers (EM prevalence ~93% in Europeans and 80% of African Americans) and excessive AUCs in 67% of PM's. In contrast, CYP2B6 genotype directed dosing allowed for 83% of EM and 89% of PM children to achieve target EFV PK levels. Given the importance of achieving appropriate drug levels in this population, CYP2B6 genotyping prior initiation of EFV will help optimize dosing in this age group.

EFAVIRENZ Area Under the Curve (AUC)				
EM (CYP2B6 516 GG/GT) n=29	Median AUC (mcg*h/mL)	# w/ Estimated Plasma AUC	# w/ Estimated Plasma AUC 35-180 mcg*h/mL	#w/ Estimated Plasma AUC >180 mcg*h/mL
P1070 V1 & V2 dosing	106.3	4 (14%)	24 (83%)	1 (3%)
FDA dosing	51.3	11 (38%)	17 (59%)	1 (3%)
PM (CYP2B6 516 TT) n=9				
P1070 V2 dosing	113.2	0 (0%)	8 (89%)	1 (11%)
FDA dosing	245.1	0 (0%)	3 (33%)	6 (67%)

904 High Nevirapine and Low Lopinavir/Efavirenz Exposures in Resource-Poor Ugandan Children

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Background: Malnutrition may impact antiretroviral (ART) pharmacokinetics (PK) and clinical response in children. We evaluated the PK of nevirapine (NVP), efavirenz (EFV) and lopinavir (LPV) by nutritional status among HIV-infected children stabilized on ART in Tororo, Uganda.

Methodology: Sparsely sampled dried blood ¬spot (DBS) ART samples, collected in Ugandan children residing in resource poor country (RPC) were corrected using hemoglobin and % protein bound to generate plasma concentrations, and then analyzed in the context of previously published rich PK-data from children from resource-rich countries (RRC) (United States, the Netherlands and France). Analysis was performed used nonlinear mixed-effects

modeling. PK parameters were compared between RRC and RPC, and between RPC children of varying nutritional status: weight-for-age (underweight), body mass index (BMI)-for-age (wasted), height-for-age (stunted).

Results: 103, 62 and 165 single DBS samples derived from 48, 32 and 83 Ugandan children managed with NVP, EFV and LPV respectively were combined with 611, 394 and 184 plasma samples from 96, 52 and 56 children from RRC on the same ART respectively. Median age and weight of Ugandan children was 4.0 yrs (range 0.7-7) and 15kg (range 5.2-25), respectively. 96% of Ugandan children had moderate to severe insecure access to food, 48% were malnourished (defined as wasted, underweight or stunted). 22% were underweight compared to 8% from RRC. Compared to RRC children, PK exposure of NVP was 52% higher in Ugandan children ($p<0.001$) and showed a trend towards higher exposures in malnourished versus non-malnourished Ugandan children. In contrast, EFV and LPV PK exposures were reduced by 30% ($p=0.022$) and 17% ($p=0.015$), respectively in Ugandan compared to RRC children with no significant difference between non-malnourished and malnourished Ugandan children. Using current WHO dosing guidelines, simulations based on study results indicate that NVP minimum concentrations (Ctrough) may exceed a maximum recommended Ctrough of 8 mg/L in 67% of malnourished children. However, EFV and LPV dosing should result in appropriate Ctroughs in most Ugandan children.

Conclusions: Children residing in the resource poor area of Uganda exhibit high levels of malnutrition and show increased NVP and reduced EFV and LPV PK exposure compared to children from RRC. WHO guided dosing in Ugandan children, especially those malnourished may result in excessive NVP exposure while EFV and LPV exposure is expected to fall within target values. Further studies investigating the clinical impact of these PK changes during malnourishment is required, using more dense data and better knowledge of adherence, especially for NVP.

905 Bone and Renal Safety at 96 Weeks of TDF-Containing Regimens in HIV-Infected Thai Children

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Background: Tenofovir (TDF) is currently recommended in first- and second-line ART regimens for children. This study was aimed at determining the impact of TDF on bone mineral density (BMD) and renal function among HIV-infected adolescents after 96 weeks.

Methodology: Of 62 HIV-infected children on TDF-containing regimens, 35 children had CD4, HIV-RNA, BMD and renal function assessments over 96 weeks. An additional 27 children had cross-sectional renal toxicity assessments and mid-dose plasma TDF concentrations at 10-14 hours after dosing. Renal toxicity criteria were based on glomerular filtration rate (GFR), spot urine protein, glucose, calcium and uric acid, tubular reabsorption of phosphate (TRP) and beta-2 microglobulin levels. BMD was assessed yearly using dual-energy x-ray absorptiometry (DEXA). Longitudinal regression model was used to assess the overall change of renal and bone parameters. Geometric means for mid-dose TDF concentration are presented with coefficient of variation percentage (%CV).

Results: Among 35 children with 96-week follow-up, median (IQR)age was 15.7 (11.2-18.0) years, median weight was 43 (38-47) kg and 31 (89%) were ≥ Tanner stage 4. Median duration on TDF was 5 (2-15) months. The median CD4 was 694 (558-1123) cells/mm^3; 32 (92%) had HIV-RNA <50 copies/ml.

At week 96, median GFR decreased from 102 (90-120) at baseline to 92 (88-104) mL/min/1.73m^2 ($p<0.01$). In a longitudinal regression model, protease inhibitor (PI) use ($p=0.02$), female sex ($p<0.01$)and longer duration on TDF ($p<0.01$) were associated with GFR reduction. Twenty (57%) developed ≥1 criteria for renal toxicity over 96 weeks including proteinuria ≥2+ (6%), glucosuria ≥1+ (9%), hypercalciuria (3%), hyperuricosuria (6%) and urine beta-2 microglobulin >300 (24%) mcg/L. None had clinically significant renal toxicity. Half had BMD z-score >-1.5 at baseline. The median BMD z-score decreased from -1.5 (-2.4 to -0.6) to -1.6 (-2.3 to -0.9) ($p=0.13$). Majority (83%) remained virologically suppressed and 9% developed virological failure.

Among 50 children who had mid-dose TDF concentrations, median duration of TDF use was 16 (8-24) months and TDF dose was 219 (203-235) mg/m^2. Cross-sectional evaluation revealed 18 (36%) children with ≥1 renal toxicity criterion. The geometric mean (% CV) mid-dose TDF concentration among children with renal toxicity (108.8 [42%] ng/mL) was significantly higher than those without renal toxicity (87.7 [29%]ng/mL; $p=0.03$).

Conclusions: There were no significant changes in BMD during 96 weeks of follow-up. About one-third of children had at least one abnormal parameter of renal function. Longer duration of TDF treatment, concomitant PI use and higher mid-dose TDF concentrations were associated with renal abnormalities.

906LB Safety and Efficacy of Dolutegravir in HIV Treatment-Experienced Adolescents: 48-Week Results

Rolando M. Viani[1], Carmelita Alvero[2], Terry Fenton[2], Edward Acosta[3], Rohan Hazra[4], Ellen O'Gara[5], Barbara Heckman[6], Debra McCarty-Steimers[7], Sherene Min[8], Andrew Wiznia[9]

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Background: P1093 is an ongoing Phase I/II multicenter open-label pharmacokinetic (PK), safety, dose finding study of dolutegravir (DTG) plus optimized background regimen (OBR) in children and adolescents in age defined cohorts. The pediatric weight band dosing of ~1 mg/kg once a day achieved PK exposure in adolescents comparable to those observed at 50 mg once daily in adults.

Methodology: HIV infected treatment experienced children ≥12 to <18 yrs on a failing antiretroviral (ARV) regimen with an HIV RNA of ≥1000 copies/mL (c/mL) were enrolled in Stage 1 (intensive PK) or Stage 2 (no PK, safety and efficacy). Stage 1: DTG was added to a stable, failing ARV regimen, with an OBR added after intensive PK (~Day 5-10); Stage 2: DTG was started with an OBR. Safety, tolerability, CD4 cell count and HIV-1 RNA were evaluated at Week 48. Virologic success was defined as achieving an HIV-1 RNA < 400 c/mL by Week 48 based on the FDA snapshot algorithm, with an additional secondary outcome of HIV-1 RNA <50 c/mL.

Results: Twenty three adolescents (Stage 1, n=10; Stage 2, n=13) were enrolled and 22 (95.7%) completed the 48 week study visit. Demographics were as follows: 78% (18/23) female, 52% (12/23) African American, 35% (8/23) Caucasian, 26% (6/23) were of Hispanic ethnicity. Median age (range) was 14 yrs (12, 17) and median weight (range) was 52.2 kg (33, 91). Median (IQR) baseline CD4+ cell count and % were 466 cells/μL (297, 771) and 22% (18.4, 29.2), respectively. Median (IQR) baseline HIV-1 RNA $\log_{10}$ was 4.3 $\log_{10}$ c/mL (3.9, 4.6). Nineteen adolescents received 50 mg/day and 4 received 35 mg/day of DTG. Virologic success, an HIV RNA < 400 c/mL was achieved in 73.9 % (17/23; 95% CI: 51.6 % to 89.8%) at Week 48. Additionally, 60.9% (14/23; 95% CI: 38.5% to 80.3%) had an HIV RNA load < 50 c/mL at Week 48. Median (IQR) gain in CD4 cell count and % at Week 48 was 84 cells/μL (-81, 238) and 4.7% (0, 9.4) respectively. DTG was well tolerated, with 2 subjects experiencing Grade 3 laboratory abnormalities: one developed unconjugated bilirubin elevation while on atazanavir as part of the OBR, and another subject developed asymptomatic lipase elevation, which was deemed treatment unrelated. One subject discontinued DTG after virologic failure due to inability to meet study related appointments. Invariably, all participants who experienced virologic failure had incomplete adherence based on three day pill recall questionnaire. There were no Grade 4 AEs, SAEs or discontinuations due to AEs.

Conclusions: DTG plus OBR was safe and well tolerated in HIV infected adolescents. In addition, DTG treatment as part of an OBR provided good virologic efficacy through Week 48.

907 Simulation and Exposure-Based Assessment of Pediatric Lopinavir Fixed-Dose Combination Product

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Background: Currently, only one boosted PI is approved for use in infants: lopinavir/ritonavir (LPV/r). The LPV/r formulation is not ideal for infants and children living in resource-poor settings, as it is poorly tolerated, needs refrigeration, contains large amounts of undesirable excipients, and is more expensive than other regimens for most national HIV programmes. The development of low-cost, solid fixed-dose combinations of LPV/r with various nucleoside reverse transcriptase inhibitor (NRTI) backbones in modular unit forms (LPV/ABC/3TC and LPV/ZDV/3TC) is thus greatly needed to improve both management and adherence of children especially in resource-limited settings.

Methodology: The pharmacokinetic (PK) analysis combined 25 datasets including therapeutic drug monitoring and published clinical studies from IMPAACT and PENTA. Intensive and sparse PK data totaling 1394 LPV concentrations from 338 subjects, aged 2 days to 24 years old, were analysed. For 3TC, ABC, and ZDV, a total of 927 patients with 3820 concentrations, 188 patients with 1232 concentrations, and 756 patients with 3312 concentrations were used, respectively. Population PK analyses were performed for each drug using MONOLIX 4. Simulations of current dosing recommendations were performed to assess their ability to provide optimal exposure in children weighing 4 to 25 kg. For the NRTIs, dose ratios of 0.375 and 2 were respectively used for 3TC to LPV and ZDV-ABC to 3TC.

Results: After allometric scaling, a PK age effect was observed for all drugs. This age effect described increasing apparent clearance for all NRTIs and increasing bioavailability for LPV with age. The simulations indicated that the WHO dosing recommendations resulted in more than 95% of subjects with LPV Cmin > 1.0 mg/L. However, using the recommended drug ratios, the combination dosage for the 4-6 kg weight band (LPV/ZDV: 120/90mg BID) resulted in high ZDV exposure with more than 20% of subjects at levels associated with high risk of neutropenia (Cave>0.8 mg/L). Reducing the LPV/ZDV dosage to 80/60 mg BID dramatically decreased frequency of high ZDV concentrations and risk of neutropenia. This dosage reduction retained LPV Cmin >1.0 mg/L in more than 95% of subjects and did not adversely affect therapeutic target obtainment for the NRTIs. Moreover, this proposed dosage fully corresponded to the WHO guidelines for all NRTIs.

Conclusions: These simulations suggest that a pediatric fixed-dose LPV/3TC/ZDV or ABC formulation could be developed to achieve targeted therapeutic levels for all ARV components. Each unit would include 40 mg LPV, 10 mg RTV, 15 mg 3TC and 30 mg ABC or ZDV. According to the weight bands, i.e. 4-6 kg, 6-10 kg, 10-14 kg, 14-20 kg, 20-25 kg, therapeutic doses would be 2, 3, 4, 5, or 6 units twice daily of this formulation.

908 Bioequivalence of Two Pediatric Formulations vs Adult Tablet Formulation of Cobicistat

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Background: There are limited antiretroviral pharmacoenhancers available for pediatric use. Cobicistat (COBI) is a mechanism-based CYP3A inhibitor devoid of antiretroviral activity approved for adults as a pharmacoenhancer of atazanavir 300 mg or darunavir 800 mg in the European Union and as a pharmacoenhancer in the single tablet regimen elvitegravir/COBI/emtricitabine/tenofovir disoproxil fumarate (ECF/TDF; Stribild™) for treatment of HIV-1 infection in numerous countries. This study evaluated the pharmacokinetics (PK) of COBI administered as a 50 mg pediatric immediate release tablet (test) and as a 20 mg pediatric dispersible tablet (test) vs the 150 mg adult tablet formulation (reference).

Methodology: This was a prospective, open-label, randomized, multiple cohort, single dose, crossover study in healthy adult subjects. Cohort 1 (n=32) evaluated the pharmacokinetics (PK) of the pediatric immediate release tablets (3 X 50 mg) vs reference. Cohort 2 (n=30) evaluated the PK of the pediatric dispersible tablet (7.5 X 20 mg; tablet split using standard pill cutter) vs reference. All treatments were administered under fed conditions with 240 mL of water. Intensive PK sampling was conducted over 48 hours post dose and PK parameters were calculated using noncompartmental methods. Bioequivalence (BE) was assessed in both Cohorts using geometric mean ratios (GMR) and associated 90% confidence interval (CI) bounds of 80%-125% (>90% power to conclude BE). Palatability was assessed by questionnaire after each treatment. Safety assessments were performed throughout the study and during follow-up.

Results: Study treatments were generally well tolerated and all enrolled subjects completed the study, except one subject whom withdrew consent. All formulations were considered palatable. All adverse events (AE) were Grade 1, with one subject experiencing Grade 2 AE while receiving the pediatric immediate release tablets. Mean (%CV) and the GMR (90%CI) of COBI PK parameters are presented in Table 1. COBI exposure (AUClast, AUCinf, and Cmax) were within the protocol-defined BE bounds for both the pediatric immediate release and dispersible tablet formulations vs the reference (adult) tablet formulation.

Table 1: Results of Pharmacokinetic Analysis

COBI PK	Mean (%CV)		GMR (%)	90% CI
	Test	Reference		
Cohort 1: 3 × 50 mg Pediatric Immediate Release Tablets (Test) vs 150 mg Adult Tablet (Reference)	n = 30	n = 30		
AUC_{last} (ng*h/mL)	4470	4700	95.0	(88.9, 101)
AUC_{inf} (ng*h/mL)	4510	4750	95.0	(88.9, 101)
C_{max} (ng/mL)	804	804	100	(92.8, 108)
Cohort 2: 7.5 × 20 mg Pediatric Dispersible Tablets (Test) vs 150 mg Adult Tablet (Reference)	n = 30	n = 30		
AUC_{last} (ng*h/mL)	5470	5660	96.6	(90.0, 104)
AUC_{inf} (ng*h/mL)	5510	5710	96.6	(90.0, 104)
C_{max} (ng/mL)	850	924	91.9	(86.8, 97.4)

Conclusions: Pediatric formulations of COBI, administered either as 50 mg immediate release tablets or as 20 mg dispersible tablets, were each bioequivalent to the COBI adult tablet formulation, supporting evaluation of these pediatric formulations in HIV infected children.

909 Pharmacokinetics, Efficacy, and Safety of an Integrase Inhibitor STR in HIV-Infected Adolescents

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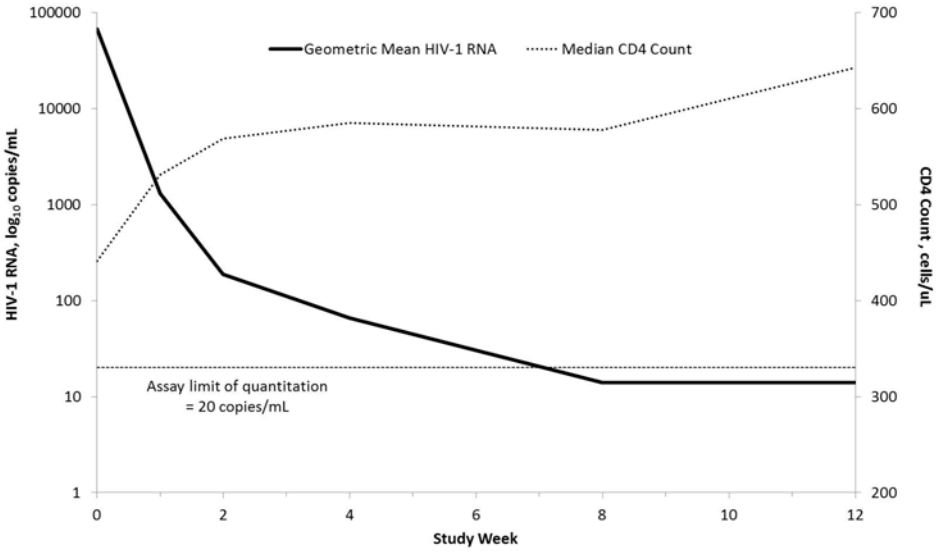
Background: The integrase inhibitor-based E/C/F/TDF single-tablet regimen (STR) contains elvitegravir (EVG) 150 mg, the pharmacoenhancer cobicistat (COBI) 150 mg, emtricitabine (FTC) 200 mg and tenofovir disoproxil fumarate (TDF) 300 mg. The PK, efficacy, and safety of E/C/F/TDF were evaluated in adolescents in the initial "Part A" of a prospective, 48-week, single-arm, open-label trial.

Methodology: Treatment-naïve patients 12 to <18 years of age, weighing ≥35 kg with HIV-1 RNA > 1000 copies/mL (c/mL), CD4 counts > 200 cells/uL and eGFR ≥90 mL/min received one E/C/F/TDF tablet once daily. Intensive PK was performed on Day 10 (steady state). The primary endpoint was EVG AUC_{tau}. Exposures were compared to population PK-based exposures in adults from E/C/F/TDF Phase 2 and 3 trials by ANOVA. HIV-1 RNA, adverse events (AE) and routine laboratory tests were assessed through Week 12.

Results: Part A enrolled 14 subjects (64% male, 29% Asian, 64% black and 7% white) with a median age of 16 years (range: 13-17), a median weight of 57 kg (range: 35-80), and a median BMI of 21 kg/m^2 (range: 17-26). At baseline, geometric mean HIV RNA was 4.83 log_{10} c/mL; 4 subjects (28.6%) had HIV RNA >100,000 c/mL, and median CD4 count was 442 cells/uL. At Day 10, the EVG geometric least squares mean (GLSM) AUC_{tau} was 130% of the adult level (90% CI: 105-162%) and the GLSM C_{max} was 142% of the adult level (90% CI: 116-173%). The GLSM C_{tau} was 410 ng/mL, 106% of the adult level (90% CI: 70.0-160%) and 9.2 times the protein-adjusted IC_{95} of 44.5 ng/mL. COBI, TDF and FTC exposures were similar to exposures in adults. Among 11 subjects with data at Week 12, geometric mean HIV RNA was 1.61 log_{10} c/mL, 100% of subjects had HIV RNA < 400 c/mL, 9/11 (81.8%) had HIV RNA <50 c/mL, and median CD4 count was 643 cells/uL (Figure). No subject met the criteria for virologic failure. The most frequent AEs were gastrointestinal (7/14, 50%). Related AEs were mild and included vomiting (2), abdominal pain (1), nausea (1), and headache (1). No AE led to discontinuation. Median serum creatinine (Cr) increased by 0.07 mg/dL at Week 12, similar to the increase seen in adults and consistent with COBI's inhibition of tubular Cr secretion. No cases of renal tubulopathy or renal failure occurred.

Figure: HIV-1 RNA and CD4 Count through Week 12 of ECF/TDF Treatment



Conclusions: In adolescents, the E/C/F/TDF STR provides component ARV exposures similar to adults, exhibits robust antiviral activity, and appears well tolerated. These findings support continued evaluation of this integrase inhibitor-containing STR in pediatric populations.

Session P-U4 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Host and Immune Response in Children and Adolescents

910 Complex Pattern of Inflammatory Biomarkers After ART Initiation in HIV-Infected African Children

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Background: HIV infection is characterized by immune activation, likely driven by viral replication, microbial translocation, malnutrition and co-infections, particularly in sub-Saharan Africa. Although characterized in HIV-infected adults, changes in inflammatory biomarkers have not been well described in African children starting ART with advanced disease.

Methodology: 316 children/adolescents (median (IQR) age 5 (2,9) years, 67% WHO stage 3/4) initiating ART in the ARROW trial in Uganda/Zimbabwe were enrolled in a substudy measuring inflammatory biomarkers (CRP, TNF-α, IL-6, sCD14) by ELISA on cryopreserved plasma at enrolment and then every 24 weeks to 192 weeks. VL was assayed using Abbott Taqman and Roche Amplicor,with lower detection limit 80 c/ml. Log_{10} absolute cytokine levels after ART initiation were modelled using random effects models with child-level intercepts and slopes, adjusting for site performing the assay.

Results: At ART initiation, geometric mean CD4% was 10.2%, VL 209261c/mL, CRP 4.8 mg/L, TNF-α24.3 pg/mL,IL-6 6.6pg/mL and sCD14 $1.9x10^6$ pg/mL. Children with lower pre-ART CD4% had higher pre-ART CRP (p=0.01), IL-6 (p<0.001) and sCD14 (p=0.005), but there was no association with pre-ART TNF-α(p=0.77). In contrast, children with higher pre-ART VL had significantly higher TNF-α(p<0.001), higher IL-6 (p<0.001) and higher sCD14 (p=0.006), but there was only weak association with CRP (p=0.09). VL suppression <80 c/ml was achieved by 79% children at 24 weeks; then 74%, 67%, 68%, 65% and 64% at 48, 72, 96, 144 and 196 weeks. IL-6 dropped by 32% [95% CI 24-41%] over the first 24 weeks on ART (p<0.0001), but did not change significantly thereafter (p=0.87). CRP dropped by 48%[35-60%] over the first 48 weeks on ART (p<0.001), again with no evidence of change thereafter (p=0.87).TNF-αdropped by 70%[66-74%] over the first 48 weeks on ART, but then rose again by 47% [39-55%] to week 72, subsequently declining more modestly by 38% [33-42%] every 24 weeks (all p<0.001). This effect was seen independently in each site conducting assays, and in all pre-ART CD4% groups.sCD14 declined much more slowly throughout follow-up, dropping by only 1% [1-2%] every 24 weeks (p<0.001).

Conclusions: Children starting ART with advanced disease have elevated inflammatory biomarkers, which are related to pre-ART CD4 levels (except for TNF-α).All biomarkers dropped after starting ART, although declines in sCD14 were very slow.IL-6 and CRP tended to drop rapidly and plateau after 24-48 weeks; by contrast, TNF-α showed more variability, perhaps in response to changes in VL. Better understanding changes in inflammatory biomarkers on ART may help to define subgroups of children with residual immune activation, who would benefit from adjunctive treatment strategies.

911 Preferential Preservation of Helios+Foxp3+ Regulatory T Cell Subset in HIV Infected Children

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Background: Foxp3+ regulatory T cells (Tregs) are a unique subset of CD4+ that play a critical role in immune homeostasis and tolerance. Most Tregs in peripheral blood are generated in the thymus; the remainder is induced in the periphery. Data are limited on the impact of HIV infection on Tregs, but none exist for Helios+Tregs in children with HIV infection. Since thymic function is highly active during childhood and can be severely damaged by HIV infection, our study investigated Tregs and their Helios+ subset in children with perinatally acquired HIV infection.

Methodology: A prospective cross-sectional cohort study was made on HIV infected children and adolescents receiving care through UTHealth. The study was IRB approved and required informed consent. Sample processing, FACS and data processing were by established methods and with commercially available reagents. Foxp3 and Helios intracellular staining was performed with an eBioscience kit. Tregs were defined as Foxp3+ within CD4+ T cells and Helios+Tregs as Helios+ within Tregs.

Results: 59 patients were enrolled: median age 14.4 (range 0.8-21.3 years); 48.3% female; and 70% black (30% Hispanic/other). Most had previous clinically severe HIV (55% CDC Immune Status >1, CD4 nadir 18%, 371/µl, medians) but were clinically improved at the time of study (CD4+ 32%, 794/µl). Most (83.8%) were on cART at the time of Treg measurement. %Tregs negatively correlated with %CD4 (r=-0.439, p<0.001) while their numbers were positively correlated (r=0.727, p<0.001). %Helios+Tregs had no correlation with %CD4 (r=0.014, p=0.915), but their numbers were positively correlated (r=0.603, p<0.001). When compared to viral load, there was a modest positive correlation with %Tregs (r=0.382, p<0.01) but none with %Helios+Tregs. For Treg numbers, there was a negative correlation (r=-0.286, p=0.027) but none for Helios+. For Tregs vs. Helios+, there was a positive correlation, particularly with numbers (r=0.924, p<0.001). % and # of Tregs and Helios+Tregs also positively correlated with CD38+CD8+ cells (r=0.321-0.477, p<0.01). When the patients were segregated into three groups, good (n=24, ≥25% CD4, <20 HIV RNA copies/ml), intermediate (n=26, ≥25% CD4, >20 HIV) and poor (n=9, <25% CD4, >20 HIV), those with the highest %Tregs were in the poor, but the %Helios+Tregs was similar in all groups. The poor group also had the highest ratio of % and # of Tregs to CD4+ cells.

Conclusions: There is a selective expansion or survival of Tregs associated with CD4 depletion and increased viremia. This preservation of Tregs is within the Helios+ subset, which could be reconstituted from the thymus. While this expansion appears ineffective in suppressing immune activation, it might be important in regulating autoimmunity.

912 Perturbation of Regulatory T Cell Subsets in HIV Infected Children

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Background: Regulatory T cells (Tregs) mediate immune tolerance during autoimmune disease and chronic infections. During HIV infection, Tregs may act either beneficially to curb immune activation or pathologically to suppress HIV-specific immune responses. Previous reports of Tregs during chronic HIV have conflicting results with higher or lower levels compared to controls. Identifying true Tregs with suppressive activity proves challenging during HIV infection, as traditional Treg markers, CD25 and FOXP3, may transiently upregulate expression as a result of immune activation. Helios is a recently identified transcription factor that marks natural Tregs with suppressive activity. Moreover FOXP3+Helios+ CD4 T cells do not produce the cytokine IL-17, and have been called "bona fide" Tregs. We sought to identify these bona fide Tregs in vertically infected HIV positive children.

Methodology: We evaluated Treg levels by flow cytometry in the peripheral blood of 60 children from Bomu Hospital in Mombasa, Kenya. The cohort included age-matched children between 3 to 12 years old in the following categories: HIV negative (HIV-), HIV positive antiretroviral therapy naïve (ART-), and HIV positive on antiretroviral therapy (ART+). Peripheral blood mononuclear cells (PBMCs) were isolated and cryopreserved from each subject. Thawed PBMCs were stained for surface antibodies CD3, CD4, CD25, CD38, CD45RO, and intracellular transcription factors FOXP3 and Helios. All statistical analysis was performed with GraphPad Prism software using Mann-Whitney or Spearman's correlation tests.

Results: HIV+ children (ART- and ART+) expressed higher levels of FOXP3 and Helios in CD4 T cells compared with HIV- controls (ART-: $p=0.0012$, ART+: $p=0.0057$). FOXP3+Helios+ expression inversely correlated with the percent of CD4 T cells ($p<0.0001$, $r= -0.4883$), despite nearly normal CD4 levels in ART+ children. As previously reported, HIV infected children had higher immune activation as measured by CD38+HLA-DR+ expression on CD8+ T cells (ART-: $p<0.0001$, ART+: $p=0.0223$). This immune activation (CD38+HLADR+ CD8 T cells) positively correlated with FOXP3+Helios+ Treg levels ($p=0.0008$, $r=0.4301$). The ART- group also demonstrated an activated phenotype by increased CD38 expression in memory ($p=0.0001$) and in FOXP3+Helios+ memory CD4 T cells ($p=0.0010$) that was not present in the ART+ subjects.

Conclusions: Bona fide Treg levels increase during HIV infection and correlate with waning CD4 T cells and higher immune activation. While antiretroviral therapy decreases the activated state in these bona fide Tregs, it does not restore Treg levels to the homeostatic proportion in HIV negative children. This increase in Helios+ Tregs may act to ameliorate chronic immune activation during HIV infection.

913 Incomplete Immune Reconstitution in HIV-1-Infected Children With Virological Suppression

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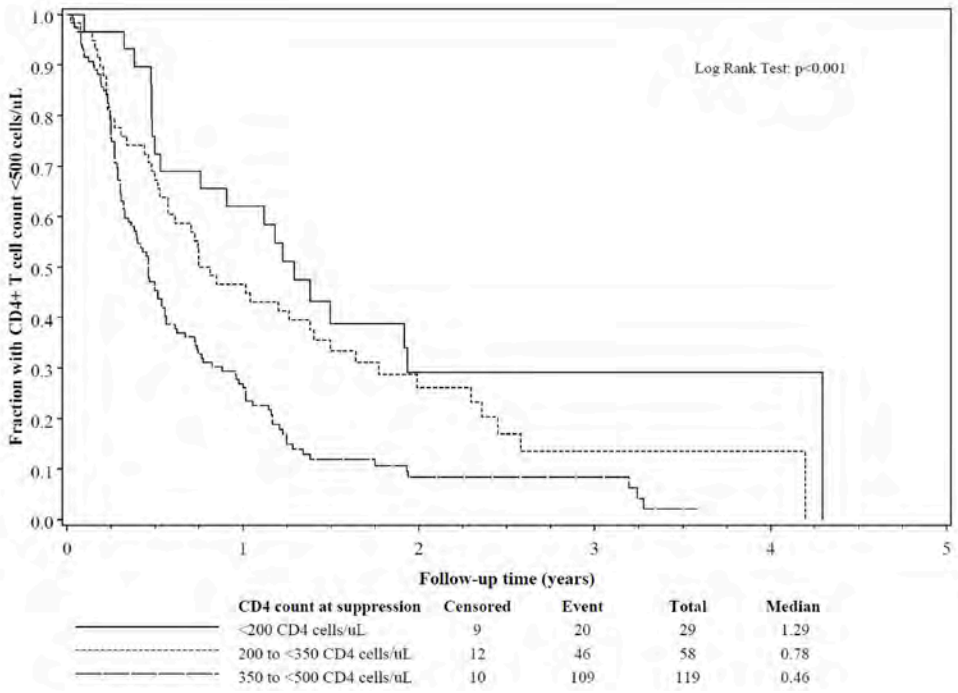
Background: Suppression of plasma viremia by antiretroviral therapy (ART) is generally associated with improvements in immunological status, but some individuals fail to achieve normalization of CD4 T cell counts. In adults, AIDS defining events rapidly decrease once virological suppression is achieved, even when CD4 T cell lymphocytopenia persists. Similar data are not available for children to determine the frequency of and risks associated with persistence of CD4 lymphocytopenia despite effective ART.

Methodology: Data were pooled from 3,784 children enrolled in the 219C, NISDI and AMP cohorts, and 933 perinatally HIV-1 infected youth were identified with virologic suppression (VS) lasting at least 1 year at an age of ≥5 years, with available CD4 counts. For each child's first period of virologic suppression (VS) (plasma HIV RNA < 400 copies/ml), piecewise linear regression models were used to examine CD4 T cell trajectories during VS by CD4 at start of VS and Kaplan-Meier estimates for time to CD4≥500 cells/μL were generated for CD4 categories < 500 copies/μL.



Results: Of the 933 children in the study population, 50% were black, 36% Hispanic/Latino, and 14% white/Asian with a median age of

8.8 years at the start of ART that resulted in VS. 108 (12%) were from NISDI sites in Argentina, Brazil, Mexico, and Peru; 88% were from the United States and Puerto Rico. At the start of ART leading to VS, 92 (10%), 118 (13%), and 138 (15%) had CD4 T cell counts of <200, 200-350, and 350-499 cells/μL, respectively. Most (99%) children achieved a CD4 count of 200 cells/μL after 1 year of VS, but 13% failed to exceed 500 cells/μL. The rate of initial increase in CD4 T cells counts was inversely proportional to baseline CD4 T cell strata. The median times to first CD4 T cell counts > 500/μL were 15, 9, and 6 months for children with <200, 200-350, and 350-499 CD4+ T cells/μL at the time of VS (Figure). CDC C events occurred in 8 children after VS, including encephalopathy, bacterial peritonitis, pneumonia, and candida esophagitis. 3 such events occurred in the first 6 months following VS; the others occurred 6.6 to 21 months after VS. 5 events were in children with CD4 T cell counts> 500 cells/μL.

Conclusions: Most children who maintain virological suppression improve their CD4 T cell counts. The time to achieving a CD4 count of ≥500 T cells/μL is highly variable and depends upon CD4 counts at the start of VS. Although rare, AIDS defining events continued to occur in 1% of the population studied, despite VS and improved T cell counts.

914 Lower Inflammatory Biomarkers in Children Randomized To Prolonged Cotrimoxazole Prophylaxis

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Background: Cotrimoxazole (CTX) prophylaxis reduces morbidity and mortality in HIV-infected children onlong-term ART, despite high-level pathogen resistance. Children taking CTX also have improved growth and reduced anemia, for reasons that are unclear. We hypothesized that benefits of CTX may be partly driven by reductions in inflammation.

Methodology: 758 children/adolescents (median (IQR) age 7 (4,11) years) in the ARROW trial in Uganda/Zimbabwe were randomized to stop (n=382) vs continue (n=376) daily CTX after median(IQR) 2.1(1.8,2.2) years on ART.Inflammatory biomarkers (CRP, TNF-α, IL-6, sCD14) were measured by ELISA on cryopreserved plasma in a subset of 304 children at randomization (155 stop, 149 continue), then at 12, 24, and 96 weeks. Those co-enrolled in a cross-sectional metabolic substudy also had albumin, total protein and lipid profile measured 3 years after ART initiation.Change in $\log_{10}$ cytokine levels after randomization were modelled using normal interval regression, adjusting for site performing the assay.

Results: CRP was significantly higher in those randomized to stop CTX at 12, 24 and 96 weeks after ART initiation (2.22-fold [95% CI 1.23-4.01], p=0.008; 1.98-fold [1.26-3.14], p=0.003; and1.95-fold [1.10-3.46], p=0.02, higher, respectively; N=193, 260, 192 to date). There was a trend towards higher TNF-α in the stop CTX group at week 12 (1.16-fold higher vs continue [0.99-1.36], p=0.07), but this attenuated at 24 weeks (p=0.19) and had disappeared at 96 weeks (p=0.30). For sCD14 and IL-6, there was no evidence of a difference between stop vs continue CTX groups at week 12 (p=0.16 and p=0.17 respectively); by 24 weeks differences had widened (difference stop vs continue: sCD14 1.10-fold higher [1.00-1.21], p=0.06; IL6 1.35-fold higher [0.99-1.84], p=0.06), but were absent at week 96 (sCD14 p=0.91; IL-6 p=0.34). At a single measurement taken at median 48 (IQR 36-60) weeks after randomization in 169 children, albumin was also significantly lower in those randomized to stop CTX (difference -1.77 g/L vs continue [-2.97,-0.57] p=0.004), with non-significant trends towards higher total protein (+1.76 g/L vs continue [-0.13,+3.66] p=0.07) and LDL cholesterol (+0.17mmol/L vs continue [-0.04,+0.38] p=0.11).

Conclusions: Children on long-term ART randomized to stop CTX showed a rise in inflammatory biomarkers compared to those continuing CTX, in particular with increases in CRP persisting for two years after stopping prophylaxis. Previously reported benefits of CTX, particularly for anemia and growth, may therefore be partly driven by reductions in chronic inflammation, either directly through the well-described immunomodulatory properties of CTX, or indirectly through modulation of microbial translocation.

915 CD127 Expression On Naive T-Cells and HIV Replication in Youths Infected in the Perinatal Period

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Background: In a cohort of youths infected with HIV-1 in the perinatal period, we previously reported that naive CD4 T-cell levels were in the same range as in uninfected individuals and that thymopoiesis was maintained in both viremic and aviremic patients. Here, we studied naive T-cell homeostasis by assaying plasma IL-7 and cellular expression of CD127, its high-affinity receptor.

Methodology: The ANRS-EP38-IMMIP study comprised 93 perinatally HIV-infected youths between 15 and 24 years old. At the time of the study, 85% were on HAART and 65% were aviremic. CD127 expression on T-cells was quantified by flow cytometry. Plasma cytokines were quantified by ELISA or multiplex assays. Mann-Whitney and Spearman tests were used for univariate analyses. Multivariate linear regressions were performed.

Results: Plasma IL-7 levels were significantly higher in viremic patients than in aviremic patients (4.5 vs. 3.9 pg/ml, P=0.02) and were negatively correlated with the CD4 T-cell counts in viremic patients (rho=-0.355, P=0.04), but not aviremic patients (rho=-0.137, P=0.31). CD127 expression on memory CD8 T-cells was lower in aviremic than viremic patients (41.6 vs. 59.8%, P=0.03) but CD127 expression on memory CD4 T-cells was similar (88.9 vs. 88.1, P=0.41). In sharp contrast, CD127 expression on naive CD4 T-cells was higher in viremic than aviremic patients (91.3 vs. 87.1%, P=0.007). In aviremic patients, the CD127hiCD4N percentage was independently associated with the CD4 T-cell count (adjusted estimate per 100 cells: 1.2; 95%CI: 0.3; 2.0), the detection of plasma IFN-alpha (adjusted difference: 7.1; 95%CI: 2.4; 11.8) and the plasma sTNFR2 level (adjusted estimate per pg/ml: -0.010; 95%CI: -0.017; -0.003). However, it was not associated with the plasma IL-7 level or the naive CD4 T-cell percentage. For viremic

patients, the CD127hiCD4N percentage was significantly lower in patients with detectable plasma IL-4 (adjusted difference: -7.8; 95%CI: -14.2; -1.4), and was not associated with the CD4 T-cell count (adjusted estimate per 100 cells: -0.4; 95%CI: -1.6; 0.8). The expression level of CD127 on naive CD8 T-cells were similar to that on naive CD4 T-cells.

Conclusions: After at least 15 years of exposure to perinatally acquired HIV infection, adolescents and young adults have elevated expression of CD127 on naive CD4 T-cells in the presence of active HIV replication. This contrasts with the down-regulation of CD127 reported in viremic adults, but is consistent with the preservation of naive CD4 T-cell homeostasis in these young patients.

Session P-U5 Poster Session
Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**
Complications of HIV and ART in Children and Adolescents

916 Pediatric HIV Infection and Dental Caries in the Era of Antiretroviral Therapy in West Africa

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Background: The prevalence of dental caries is believed to be higher among HIV-infected (HIV+) children than in the general pediatric population. However, dental caries are not described as opportunistic infections and the association between dental caries and HIV infection is unclear in the literature. The objective of this study was to assess the association between the number of decayed, missing and filled permanent and temporary teeth surfaces (DMFdefS) and the HIV infection status among children in West Africa.

Methodology: A multi-center two-step cross-sectional survey was conducted within five clinical centers in Mali, Senegal and Côte d'Ivoire. A random sample of 5 to 15 years old HIV+ children in care and a sample of their non-infected siblings (HIV-) were recruited in 2011-2012. Seronegative status for HIV infection in this latter group was confirmed by ELISA tests conducted in the context of the national HIV program. Oral health data collection was conducted by five trained and calibrated dentists (Cohen's kappa coefficient 0.59 to 0.93). The association between the DMFdefS and the HIV infection status was analyzed using a zero-inflated negative binomial (ZINB) model.

Results: 420 HIV+ children (84 or 20.2% with CD4 count<350 cells/mm³) and 418 HIV- siblings aged 4.4 to 15.7 years-old were enrolled. HIV+ children were more likely to attend school (93.0%) than their HIV- siblings (86.4%), had less frequently sweet drink intakes (71.7% vs. 80.6%) and were more likely to have ≥3 meals per day (68.8% vs. 79.4%). The median DMFdefS was 7 (interquartile range IQ: [2-15]) in HIV+ children and 2 (IQ: [0-7]) in HIV- siblings. The median defs and DMFS scores were respectively 5 and 2 in HIV+ children vs. 2 and 0 in HIV- children. The percentage of children affected with dental caries (%DMFdefS≥1) was significantly higher in HIV+ children (86.0%) than the non-infected ones (64.4%, p-value<0.001). The d- and D- components contributed to 94.8% of the DMFdefS in HIV+ children and to 96.6% in HIV- children. The multivariate analysis showed that HIV infection was significantly associated with a higher probability of presenting dental caries. In children at-risk for dental caries, HIV+ children had a mean DMFdefS significantly higher than HIV- children.

Conclusions: Even if HIV+ children seemed to be less exposed to common risk factors for dental caries, they were more affected. Dental care and prevention for oral health are needed for HIV+ children and have to be included in pediatric multidisciplinary care teams in order to decrease comorbidities.

917 Preclinical Atherosclerosis in Eastern Africa: Results From a Pediatric Ethiopian Cohort

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Background: HIV-infected pediatric patients on antiretroviral therapy (ART) demonstrate an elevated incidence of dyslipidemia, lipodystrophy, and cardiovascular disease risk (CVD). Most studies, however, focus on cohorts from developed countries, with fewer data available for these co-morbidities in sub-Saharan Africa, where the prevalence of HIV-infected youths is much higher.

Methodology: Six- to 18-year-old age- and sex-matched HIV-infected subjects who were ART-naïve (n=45), efavirenz (EFV)-treated (n=90), nevirapine (NVP)-treated (n=76), or ritonavir-boosted lopinavir (LPV/r)-treated (n=19) were recruited from Black Lion Hospital in Addis Ababa, Ethiopia. Pulse wave velocity (PWV) was assessed via applanation tonometry, as a measure of arterial stiffness, and carotid intima-media thickness (cIMT) and brachial artery flow-mediated dilation (FMD) were assessed via non-invasive ultrasound as a measure of subclinical atherosclerosis and endothelial function, respectively. Body mass index, waist-to-hip circumference ratio, and skin-fold thickness were used to characterize body composition. CD4+ cell count, fasting glucose, total-, HDL-, and LDL-cholesterol, triglycerides, and complete blood counts were measured. Results are presented as medians (interquartile range). Kruskal-Wallis non-parametric one-way ANOVA was performed to determine statistical significance across groups.

Results: PWV was elevated in LPV/r-treated subjects compared to EFV- and NVP-treated and ART-naïve subjects [5.2 (4.6-5.9) vs. 4.7 (4.3-5.3), 4.6 (4.2-5.2), and 4.6 (4.1-5.0) m/s, respectively, p=0.016]. No differences in cIMT or FMD were observed across groups. LPV/r-treated subjects also exhibited elevated total- and LDL-cholesterol and total:HDL-cholesterol ratio compared to the other groups. EFV- and NVP-treated subjects exhibited elevated total-, LDL- and HDL-cholesterol, compared to ART-naïve subjects; however, no differences were observed in total:HDL-cholesterol ratio between EFV-treated, NVP-treated, and ART-naïve subjects.

Conclusions: LPV/r-treatment was associated with increased arterial stiffness and dyslipidemia in pediatric HIV-infected subjects in Ethiopia. Given the increased use of LPV/r in developing countries, this raises concern regarding the long-term CVD risk in this vulnerable population.

918 Insulin Resistance in HIV-Infected Youth Is Associated With Decreased Mitochondrial Respiration

Jody K. Takemoto[1], Jiajia Wang[2], Denise L. Jacobson[2], Tracie L. Miller[3], Mitchell E. Geffner[4], Russell B. Van Dyke[5], Daniel E. Libutti[1], Patricia Graham[3], Mariana Gerschenson[1], for the Pediatric HIV/AIDS Cohort Study

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Background: Antiretroviral therapy (ART) has dramatically reduced vertical HIV transmission and prolonged survival of HIV-infected children. However, these advances may lead to progressive long-term metabolic complications including insulin resistance (IR). We hypothesize that HIV and/or ART cause mitochondrial dysfunction, decreasing cellular respiration and thereby increasing oxidative stress and lactate/pyruvate levels, resulting in IR.

Methodology: A subset of children with perinatal HIV enrolled in the Pediatric HIV/AIDS Cohort Study were co-enrolled in a mitochondrial substudy. Fasting venous lactate, glucose, and insulin levels were measured. IR was defined by Homeostasis Model Assessment (HOMA-IR) >4.0. Mitochondrial respiration was measured from peripheral blood mononuclear cells utilizing the Seahorse XF24 analyzer (http://www.seahorsebio.com) in a random sample of 25 with IR (IR+) and 50 without (IR-). Unadjusted differences in mitochondrial respiration between IR+ and IR- were evaluated using the Wilcoxon rank sum test. Correlations between mitochondrial respiration (basal, ATP production, proton leak, maximal, spare, and non-mitochondrial respiration) and metabolic measurements were evaluated by Spearman correlation.

Results: IR+ were similar to IR- in age (median 16.5 v 15.6 yr), males (60% v 50%), Non-Hispanic black (68% v 72%), and current CD4 counts (574 v 686 cells/mm3). IR+ trended toward a lower nadir CD4 (12% v 17%, $p=0.07$) and a higher peak viral load (607K v 185K, $p=0.07$). There were no significant differences in past or current type of ART. Median venous lactate (1.5 v 1.1 mM, $p<0.001$), pyruvate (0.12 v 0.09 mM, $p=0.003$), and glucose (88 v 85 mg/dL, $p=0.007$) were higher in IR+. Furthermore, proton leak (585 v 790 pMoles, $p=0.03$), maximal respiration (1815 v 2499 pMoles, $p=0.025$), and spare respiratory capacity (1162 v 2017 pMoles, $p=0.03$) were significantly lower in the IR+ group. Basal respiration, ATP production, proton leak, maximal respiration, and spare respiratory capacity were negatively associated with HOMA-IR ($p<0.009$), while non-mitochondrial respiration was positively associated with glucose ($p=0.02$).

Conclusions: Insulin resistance is associated with lower mitochondrial respiratory activity in HIV+ youth. These findings provide a possible mechanism for metabolic dysfunction in HIV+ youth.

919 The Effect of Long-Term Zidovudine On Hematological Parameters in the ARROW Randomized Trial

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Background: Both zidovudine (ZDV) and advanced HIV are associated with hematological abnormalities, but the relative contribution of each to toxicity in children initiating ART has not been described.

Methodology: 1206 ART-naïve Ugandan/Zimbabwean children were randomized to standard 3-drug NNRTI+3TC+ABC (no ZDV) vs 4-drug NNRTI+3TC+ABC+ZDV induction, decreasing at 36 weeks to 3-drug NNRTI+3TC+ABC (short-term ZDV) or to 3TC+ABC+ZDV (long-term ZDV). CD4 and hematology/biochemistry were done 12-weekly but results only routinely returned for half the children in a monitoring strategy randomization. Changes in hemoglobin, neutrophils and platelets after ART initiation, and incidence of grade 3/4 toxicity and hematology-related ART substitutions, were compared between randomized arms.

Results: Median follow-up was 4 years; 5%, 21%, and 95% follow-up was spent on ZDV in the no, short- and long-term ZDV arms respectively. Hemoglobin increased significantly on ART in all arms at all time points. However increases were ~0.5 g/dL smaller in long-term ZDV vs no ZDV arms throughout follow-up ($p<0.001$), with mean increases of +2.0 vs +1.5 g/dL respectively at 4 years. Following ZDV discontinuation at 36 weeks in the short-term ZDV arm, hemoglobin rebounded to levels seen in the no ZDV arm, with

no evidence of permanent impairment. Graded toxicity was infrequent; 32 (8%) no, 36 (9%) short-term and 41 (10%) long-term ZDV children had grade 3/4 anemia during follow-up ($p=0.61$), and 15 (4%), 20 (5%), and 23 (6%) grade 4 ($p=0.47$). Despite similar incidence, anemia led to 0 vs 13 vs 14 ART modifications respectively. Neutrophils declined slightly over time in the no ZDV arm, but initiation of ZDV-containing ART was associated with an immediate drop in neutrophils of ~0.6×10^9/L, a deficit which persisted throughout follow-up in the long-term ZDV arm, but was reversed on ZDV discontinuation in the short-term ZDV arm ($p<0.001$). 68 (17%), 105 (26%) and 136 (34%) children respectively ever had grade 3/4 neutropenia ($p<0.001$), and 10 (3%), 27 (7%), and 27 (7%) grade 4 ($p=0.01$). However, neutropenia led to only 0 vs 2 vs 4 ART modifications. In all arms, platelets increased sharply following ART initiation and then modestly declined; if anything declines were greater in the no ZDV arm ($p=0.07$). 19 (5%), 12 (3%) and 22 (5%) children respectively ever had grade 3/4 thrombocytopenia ($p=0.20$).

Conclusions: Incidence of severe anaemia was similar regardless of ZDV use in a randomized comparison, strongly suggesting that its occurrence on ZDV-containing ART predominantly reflects HIV disease. ZDV was associated with severe neutropenia in a minority of children, although this rarely led to ART modification, reflecting uncertainty about the interpretation of low neutrophils in African children.

920 Bone Quality Determination by Ultrasonometry in Young South African HIV-Infected Children

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Background: Skeletal abnormalities, including decreased bone mineral content and density (BMC; BMD) by dual-energy X-ray absorptiometry (DXA) have been described in children and adolescents with HIV-infection. Although DXA is the most common method for characterizing bone, it is not widely available in resource-constrained settings (RCS) where the majority of HIV-infected children reside. Quantitative ultrasonography (QUS) assesses bone quality by measuring the attenuation and speed of an ultrasound wave through bone. It does not require radiation exposure or high-level training, is portable, costs less than DXA to perform, and has a short scan time, making it potentially well-suited for assessing and tracking bone acquisition in RCS. Here, we evaluate the relationship between QUS and DXA in young South African HIV-infected children.

Methodology: Data for this analysis was obtained at outpatient study visits from CHANGES (Childhood HAART Alterations in Normal Growth, Genes, and aGing Evaluation Study), a longitudinal cohort study of perinatally HIV-infected children who initiated ART before age 2 in Johannesburg, South Africa. BMC and BMD of the whole body and lumbar spine were measured by DXA (Hologic Discovery Wi bone densitometer) and analyzed using Apex Version 3.4 software. Speed of sound (SOS) and the broadband ultrasound attenuation (BUA) at the heel/calcaneus were obtained 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: Forty seven children with a mean age of 7.7 ± 1.2 years (age range 6.0 to 9.8 years), including 26 (55.3%) boys and 21 (44.7%) girls were evaluated. The mean weight-for-age z-score (WAZ) was -0.62 ± 1.0 and mean height-for-age z-score (HAZ) was -1.33 ± 1.0. Twenty one (44.7%) of the children were on a LPV/r-based regimen and 26 (55.3%) were on an EFV-based regimen. All children were also on two NRTIs, including 3TC and ABC or d4T, but not TDF. BUA was moderately correlated with whole body BMC (0.50, $p<0.01$) and BMD (0.49, $p<0.01$) as well as lumbar spine BMC (0.50, $p<0.01$) and BMD (0.48, $p<0.01$). SI was also moderately correlated with whole body BMC (0.40, $p<0.01$) and BMD (0.39, $p<0.01$) as well as lumbar spine BMC (0.37, $p<0.01$) and BMD (0.43, $p<0.01$). Independently, SOS did not have significant correlations with whole body or lumbar spine BMC and BMD.

Conclusions: In this sample of young children with HIV receiving ART, QUS BUA and SI correlate significantly with whole body and lumbar spine BMC and BMD. Although additional research is necessary, QUS may prove to be a valuable method to assess bone quality and acquisition in HIV-infected children in RCS.

Session P-U6 Poster Session
Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Response To Early ART Initiation in Infants

922 Routine Antibody Tests Have No Place in Determining HIV Status After Early ART: Evidence From CHER

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Background: HIV-1-infected infants starting early ART may become HIV-antibody seronegative following decay of passively acquired maternal antibody and suppression of viral replication. As ART guidelines recommend immediate ART for all HIV-infected children under 2 years, the frequency of seronegative status following early ART has management implications in young children.

Methodology: The randomised Children with HIV Early Antiretroviral Therapy (CHER) trial compared early limited with deferred ART (ART-Def) in HIV-infected infants &lt12 weeks of age with baseline CD4 ≥25%. HIV infection was diagnosed by HIV DNA PCR confirmed with a RNA viral load >1000 copies/ml. Here we compare early ART until 96 weeks (ART-96W) with ART-Def. Median age at ART start was 23 weeks (IQR 18-32) for ART-Def versus 7 weeks (IQR 7-8) for ART-96W. HIV-1 antibody was measured in stored plasma from 75/125 ART-Def and 109/126 ART-96W children at median age 92 weeks (IQR 90.6 - 93.4) by 3 techniques: (1) 4th generation microparticle enzyme immunoassay HIV antigen/antibody combination; (2) HIV-1/2 qualitative immunochromographic rapid antibody test assessed by an independent, blinded clinician; (3) a sensitive in-house ELISA to quantify anti-gp120 IgG and total IgG.

Results: Children in ART-Def had significantly more antibody than ART-96W in all 3 tests: automated serology (90% versus 54% seropositive, p&lt0.0001), rapid test (88% versus 47%, p&lt0.0001), and quantitative anti-gp120 IgG ELISA (median 6,870 µg/µl (IQR 1,706-53,645) versus 230 (IQR 133-13,129) $p=0.04$). Levels of total IgG were similar in both groups ($p=0.28$) indicating that this effect was specific to HIV responses. While all children had detectable anti-gp120 IgG antibody, 8 (10%) from ART-Def and 49 (46%) from ART-96W were seronegative using automated serology. In ART-Def, there was no difference between the automated and rapid test; however, in ART-96W 9 children with weakly positive automated results had negative rapid tests. In ART-Def, older age at ART initiation was associated with increased anti-gp120 IgG ($p=0.002$). By automated serology, starting ART between 12-24 weeks had a 13.7-fold higher odds of being seropositive by 92 weeks old, compared to starting ART aged 0-12 weeks (95% CI: 3.1 - 60.2, $p=0.001$); all 33 children starting ART >24 weeks of age were seropositive.

Conclusions: Almost half children starting ART within 12 weeks of life and 6% of those starting at 12-24 weeks were seronegative by commercial serology or rapid tests at ~2 years of age. Therefore, routine antibody tests should not be used to confirm HIV status among children already diagnosed and started on ART at <6 months of age. Whether persistence of anti-gp120 IgG represents slow decay or is a response to low levels of HIV replication, requires further study.

923 Different Profiles of HIV in Early Treated HIV-Infected Children Seronegative by ELISA in Cameroon

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Background: Recent data on early treated HIV-infected adults and infants, describing long term virological control after treatment interruption has raised the possibility of a functional HIV cure. We aimed to explore residual HIV using ultra-sensitive virological methods in HIV-infected children receiving early cART in an ongoing project in Cameroon.

Methodology: From 2007 to 2011, 210 HIV-infected infants diagnosed before 7 months of age were included in this study from three urban referral

hospitals in Yaounde and Douala. Among them, 147 infants on cART were serologically tested with one ELISA and two rapid HIV tests at a median age of 19.1months [IQR, 18.2-20.1] and 26 (17.7%) of them were negative. Of the later, whole blood samples were collected from 12 infants and stored at -80°C. HIV level of infection was quantified by measuring total cell associated HIV-DNA in PBMC and plasma HIV-RNA using ultra-sensitive real-time PCRs.

Results: All the 12 children were on cART initiated at a median age of 3.4 months [range, 2.0-7.6] with a median follow up of 47.6 months [range, 21.8-65.1]. They were re-tested serologically at a median age of 50.1 months [range, 26.9-72.7] and 9 of them remained negative. These 9 HIV-seronegative children presented varying profiles of HIV-DNA and HIV-RNA in blood. One child had no replicating

virus (HIV-RNA < 24 copies/ml) and no detectable HIV-DNA. Five children had no replicating virus and various low or high HIV-DNA levels (mean 2.35 log copies/10^6 PBMC; range, 2.22-2.59). The last

three children had replicating virus (HIV-RNA < 100 copies/ml) with one of them presenting very low viral replication with HIV-RNA at 36 copies/ml and HIV-DNA at 1.6 log copies/10^6 PBMC. HIV-1 Western blot profiles varied from only one p24 antibody in the case of none replicating virus to several antibodies to the Gag and Pol peptides in the case of replicating viruses

Conclusions: This exploration shows heterogeneous profiles of HIV reservoir in early treated HIV children on cART and seronegative by ELISA. In this preliminary study, two infants had undetectable or a lower blood HIV reservoir. Further immunological investigations are ongoing to better assess the potentiality of HIV control in these infants.

924 Greater Virologic Control in Infants Initiated On ART Before 6 Months of Age

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Background: The recent report of an HIV-infected infant with viral control post-antiretroviral therapy (ART) interruption brings to light the possibility of "functional cure" for infants initiated on ART close to birth. However, there are limited data on the effects of early ART initiation before 6 months of age on the establishment and persistence of viral reservoirs. Here, we examine viral dynamics post-ART initiation by age at initiation.

Methodology: Viral dynamics by age at ART initiation (<6 months vs. 6-24 months) was evaluated in 3 cohorts at Rahima Moosa Mother and Child Hospital in Johannesburg, South Africa. Children in Cohort 1 were initiated on ritonavir-boosted lopinavir (LPV/r)-based ART <24 months of age and randomized to remain on LPV/r or switch to nevirapine after achieving viral suppression. Children 3-5 years of age at enrollment in Cohort 2 were suppressed on LPV/r and randomized to remain on LPV/r or switch to efavirenz. Cohort 3 included children in routine services starting ART <24 months of age.

Results: Of 323 children in Cohort 1, HIV RNA levels were higher pre-ART in 102 children <6 months at ART start vs. 221 children 6-24 months at ART start (75.6 vs. 58.4% >750,000 copies/mL (cpm); 4.7 vs. 10.7% <100,000 cpm, p=0.02) but time to and likelihood of achieving viral suppression were similar by age at ART start, suggesting faster trajectories of decline in the younger children. Of 195 children who achieved suppression and were randomized in Cohort 1, mean plasma HIV RNA was 64 cpm in 54 children who started ART <6 months vs. 1502 copies/mL if 6-24 months (NS) after a median of 9 months of ART. Children <6 months at ART start were less likely to fail (>1000 cpm) by 52 weeks post-randomization (p=0.02, adjusted for group). The failures were primarily in those switched to nevirapine. In those retained on LPV/r where failure was rare, children <6 months at ART start were less likely to blip >50 cpm by 52 weeks post-randomization (p=0.04, adjusted for group). Of 300 children in Cohort 2, children <6 months at ART start were less likely to blip above 50 cpm than children 6-24 months at ART start (p=0.002). Of 239 children in Cohort 3, children who started ART <6 months were more likely to suppress <1000 cpm by 6 months (54.8%) than those starting 6-12 months (31.4%) or 12-24 months (35.9%) (p=0.03).

Conclusions: Across three separate cohorts, we observed greater virologic control in infants initiating ART <6 months of age. These results are consistent with the notion that early initiation of ART may limit formation of the long-lasting viral reservoir in infants.

925 Early Viral Suppression Improves Neurocognitive Outcomes in HIV-Infected Children

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Background: Children and adolescents with perinatally-acquired HIV infection (PHIV+) are vulnerable to subtle to severe neurocognitive deficits during development. Initiation of antiretroviral therapy (ART) in infancy is associated with improved longevity; however, it is unclear if timing of ART or a specific ART regimen improves neurocognitive outcomes. Early childhood represents a sensitive period of neurodevelopment and we hypothesized that both early virologic control and use of ART regimens with better central nervous system (CNS) penetration are associated with improved neurocognitive outcomes among school-aged PHIV+ children.

Methodology: We analyzed data from PHIV+ children from two US-based prospective cohort studies: PHACS AMP (enrolled from 2007 - 2009) and IMPAACT 219C (enrolled from 2000 - 2006) who completed a neurocognitive assessment (WISC-III or WISC-IV) at 6 years of age or older, and who had ≥1 HIV-1 viral load measurement prior to or within 6 months after ART initiation. Viral suppression was defined as two consecutive viral loads ≤400 copies/mL obtained 1-6 months apart, and age of viral suppression was defined as the age at first viral load ≤400 copies/mL. CNS penetration effectiveness (CPE) scores were calculated for initial ART regimen and a weighted average CPE score was calculated for each time period of interest. Multivariable general linear regression models were used to evaluate associations of viral suppression and CPE scores with full scale IQ (FSIQ), adjusted for demographic and clinical covariates with p-value < 0.1 from univariable analyses.

Results: 396 PHIV+ children were included (mean age at time of WISC evaluation=9.6yrs); 54% were female, 66% Black, 27% Hispanic, and 83% spoke English as the primary language. The percent of children achieving viral suppression increased from 11% by 1 year of age to 41% by age 5. The estimated difference in mean FSIQ (comparing children who were virally suppressed vs. unsuppressed) by each age cutoff was 3.48 at age 1 (p=0.17), 3.43 at age 2 (p=0.10), 2.67 at age 3 (p=0.16), 3.79 at age 4 (p=0.03), and 3.42 at age 5 (p=0.05) after adjusting for age of ART initiation, age at neurocognitive assessment, caregiver education, ethnicity, birth weight and child's primary language. CPE score of initial regimen and weighted average CPE score were not associated with higher FSIQ.

Conclusions: Virologic suppression during infancy or early childhood is associated with improved neurocognitive outcomes in school-aged PHIV+ children. Although the association attained statistical significance only at ages 4 and 5, the effect size was consistent across all age groups, providing support for early initiation of ART. In contrast, CPE scores showed no significant association with improved neurocognitive outcomes.

926 Early Cytomegalovirus Viraemia and Clinical Outcomes of HIV-Infected Children in the Early ART Era

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Background: Cytomegalovirus (CMV) is an important cofactor for HIV disease progression and is associated with poor outcomes in HIV-infected infants not on antiretroviral therapy (ART). In sub-Saharan Africa, 90% of infants acquire CMV post-natally in their first year of life but its effect on HIV infection among infants on ART is unknown. The purpose of this study was to describe the first year clinical outcomes of young infants with CMV/HIV co-infection who receive antiretroviral therapy.

Methodology: This study is based on the prospectively assembled cohort from the Children with Early Antiretroviral Therapy (CHER) trial in which 411 infants with CD4 ≥25% were randomized to immediate or deferred ART and 40 infants with CD4 <25% into a parallel observation group receiving early ART. Early CMV viraemia was determined by Roche COBAS AmpliPrep/COBAS TaqMan CMV PCR (Roche Molecular Diagnostics, Branchburg, New Jersey) using baseline plasma samples. Qualitative and quantitative CMV data was correlated with baseline clinical, immunological and virological parameters and outcomes from the study. Analyses were performed in early and deferred ART strata to determine the confounding effect of early ART on CMV viraemia and outcomes. Outcomes in the first year of life were censored at 40 weeks post enrolment. Immunological failure was defined as a CD4% <25% or <baseline value at the last visit.

Results: Of 451 infants in the trial, CMV PCR results were available for 363 (median age at enrolment, 7.7 (6.7-9.1) weeks); 89 (25%) were CMV PCR positive at enrolment. Of the children with CMV PCR available, 342 (94%) children initiated ART during follow-up (100%, n=267 in the early treatment group and 78%, n=75 in the deferred treatment group). At enrolment CMV viraemia was associated with breastfeeding exposure (p=0.025), lower CD4 percentage (p<0.001) and higher HIV viral load (p=0.005). Among infants receiving early ART, the proportion reaching a clinical endpoint at one year of life was similar between CMV PCR positive and negative infants (5/75 vs. 8/194; p=0.383) but infants with CMV viraemia had more immunologic failure (12% vs 5%, p=0.049). However no such associations were observed in children in the deferred treatment group (p=0.269) and there was no association between CMV viraemia and death in either group (p=0.862).

Conclusions: Our study confirms that early CMV viraemia is strongly associated with breastfeeding exposure and poorer immunological status prior to ART initiation. Early ART appears to ameliorate most effects of concurrent CMV infection.

Session P-U7 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM Exhibit Hall D

Co-Infections and Treatment Responses in Children and Adolescents

927 Risk Factors Associated With TB in Children Receiving ART in a South African Multicenter HIV Cohort

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Background: Tuberculosis (TB) in children is a direct consequence of adult TB and a good marker of current trends in community transmission. We estimated rates of, and risk factors for, incident TB among HIV-infected children and adolescents receiving antiretroviral treatment (ART) in South Africa.

Methodology: Prospective cohort analysis of HIV-infected children ≤18 years old who initiated ART between April 2004 and May 2011 at one of 12 HIV clinics in Gauteng and Mpumalanga provinces. Duration on ART was categorized as 0-5.9 and ≥6 months. We used log-binomial regression with a Poisson distribution to determine predictors of TB risk for children <5 and for those 5-18 years, separately, controlling for, gender and current predictors of TB (e.g. age, duration on ART, viral load and hemoglobin). For children <5 we also controlled for CD4 percent and weight-for-age Z-score over time. For children 15 18 we also controlled for CD4 count and body mass index over time.

Results: During 2,828 person-years of follow-up, 113 TB cases (diagnosis confirmed by sputum microscopy) occurred among 3,329 pediatric ART patients. This corresponded to an overall incidence rate of 4.0 cases/100 person-years (95% CI: 3.3-4.8). The highest incidence rate was observed in the first 6-months on ART (5.9/100 person-years; 95% CI: 4.7-7.4). Log-binomial models for children <5 years and 5-18 years showed all patients had over a 2-fold increase in the risk of TB in the first 6-months on ART compared to ≥6-months (Table). Children <5 years of age with a detectable viral load (≥400 copies/mL) had a 70% increase in the risk of TB compared to those children who achieved viral load suppression (risk ratio (RR): 1.7; 95% CI: 0.8-3.7) and patients with a low hemoglobin (<10 ug/dL) (<5 years - risk ratio (RR): 1.7; 95% CI: 0.6-4.8 and 5-18 years - RR 1.7; 95% CI: 0.8-3.6) were also at increased risk. Amongst children 5-18, those younger in age (5-9.9 vs. ≥10 years-RR 2.4; 95% CI: 1.0-6.0) and patients with low current CD4 count (<100 vs. ≥500 - RR 4.6; 95% CI: 1.5-14.2) were at increased risk of TB.

Conclusions: Our results show that younger age and poor immunologic response to treatment are associated with increased risk of TB. Patients are also at increased risk of TB in the first 6-months after initiation onto ART, potentially a result of immune reconstitution inflammatory syndrome (IRIS). Early ART initiation and intensified TB screening at ART initiation may help improve treatment outcomes in younger HIV-positive children and adolescents.

Table. Incidence rates and risk factors of tuberculosis among children and adolescents (n=3,329)

	TB event / person-years	Rate (per 100 person-years)	Adjusted Model <5 year olds RR (95% CI)	Adjusted Model ≥5-18 year olds RR (95% CI)
Current Viral Load (copies/mL)				
<400	37/1,414.8	2.6 (1.8-3.6)	Reference	Reference
≥400	76/1,413.3	5.4 (4.2-6.7)	1.68 (0.77-3.67)	1.16 (0.50-2.68)
Current CD4 Count (cells/mm^3)				
<100	11/147.8	7.4 (3.7-13.3)	-	4.60 (1.49-14.2)
100-199	11/156.3	7.0 (3.5-12.6)	-	3.22 (1.28-8.05)
200-349	10/265.3	3.8 (1.8-6.9)	-	2.37 (0.91-6.15)
350-500	6/267	2.2 (0.8-4.9)	-	1.49 (0.34-6.56)
≥500	17/891	1.9 (1.1-3.1)	-	Reference
Current CD4 percent				
≥25	28/580	4.8 (3.2-7.0)	Reference	-
<25	30/520.8	5.7 (3.9-8.2)	1.14 (0.57-2.26)	-
Time (months)				
≥6	30/1,431.8	2.1 (1.4-3.0)	Reference	Reference
<6	83/1,396.3	5.9 (4.7-7.4)	2.16 (1.12-4.16)	2.07 (1.15-3.74)
Age (years) for children <5				
1-5	41/894.8	4.6 (3.3-6.2)	Reference	-
<1	17/206	8.3 (4.8-13.2)	1.27 (0.65-2.49)	-
Age (years) for children ≥5				
≥10	21/751.5	2.8 (1.7-4.3)	-	Reference
5-9.9	34/975.8	3.5 (2.4-4.9)	-	2.43 (0.98-5.99)
Gender				
Female	56/1,447.3	3.9 (2.9-5.0)	Reference	Reference
Male	57/1,380.8	4.1 (3.1-5.3)	1.12 (0.65-1.95)	0.93 (0.54-1.61)
Current BMI (kg/m^2)				
≥18.5	11/490.3	2.2 (1.1-4.0)	-	Reference
<18.5	44/1237	3.6 (2.6-4.8)	-	1.42 (0.50-4.03)
Current Weight-for-age Z-score				
Normal	41/881.25	4.7 (3.3-6.3)	Reference	-
Moderate/Severe	17/219.5	7.7 (4.5-12.4)	1.17 (0.5-2.68)	-
Current Hemoglobin (ug/dL)				
≥10.0	74/2,323	3.2 (2.5-4.0)	Reference	Reference
<10.0	39/505	7.7 (5.5-10.6)	1.74 (0.63-4.84)	1.71 (0.81-3.60)

928 Hepatitis B Treatment Response To TDF in 3TC-Experienced Perinatally HIV-Infected Adolescents

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Background: HIV and Hepatitis B (HBV) coinfection is associated with high risk of progression to chronic liver diseases. Loss of the hepatitis B surface (HBsAg) and envelop (HBeAg) antigens are the ultimate goals of treatment. This study aims to determine the incidence rate of seroconversion and kinetics of HBV in perinatally HBV/HIV coinfected adolescents treating with tenofovir (TDF) and lamivudine (3TC).

Methodology: A prospective multicenter cohort study was conducted in 4 HIV clinics in Thailand. The antiretroviral regimen was modified to include both TDF and 3TC. HBV infected status was monitored by HBsAg and HBeAg levels using semiquantitative method based on the ratio of sample relative light units to a control cut-off (S/CO), hepatitis e antibody (anti-HBe) and HBV DNA level. Treatment response of HBV infection and serum alanine aminotransferase (ALT) were captured at 12, 24, and 48 weeks. Hepatic flare was defined as ALT > 5 times of upper limit of normal.

Results: From March-October 2012, 12 perinatally HBV/HIV infected adolescents with median age of 17.6 (range 14.2-21.9) years, and mean body mass index of 19.0 (± 2.4) kg/m2 were enrolled. Their mean CD4 lymphocyte count was 678 (± 183) cells/mm3; 83% had HIV RNA level < 40 copies/mL. At week 12, 24, and 48 follow-up, significant decreases in HBV DNA and HBeAg levels from baseline value were observed. The median HBV DNA reduction from baseline were 3.3 (range 0-8.2) and 7.2 (range 1.2-8.2) log10 copies/mL at week 12 and 24, respectively. At the end of follow-up, HBV DNA level were < 2.0 log10 copies/mL in 77%, and < 20 copies/mL in 33% of cases. Only one case developed HBsAg seroconversion at week 48; however, there was a persistent low-level HBeAg titer and anti-HBe remained negative. No case experienced hepatic flare.

Conclusions: TDF suppressed viral replication in most HBV/HIV co-infected adolescents who had previously been exposed to 3TC, at least half of whom had pre-existing HBV-3TC associated resistance. Hepatic flare was not evidenced in this population. Long term follow-up study on efficacy of HBV combination therapy with TDF/3TC as well as liver outcome among HBV/HIV coinfected adolescents is required.

Characteristics	week 0	week 12	week 24	week 48	P-value[b]
Number of children[a]	12	12	11	9	
Hepatitis B profile					
HBs Ag positive	12/12 (100)	not done	11/11 (100)	8/9 (88)	
HBsAg level (S/CO)	3017 (1619)		2822 (1249)	2364 (1441)	0.546
HBeAg positive	8/9 (88)		10/11 (91)	7/9(77)	
HBeAg level (S/CO)	1108 (684)		1020 (566)	804 (539)	0.014
anti-HBe positive	1/9 (11)		1/11 (9)	1/9 (11)	
HBV DNA level (log_{10}copies/mL)	6.37 (2.71)	3.46 (1.64)	2.89 (1.71)	1.74 (0.56)	0.018
HBV DNA level <2.0 log_{10}copies/mL	2/12 (17)	3/12(36)	4/11(44)	7/9(77)	
HBV DNA level <20 copies/mL	2/12 (17)	2/12 (24)	2/11 (18)	3/9 (33)	
Liver inflammation					
ALT (U/L)	24 (10-99)	41(14-129)	43 (19-102)	26 (15-86)	0.081
ALT >30 U/L	6/12 (50)	9/12 (75)	9/11 (82)	5/9 (45)	

Data in mean (SD), median (range), or proportion (%) as appropriate; S/CO sample relative light units to a control cut-off (S/CO)

[a] decrease due to 1 missed visit at week 24, 1 lost to follow-up at week 48, and 1 did not reached week 48 due to staggered enrollment

[b] one-way repeated measured ANOVA

929 T-Cell Senescence and CMV Positivity and Viremia Status in Perinatally HIV-Infected Children

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Background: We examined longitudinal effects of cytomegalovirus (CMV) co-infection and viremia on CD4 and CD8 T cell subsets in a cohort of treated perinatally HIV infected (PHIV+) children with severe disease.

Methodology: Pediatric AIDS Clinical Trials Group protocol 366 (P366) was an open-label, multicenter 96 week study where PHIV+ children received 2-4 new drugs (Table) depending on their previous antiretroviral therapy (ART). The analysis included 107 P366 enrollees ≥1 year old with available T cell subset data and baseline stored plasma samples. CMV IgG and CMV DNA testing was performed on stored plasma specimens. Linear mixed models assessed associations between baseline CMV status and percentages of 24 CD4 and CD8 T cell phenotypes weeks 0, 12, 20, and 40, adjusting for potential covariates (Table). Interaction terms between CMV status and week were added to the models.

Results: Average participant age was 7 years, 58% were Black Non-Hispanic, 55% males; at entry, 98% were on ART, 37% in CDC category C. Forty-one % were VL responders (Table) at week 16 of the new regimen; 19% partial responders; 26% non-responders. Fourteen % had detectable CMV DNA ("CMV+ viremic"); 49% were IgG positive or had a positive baseline CMV blood or urine test result but no detectable CMV DNA ("CMV+ non-viremic"); 37% were IgG negative and had no recorded CMV+ result ("CMV-negative"). The percentages of four CD8 phenotypes (CD8+CD62L-CD45RA+; CD8+CD62L+CD45RA+; CD8+CD95+CD28-; CD8+CD95-CD28+) were significantly associated with baseline CMV status in longitudinal adjusted models. The trends over time differed by CMV category and/or treatment arm, with significant week*CMV status and/or week*treatment arm interactions. (Table) None of the CD4 phenotype percentages, activated CD8 phenotypes percentages, CD8+CD62L+CD45RA-%, CD8+CD62L-CD45RA-%, CD8+CD95+CD28+%, or CD8+CD95-CD28-% differed by CMV status in multivariate models.

Conclusions: In PHIV+ children with severe disease, changes in percentages of CD8+CD62L+CD45RA+, CD8+CD95+CD28- and CD8+CD95-CD28+ after switching to new multi-drug ART regimen depended on the children's CMV positivity and viremia status and treatment arm; the effect was independent of VL treatment response. Combined, these findings suggest an independent role of CMV co-infection in alterations in CD8 T cell functional recovery following switch to a multi-drug ART regimen in PHIV+ children.

Table 1: Multivariate model estimates for covariates predictive of selected naïve and memory CD8+ T-cell phenotype% over time

	Naïve and memory CD8+ T-cell phenotype											
	CD8+CD62L-CD45RA+			CD8+CD62+CD45RA+			CD8+CD95+CD28-			CD8+CD95-CD28+		
Covariate	Est.	95% CI	p-value	Est.	95% CI	p-value	Est.	95% CI	p-value	Est.	95% CI	p-value
Week	-0.05	(-0.19, 0.09)	0.45	0.30	(0.13, 0.47)	<0.001	-0.20	(-0.41, -0.00)	0.05	0.20	(0.05, 0.36)	0.011
Treatment arm[2]			0.96			0.88			0.93			0.99
1a vs. 3/4	0.28	(-8.73, 9.29)	0.95	4.62	(-5.63, 14.67)	0.39	-0.40	(-11.27, 10.47)	0.94	0.44	(-8.50, 9.39)	0.92
1b vs. 3/4	-1.02	(-10.34, 8.29)	0.83	3.05	(-7.44, 13.55)	0.57	-2.15	(-13.42, 9.12)	0.71	-0.78	(-10.05, 8.50)	0.87
2 vs. 3/4	-1.85	(-8.87, 5.58)	0.66	4.16	(-4.00, 12.33)	0.32	-2.40	(-10.95, 6.15)	0.58	-0.18	(-7.18, 6.83)	0.96
Week by Treatment arm interaction			0.021			<0.001			0.004			<0.001
Week *1a	-0.23	(-0.42, -0.04)	0.017	0.39	(0.16, 0.62)	<0.001	-0.47	(-0.75, -0.19)	0.001	0.47	(0.26, 0.69)	<0.001
Week *1b	-0.18	(-0.37, 0.00)	0.06	0.27	(0.05, 0.50)	0.019	-0.34	(-0.62, -0.07)	0.016	0.39	(0.18, 0.60)	<0.001
Week *2	0.02	(-0.15, 0.18)	0.85	-0.07	(-0.27, 0.13)	0.50	-0.10	(-0.33, 0.14)	0.42	0.16	(-0.02, 0.34)	0.08
CMV status			0.049			0.029			0.038			0.33
CMV+ viremic vs. CMV-	5.51	(-2.36, 13.37)	0.17	-8.79	(-17.69, 0.12)	0.06	12.38	(2.48, 22.28)	0.016	-4.89	(-12.97, 3.19)	0.24
CMV+ non-viremic vs. CMV-	6.71	(1.26, 12.16)	0.018	-7.59	(-13.75, -1.43)	0.018	5.49	(-1.20, 12.19)	0.11	-3.47	(-8.95, 2.00)	0.22
Week by CMV status			0.38			0.025			0.003			0.004
Week by CMV+, viremic	0.18	(-0.07, 0.38)	0.17	-0.23	(-0.50, 0.04)	0.10	0.43	(0.11, 0.76)	0.010	-0.32	(-0.57, -0.07)	0.013
Week by CMV+, non-viremic	0.02	(-0.12, 0.17)	0.75	-0.24	(-0.41, -0.06)	0.008	0.33	(0.13, 0.54)	0.002	-0.25	(-0.40, -0.09)	0.002
CD4% at entry	-0.26	(-0.51, -0.00)	0.05	0.81	(0.53, 1.10)	<0.001	-0.69	(-0.99, -0.38)	<0.001	0.70	(0.44, 0.95)	<0.001

[1]Estimates are adjusted for gender, age group (1-5yrs, 6-12 yrs, >12 yrs), ARV regimen (HAART with NFV, HAART without NFV, no HAART), HIV-1 RNA (log10cp/ml), race/ethnicity (Hispanic, Black, White/other), and viral load response at week 16 (responder [<400 cp/mL by week 12/16], partial-responder [>400 cp/mL but dropped by at least 0.75 log10 cp/mL], non-responder, missing) in addition to covariates listed in table;

[2]Treatment arm 1 was subdivided into 1a and 1b, where subjects were randomized to be switched to either 2 NNRTIs different from current therapy + NVP/NFV combination (Arm 1a) or 2 new NNRTIs + NVP/RTV combination (Arm 1b). Arm 2 patients were switched to 1 new NNRTI + NVP + NFV + RTV. Arms 3 and 4 were switched to 2 new NNRTIs + NFV + RTV.

CI = Confidence Interval;

Session P-U8 Poster Session

Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Outcomes Among Adolescents: Perinatally and Behaviorally Acquired HIV Infection

930 Outcomes of Perinatally HIV-Infected Adolescents On Antiretroviral Therapy in Southern Africa

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Background: With improved pediatric antiretroviral therapy (ART) access, perinatally HIV-infected children are now surviving into late childhood and adolescence in resource-limited settings. There are limited data on the characteristics and outcomes of these children.

Methodology: We included all children with presumed perinatal HIV infection (defined as ART initiation at age <9.5 years without documented non-perinatal acquisition of HIV) and remaining in care beyond 10 years of age at 10 IeDEA-SA sites in 3 countries (Malawi, South Africa, Zimbabwe) from 2000 to 2012. We described characteristics at ART initiation, at entry into the analysis at age 10 years and at the end of follow-up. The probabilities of death, loss to follow-up (LTFU) (no visit for 270 days before database closure) and transfer out between 10 and 13 years of age were determined using the Kaplan-Meier estimator.

Results: Among 2,161 children included, median (interquartile range [IQR]) age at ART initiation was 7.3 (5.8-8.5) years, with many children having advanced clinical or immunologic disease at ART start (84% WHO III/IV Clinical Stage; 70% WHO-defined severe immune suppression) (Table). Most children initiated a regimen of stavudine+lamivudine with either efavirenz (77%) or nevirapine (10%), while 13% initiated other regimens. At age 10 years, after a median (IQR) of 33 (18-50) months on ART, few children had severe disease; only 3% had CD4<200 and 5% weight-for-age z-score <-3, with HIV-RNA <400 copies/ml in 82%. The probabilities (95% confidence interval [CI]) of death, LTFU and transfer out by age 13 years were 0.8% (0.5-1.5); 7.3% (5.9-9.1); and 30.4% (28.0-32.9) respectively. Among the 2,147 surviving children, 97% had CD4 >200 cells/µl and 77% had HIV-RNA <400 copies/ml at the end of follow-up.

Conclusions: Mortality on ART is low during early adolescence in perinatally HIV-infected children who survive to 10 years of age. The majority of those in care are virologically suppressed with CD4 >200 cells/µl. However, nearly one-third of children transfer out of pediatric care during early adolescence, and the outcomes of these children require attention.

Table: Characteristics of children with presumed perinatal HIV infection who survive to at least 10 years of age. Characteristics are desribed at ART initiation, at age 10 years, and at last follow-up.

	At ART initiation	At 10 years of age	At last follow-up visit in patients not deceased
	n=2,161	n=2,161	n=2,147
Female (n/N; %)	1,063/2,161 (49.2%)	As at ART initiation	1,052/2,147 (49.0%)
Median (IQR) age in years	7.3 (5.8 to 8.5)	All age 10 years old	11.6 (10.7 to 13.1)
WHO Stage III/IV disease (n/N; %)	1,380/1,649 (83.7%)	Not measured	Not measured
Median (IQR) CD4 count (cells/µl)	292 (137 to 490)	744 (526 to 1,004)	764 (552 to 1,012)
CD4 <200 cells/µl (n/N; %)	555/1,594 (35%)	62/1,946 (3.2%)	45/1,878 (2.4%)
Median (IQR) CD4 percent	11.0 (6.3 to 15.4)	Not measured as >5years old	Not measured as >5years old
Median (IQR) weight-for-age z-score	-1.55 (-2.45 to -0.82)	-1.22 (-1.87 to -0.52)	Not measured as >10 years old
Weight-for-age z-score <-3 (n/N; %)	228/1,574 (14.5%)	91/1,779 (5.1%)	Not measured as >10 years old
Median (IQR) BMI-for-age z-score	-0.34 (-1.12 to 0.41)	-0.24 (-0.84 to 0.34)	-0.35 (-1.01 to 0.32)
BMI-for-age z-score <-3 (n; %)	49/1,314 (3.7%)	12/1,534 (0.8%)	24/1,506 (1.6%)
HIV-RNA >100,000 copies/ml*	573/1,208 (47.4%)	N/A	N/A
HIV-RNA <400 copies/ml*	N/A	1,091/1,329 (82.1%)	987/1,283 (76.9%)

*Only reported for children from sites with routine HIV-RNA monitoring

931 Greater Early CD4 Responses To cART Initiation Not Maintained for Non-Perinatal Youth

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Background: Non-perinatally HIV (nPHIV)-infected youth are more likely to have delayed initiation of combination antiretroviral therapy (cART) and have higher nonadherence to cART than adults. Youth have residual thymic tissue and potentially greater capacity for immune reconstitution than adults. We compared CD4 responses to cART between nPHIV-infected youth (12-24 years-old) and adults (≥25-44 years-old).

Methodology: Retrospective analysis of nPHIV-infected cART-naïve individuals 12-44 years-old, who initiated their first cART between 2008 and 2011 at clinical sites in the HIV Research Network. Age was limited to <45 years to avoid the impact of co-morbidities with increasing age. A generalized linear mixed model assessed the association between the repeated outcomes of CD4 gain≥100 cells/mm3 at each visit after cART initiation and age category (12-24, 25-34, 35-44 years). The model accounted for random variation within each participant and between sites, and adjusted for gender, race/ethnicity, HIV acquisition risk, baseline CD4 and log10HIV-1 RNA, virologic suppression (<2.6 log), and cART duration.

Results: Of 3,326 individuals (523 youth, 2803 adults) included, a greater proportion of youth vs. adults were male (83% vs. 74%, p<0.001), had MSM HIV acquisition (72% vs. 50%, p<0.001), and baseline CD4 200-349 cells/mm^3 (40% vs. 31%, p<0.001). At 24 weeks after cART initiation, 45% vs. 39% (p=0.04) of youth vs. adults attained CD4 gain≥100 cells/mm^3; subsequently, the proportion fell below that of adults. Virologic suppression rates for youth vs. adults were 74% vs. 73% (24-weeks) and 73% vs. 77% (48-weeks), p=0.3 (both). When adjusting for gender and race/ethnicity alone the adjusted odds ratio (AOR) of CD4 gain>=100 cells/mm^3 was (1.2 (95% CI 0.93-1.6) and 1.3 (95% CI 1.0-1.6) for those 12-24 and 25-34 vs. 35-44 years; however, this effect was non-significant after adjusting for other potential confounders (See table).

Multivariable Regression of Factors Associated with CD4 gain≥100 cells/mm3

Predictor	AOR (95% CI)[a]
Age (years)	
35-44	1.0(Ref)
12-24	0.85 (0.6-1.2)
25-34	1.1 (0.88-1.4)
Time (weeks) since cART initiation	
0-<14	1.0 (Ref)
14-<28	**1.5 (1.3-1.8)**
28-<42	**2.5 (2.0-3.0)**
42-<56	**4.2 (3.4-5.2)**
≥56	**5.6 (3.3-6.3)**
Baseline CD4 (cells/mm^3)	
≥500	1.0 (Ref)
350-499	1.2 (0.8-1.7)
200-349	**1.9 (1.3-2.7)**
0-199	0.94 (0.64-1.4)
Baseline log10 HIV RNA (increasing by 1 $\log_{10}$)	**2.0 (1.8-2.3)**
Virologic suppression (<2.6 log10 HIV-1 RNA copies/ml)	
No	1.0 (Ref)
Yes	**5.9 (4.8-7.2)**

[a]Model also included race/ethnicity, HIV acquisition risk, and ART duration

Conclusions: With virologic suppression, youth achieved CD4 gains ≥100 cells/mm3 earlier than adults, however, this trajectory was not sustained. CART initiation for youth should not be delayed with the expectation that residual capacity for immune reconstitution will result in greater CD4 responses. Maintaining virologic suppression is the most critical factor to enhancing CD4 outcomes, especially for youth who traditionally have higher nonadherence rates.

932 Parental Absence From Clinic Predicts Virologic Failure in Adolescents in Botswana

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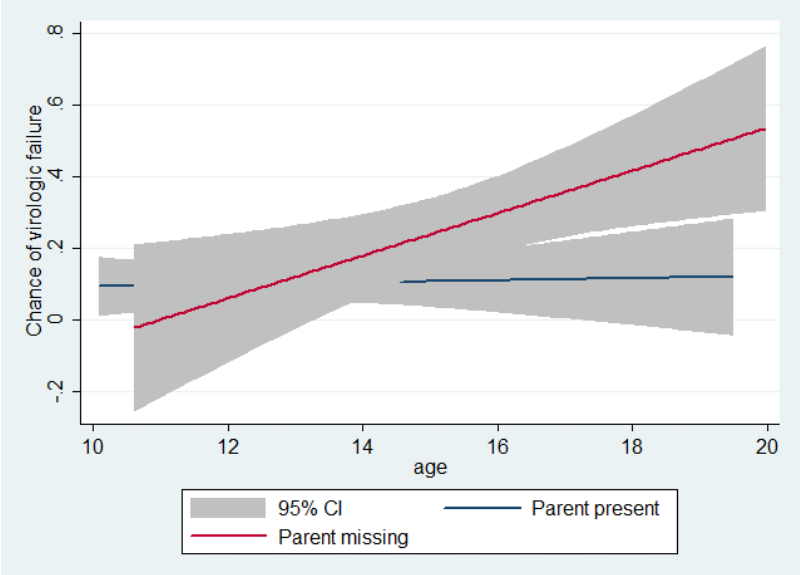
Background: HIV-infected adolescents have higher rates of non-adherence and virologic failure than younger children and adults. Adolescents may attend clinic with or without an adult caregiver (parent). We hypothesized that routine clinic attendance without a parent would increase the risk of treatment failure, particularly in younger adolescents.

Methodology: We conducted a prospective cohort study of HIV infected adolescents (age 10-19) on ART at the Botswana-Baylor Children's Clinical Centre of Excellence in Gaborone, Botswana. We calculated the relative risk of virologic failure (VL≥400cpm) between those with/without a parent present at the 3 month and 6 month study visits. We evaluated for confounding by sex, orphan status (death of either parent), and time on treatment using multivariable logistic regression. The likelihood of failure with increasing age was calculated using linear regression for those with and without a parent present at 3 months. We tested for interaction between age and parent presence using linear regression.

Results: We enrolled 298 adolescents, median age 13.3 years (IQR 11.8-15.6), 52% female, median time on treatment 7.5 years (IQR 5.4-8.8). Detectable viral load was present in 35 adolescents (12%) at month 3 and 15(9%) adolescents at month 6. Absence of a caregiver conferred a relative risk of 2.5 (95% CI 1.4-4.6) of failure at month 3 and 3.4 (95% CI 1.3-9.2) at month 6. There was no confounding. For each year of age, the risk of failure increased [6% per year (95% CI: 2-10%)] among those without a parent present, but not for those with a parent present [0.3% per year (95% CI: -0.8%-0.8%)]. The p-value for the interaction between age and parent presence was <0.001(see Figure).



Conclusions: Absence of a parent conferred a higher risk of virologic failure. Older adolescents without a parent present in clinic were at highest risk. Interventions to identify potentially supportive caregivers and strengthen the adolescent/parent dyad might lower the adolescents' risk of treatment failure. Particular attention should be paid to older adolescents who attend clinic alone.

933LB ART De-Intensification To ATVr Monotherapy in Adolescents Sustains CD4 and Activation Responses

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Background: Adolescents and young adults infected with HIV face a lifetime of antiretroviral therapy (ART). Toxicities to antiretroviral therapy persist, including negative effects on bone renal function, and lipids; thus, limiting ARV exposure may still be of benefit. Assessing the impact of such interventions requires an understanding of their influence on viral suppression and T cell reconstitution and immune activation.

Methodology: 75 subjects, ages 18-24, with CD4 T cells > 350 were started on FTC/TDF/ATVr as part of a randomized, unblended trial of therapy de-intensification. Subjects who maintained an HIV viral load (VL) < 100 copies from weeks 24 through 48 were de-intensified to ATVr monotherapy at week 52 and to week 152. Subjects failed de-intensification for a confirmed VL> 400 copies or confirmed CD4 drop of > 30% from the average of the two peak values. Markers of T lymphocyte differentiation/activation were analyzed by multi-parameter LSR II flow cytometry to define naïve, central memory (CM), and effector memory (EM) CD45RA and CD45RO subpopulations. Slopes of changes in T cell subsets and T cell activation from weeks 48 to 152 were estimated by a mixed effects model using a t-test to test whether mean slopes equaled zero.

Results: 49 of 75 subjects met criteria at week 48 of ART for de-intensification. 25 of 49 (51%) remained suppressed on monotherapy to week 152. Total CD4 gains during ART persisted during de-intensification with ongoing significant increases in naïve and CM (p=0.0167 and 0.0186, respectively) and a decrease in EMRA (p=0.0007) subsets from weeks 48 to 152. No significant changes occurred during monotherapy in any CD8 subpopulations. The significant increases in CD28 expression and decreases in CD38 and HLADR expression on CD8 subpopulations during ART were maintained during monotherapy without any significant increases to from week 48 through week 152. In 19 subjects failing de-intensification due to rebound virus, none demonstrated ATV resistance. Adherence was similar in those failing monotherapy up to the point of failure compared to those maintaining suppression.

Conclusions: In subjects treated with ART with CD4> 350, de-intensification to monotherapy with ATVr following 48 weeks of ART is effective in maintaining naïve and CM CD4 T cell reconstitution. No ATV resistance was noted in subjects with confirmed virologic failure. No increases in immune activation were found in those maintaining viral suppression. This strategy merits further investigation to determine its appropriateness selected populations.

934 Factors Associated With Successful Retention Among Non-Perinatally HIV-Infected Youth

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Background: The incidence of HIV infection continues to increase among youth infected through risk behaviors, who often face individual and structural barriers to retention in care. Retention is critical for HIV treatment success, and is associated with positive clinical outcomes and a decrease in HIV transmission risk behaviors. We evaluated the clinical and demographic characteristics of non-perinatally HIV (nPHIV)-infected youth associated with retention one year after initiating care.

Methodology: The study was a retrospective analysis of treatment-naïve, nPHIV-infected youth (ages 12-24 years) presenting for care at 16 U.S. HIV Clinical Sites within the HIV Research Network (HIVRN) between 2002 and 2008. Eligible patients were included if they had at least one CD4 value and an outpatient visit in the first four months after initiating care. The primary outcome, retention, was defined by the HRSA In+Care Campaign measure of having one medical visit during each of the three successive 4-month periods in the first year. Multivariate logistic regression was used to determine associations with retention and patient factors (age, gender, race/ethnicity, HIV transmission risk, insurance, antiretroviral therapy use (ART) use), adjusting for clinic site.

Results: Of 1,160 nPHIV-infected youth, 74% were male, 61% were Black, 58% had MSM-related HIV acquisition, and 45% were retained in care during their first year of care. Retention in the first year of care was independently associated with use of ART (adjusted odds ratio 3.47, 95% confidence interval 2.57-4.67), Hispanic ethnicity (1.66, 1.08-2.56), MSM-related HIV transmission (1.59, 1.07-2.36), and receiving care at a pediatric site (5.37, 3.20-9.01). Injection drug use transmission risk (vs. heterosexual risk) was associated with poor retention in care (0.43, 0.19-0.99).

Conclusions: The high proportion of newly enrolled nPHIV-infected youth that were not retained in care within one year after initiating care is alarming. Our study indicates specific subgroups that are at risk of not being retained in care and highlights factors that may be associated with improved retention. These findings may inform programs to optimize retention of nPHIV-infected youth.

Multivariate logistic regression of factors associated with retention in Year 1

Variable	Adjusted Odds Ratio (AOR) 95% CI
Race/Ethnicity	
Non-Hispanic White	1.00(ref)
Non-Hispanic Black	1.28(0.88-1.85)
Hispanic	**1.66(1.08-2.56)**
Other	0.81(0.40-1.63)
Risk Group	
HET	1.00(ref)
MSM	**1.59(1.07-2.36)**
IDU	**0.43(0.19-0.99)**
cART initiated in 1st year	
Yes	1.00(ref)
No	**3.47(2.57-4.67)**
Clinic site	
Adult	1.00(ref)
Pediatric	**5.37(3.20-9.01)**

Adjusted for age, gender, race/ethnicity, HIV acquisition risk group, initial insurance, initial CD4 count, antiretroviral therapy use within the first year, and clinical site of care (adult vs. pediatric); bolded values indicate significance; cART=combination antiretroviral therapy

Session P-V1 Poster Session
Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Pre-Clinical Studies of Microbicides

935 PCR as a Virological Endpoint for Testing Microbicide Efficacy in the Colorectal Explant Model

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Background: The *ex vivo* mucosal explant model is used to test the efficacy of microbicides that have the potential for preventing HIV-1 transmission. In the colorectal model, biopsies are challenged *ex vivo* with HIV-1 after study participants are exposed to microbicides *in vivo*. Product efficacy is assessed by the extent of HIV-1 p24 suppression in supernatant fluids sampled up to Day 14 after HIV-1 challenge. The purpose of this study was to determine if measurement of HIV-1 nucleic acids by real-time PCR and HIV-1 integration by *Alu-gag* PCR could be used as alternative endpoints in explant studies.

Methodology: Twenty rectal biopsies each, from five HIV-1-negative individuals, were placed in culture medium and challenged with 1 x 10^5 virions/mL of $HIV\text{-}1_{BaL}$ for two hours at 37°C. Biopsies were then washed and returned to the tissue culture incubator. Supernatant fluids were collected on days 1, 2, 4, 6, 11 and 14 after infection and viral RNA was extracted (QIAamp Viral RNA Mini kit, Qiagen, Valencia, CA). Individual biopsies were harvested at the same time points and viral nucleic acids were extracted using the AllPrep DNA/RNA mini kit (Qiagen, Valencia, CA). HIV-1 RNA levels were measured by two different real-time PCR assays and a laboratory-developed nested PCR protocol. HIV-1 provirus was measured by real-time PCR assays targeting different regions of the HIV-1 genome as well as nested PCR. *Alu-gag* PCR followed by real-time PCR of the HIV-1 *gag* region was used to assess viral integration.

Results: Real-time PCR assays detecting HIV-1 DNA and RNA performed similarly provided there were no mismatches between the sequences of the infecting virus and sequences of the assay primers and probes. Viral RNA in supernatant fluids and biopsies could be detected at an earlier time point (Day 4) than HIV-1 provirus (Day 6). A 15 cycle nested PCR step prior to real-time PCR increased assay sensitivity of both HIV-1 RNA and proviral assays while maintaining levels that fell within standard curves. HIV-1 integration using *Alu-gag* PCR was measurable by day 11 and 14 after infection.

Conclusions: Real-time PCR is a sensitive and accurate end point for assessing levels of HIV-1 infection in the *ex vivo* mucosal explant model. RNA assays are more sensitive than DNA assays all of which coincide with the time course of p24 accumulation in supernatant fluids. Integrated virus is detectable at later time points than viral RNA and DNA in biopsies but is measurable by day 6 after infection in individual biopsies. While HIV-1 viral nucleic acids are detected several days prior to p24, the main advantage of PCR is the smaller sampling size which allows for replicate measurements and thus greater accuracy in detection.

936 Irreversible Inactivation and Breakdown of HIV1 With Env-gp120 Targeting Peptide Triazole Thiols

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Background: Entry of HIV-1 into host cells remains a compelling target for developing agents to prevent infection. This step is mediated by a sequence of interactions of a trimeric gp120/gp41 virus envelope (Env) protein complex with host cells. Peptide triazoles, a class of entry inhibitors have shown to bind to gp120 with close to nanomolar affinity, to suppress protein ligand interactions of gp120 with CD4 and co-receptor binding sites, and to inhibit cell infection by a broad range of virus subtypes. We found that sulfhydryl-containing peptide triazoles (PT-SH), irreversibly disrupts cell-free virions, leading to virus core release. We seek to understand the mechanism of this cell-free virolysis. We hypothesize that the PT-SH hijacks the viral fusion mechanism prior to cell fusion and leads to transient pore formation resulting in irreversible virolysis.

Methodology: The peptide triazoles (PTs) were synthesized using solid phase Fmoc chemistry with click conjugation. The PTs included KR13 (PT-SH); KR13b (KR13 with the thiol blocked); KR13s (containing a scrambled KR13 sequence), and the parent PT, HNG156, with no free thiol. Infection inhibition by PTs were compared using a single-round infection assay using lab synthesized pseudoviruses. Release of Env gp120 and nucleocapsid protein p24 from the PT treated virions were tested by western blot and ELISA respectively. The fixed residual virion was tested for gp41 recognition by direct ELISA using antibodies 2F5 and 4E10 and morphological analysis using transmission electron microscopy. To compare the relationship of KR13 induced cell-free virolysis and virus-cell entry, we examined the effect of T20 on the inhibition of KR13 induced virolysis.

Results: The PTs with active pharmacophore (KR13, HNG156 and KR13b) all inhibit viral infection and induce gp120 shedding; uniquely only KR13 induced release of the core protein p24. Viral inactivation and gp120 shedding had a similar time-dependence, while p24 release lagged temporally. The resulting virions lacked an organized capsid and the gp41 on the virions were antigenically active against neutralizing antibodies, 2F5 and 4E10. Viral lysis was completely inhibited by T20, which blocks formation of the gp41 6-helix bundle during membrane fusion.

Conclusions: Our data are consistent with a model in which PT-SH triggers physiologic structural changes in the HIV-1 Env including the 6 helix bundle formation that is typically associated with viral fusion and entry. The potency and specific activity of this novel compound and its ability to inactivate virions prior to target cell engagement suggest that KR13 could be highly effective as a microbicide in HIV prevention and transmission as well as a probe to understand biochemical signals required for virus-cell fusion

937 Labyrinthopeptin A1 Demonstrates Potent and Dual Anti-HSV and Anti-HIV Activity

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Background: It has been shown that genital lesions and altered innate mucosal immunity caused by HSV-2 are important cofactors to increase the rate of HIV transmission and infection. Therefore, a product that inhibits HIV and HSV would have potential benefits in the prophylaxis against these sexually transmitted viruses. Lantibiotics are peptides that contain the noncanonical amino acid lanthionine. The labyrinthopeptin A1 (LabyA1) is a prototype peptide of a novel class of carbacyclic lantibiotics. Here, we extensively evaluated LabyA1 for its broad-spectrum activity against HIV and HSV and its microbicidal application.

Methodology: Replication of HIV-1, HIV-2 and drug (such as tenofovir, maraviroc, raltegravir, saquinavir)-resistant viruses were measured in CD4+ T cell lines and in peripheral blood mononuclear cells (PBMCs) by the colorimetric MTS method and p24/p27 ELISAs. LabyA1 was also tested against HSV-1, HSV-2 strains, isolates and HSV-resistant viruses (such as acyclovir) in different cell types. It was tested alone and in combination with various other classes of anti-HIV/HSV drugs. EC50 values and potential synergy levels were calculated using CalcuSyn software based on the median effect principle. Potential cellular side-effects, cytokine induction, toxicity and growth inhibitions were measured by flow cytometry and multiplex immunoassays.

Results: LabyA1 exhibited a consistent and broad anti-HIV activity (EC50: 0.70 - 3.3 µM) and anti-HSV activity (EC50: 0.29 - 2.8 µM) in cell cultures. LabyA1 also inhibited viral cell-cell transmission between persistently HIV-infected T cells and uninfected CD4+ T cells (EC50: 2.5 µM) and inhibited the transmission of HIV captured by DC-SIGN+-cells to uninfected CD4+ T cells (EC50: 4.1 µM). In depth studies revealed that LabyA1 behaves as a novel type of viral entry inhibitor. LabyA1 also demonstrated additive to synergistic effects in its anti-HIV-1 and anti-HSV-2 activity with anti(retro)viral drugs in dual combinations such as tenofovir, acyclovir, saquinavir, raltegravir and enfuvirtide. LabyA1 was equally active against all drug-resistant HIV and HSV strains compared to wild-type viruses. It also did not induce any inflammatory cytokines/chemokines in PBMC and vaginal epithelial cells, it did not induce cellular activation markers and did not affect the growth of more than 10 different vaginal Lactobacilli populations that were evaluated.

Conclusions: LabyA1 has profound antiviral activity against HIV and HSV. Based on the lack of toxicity on the vaginal Lactobacillus strains and its synergistic/additive profile in combination with all approved anti(retro)virals, it deserves further attention as a potential microbicide candidate in the prevention of sexually transmitted (HIV/HSV) diseases.

938 GSK1265744 Demonstrates Robust In Vitro Activity Against Various Clades of HIV-1

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Background: GSK1265744 (744) is a potent integrase strand-transfer inhibitor formulated as a long acting (LA) injection; 744LA is being tested preclinically as pre-exposure prophylaxis (PrEP) in the rhesus macaque/SHIV162P3 model. To confirm the promise of 744LA as PrEP we analyzed the susceptibility of recombinant viruses containing patient-derived HIV-1 integrase from various recently acquired HIV-1 clades to 744 *in vitro.*

Methodology: We tested the susceptibility of 20 recombinant viruses with patient-derived integrase from various clades (A1, AE, B, C and D) to GSK744. The integrase genes were amplified and recombined into an HXB2-derived proviral DNA clone, and pseudotyped viral stocks were generated by cotransfecting these proviral DNAs and pCI-VSV-G into HEK293T cells. We employed a single-cycle infectivity assay to determine the relative 50% and 90% inhibitory concentrations (IC_{50} and IC_{90}) of 744 against our pseudovirus panel.

Results: Each virus showed a 744 IC_{50} and IC_{90} comparable to the wild-type control, as measured by fold change (FC) versus wild-type (Table 1), with an overall median IC_{50} FC of 0.88 (range = 0.12-1.38). Two viruses with integrase resistance mutations to raltegravir were also tested: one with G140S and Q148H amino acid changes, and the other with mutations E92Q and N155H. These viruses had significant resistance to raltegravir in this assay (IC_{50} FC of 5308 and 441, respectively), but only modest increases in IC_{50} to 744 (FC of 11 and 4).

Conclusions: GSK1265744 exhibited broad in vitro activity against integrase from multiple clades of HIV-1 in newly-infected patients. The data support the potential for 744LA as a next-generation PrEP agent.

Clade	ID	IC50 F.C.	stdev	IC90 F.C.	stdev
A1	p191084	1.38	0.13	0.99	0.21
	p9004SDM	0.90	0.67	0.78	0.12
	R462F	0.12	0.10	0.23	0.27
	R880F	0.62	0.54	0.62	0.24
AE	AA081a	0.79	0.29	0.77	0.05
	AA114a	0.85	0.21	1.11	0.11
	AA116a	0.94	0.44	0.61	0.15
	AA117b	0.95	0.22	0.88	0.30
	AA118a	0.78	0.10	1.05	0.14
	AA120b	1.17	0.18	0.94	0.42
B	610 1-1	1.07	0.03	1.15	0.11
	610 10-1	1.35	0.07	1.07	0.10
	610 21-1	0.70	0.21	0.81	0.19
	610 30-1	0.94	0.51	0.90	0.50
	610 32-1	0.67	0.38	0.70	0.41
C	ZM246F	0.78	0.11	0.99	0.07
	ZM249M	0.91	0.12	1.32	0.10
D	p190049	0.83	0.10	0.60	0.14
	p191859	1.17	0.03	0.73	0.10
	SC191727	0.52	0.40	0.57	0.21

Session P-V2 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Animal Models of Clinical Studies and PrEP

939 Does Tenofovir Gel Alter HIV Disease Progression in CAPRISA 004 Trial Seroconvertors?

Nigel J. Garrett[1], Lise Werner[1], Nivashnee Naicker[1], Thabile Mthembu[1], Vivek Naranbhai[1], Sengeziwe Sibeko[1], Natasha Samsunder[1], Carolyn Williamson[2], Quarraisha Abdool Karim[1, 3], Salim Abdool Karim[1, 3]

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Background: While topical and oral antiretroviral pre-exposure prophylaxis (PrEP) prevent HIV acquisition, it is not known if they also alter HIV disease progression in individuals acquiring HIV. This study assesses whether tenofovir (TFV) gel impacted disease progression among women who acquired HIV during the CAPRISA 004 microbicide trial.

Methodology: CAPRISA 004 trial seroconvertors were followed until antiretroviral therapy (ART) initiation. Disease progression was assessed by viral load (VL) and CD4 counts. Since a CD4 count of 350 cells/µl is the threshold for ART initiating, time to this event was used as principal measure for disease progression. Linear mixed models were fitted to all available CD4 count and VL measurements in the first 2 years of infection. Participants reaching the CD4 count threshold were compared by log rank test.

Results: Eighty-three women, median age 22 years (IQR 21-25), who acquired HIV infection during CAPRISA 004 (32 assigned to TFV gel) contributed 296 women years of ART naïve follow up. Median VL at median 2 weeks post infection was 4.74 (IQR 3.97-5.37) and 4.45 (IQR 3.56-5.17) log copies/ml in women from the TFV and placebo arms, p=0.189. Corresponding 12 months post infection median VLs were 4.24 (IQR 3.74-4.77) and 3.70 (IQR 2.60-4.66) log copies/ml, p=0.016. After adjusting for age, sexual behaviour, contraceptive use and presence of sexually transmitted infections in the first 3 months post infection, the overall mean VL was 4.07 (SE=0.48) and 3.58 (SE=0.47) log copies/ml in women assigned to TFV and placebo gel, p=0.015. Corresponding mean CD4 counts were 571 (SE=119.44) and 620 cells/µl (SE=115.59), p=0.326.

Seven placebo arm (15.6%) and one TFV arm (3.3%) women had VLs <400 copies/ml at 1 year post infection, p=0.134. No antiretroviral drugs were detected in their plasma. HLA haplotypes B57/B5801 were present in 13 women (6 TFV, 7 placebo). Adjusting for these haplotypes, mean VL for TFV and placebo were 4.49 log copies/ml (SE=0.20) and 3.97 (SE=0.19), p=0.011. Among women assigned to TFV gel, the mean VLs were 4.53 (SE=0.27) and 4.54 (SE=0.30) log copies/ml in women with detectable versus undetectable TFV levels in the genital tract, p=0.966. A total of 32 (38.6%) women reached a CD4 count <350 cells/µl at median 9.4 months post infection, 13 (40.6%) from the TFV and 19 (37.3%) from the placebo arms, p=0.786.

Conclusions: TFV gel had no impact on post infection CD4 counts and did not accelerate disease progression among women who acquired HIV in the CAPRISA 004 trial. The difference in HIV VL remains to be fully explained although a large proportion of placebo arm women had very low VL at 1 year post infection. TFV gel use as PrEP does not appear to adversely affect disease progression in women acquiring HIV.

940 Efficacy of Vaginal Gel Containing Tenofovir and Emtricitabine Against Rectal SHIV Transmission

Charles W. Dobard[1], Natalia Makarova[1], Rolieria West[1], Andrew Taylor[1], Chuong Dinh[1], Amy Martin[1], James Mitchell[1], Debra Hanson[2], Chou-Pong Pau[1], Walid Heneine[1]
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Background: Vaginal gels containing tenofovir (TFV) and Emtricitabine (FTC) dose vaginal tissues with high concentrations of drugs and fully protect macaques from vaginal SHIV infection. These vaginal gels also result in drug distribution to the rectum, raising the possibility of bi-compartmental protection. Here, we used pigtail macaques to study the kinetics of rectal drug exposures following vaginal dosing with TFV/FTC gel and assess efficacy against rectal SHIV infection.

Methodology: Six pigtail macaques were administered hydroxyethyl cellulose gel (3 mL) containing 5% FTC and 1% TFV vaginally once-weekly for 3 weeks. Kinetics of rectal drug distribution were determined by measuring drug levels in rectal secretions at 0.5, 2, and 6h. To evaluate efficacy, macaques were challenged rectally with low-dose $SHIV_{162p3}$ 30 minutes after intravaginal dosing with either HEC placebo (n=6) or 5% FTC/1% TFV (n=6) gel. Animals were challenged twice-weekly for up to 8 weeks. Infection was monitored by serology and plasma virus load by using RT-PCR.

Results: The median $AUC_{0\text{-}6h}$ for FTC and TFV in rectal secretions following vaginal gel dosing was 330 ug*hr/ml (range: 210 - 700) and 113 ug*hr/ml (range: 7.6 - 270), respectively. Median FTC and TFV concentrations in rectal secretions at 0.5, 2, and 6h were 0.54 and .047, 31.9 and 14.3, and 41.1 and 18.6 ug/ml, respectively. All macaques receiving vaginal placebo gel became infected after a median of 3.5 challenges. All 6 macaques administered vaginal FTC/TFV gel were infected after a median of 10 rectal challenges. The infection probability was not significantly different between control (0.18 [95% CL 0.07, 0.35]) and treated animals (0.12 [95% CL 0.03, 0.21]) (Fisher's exact p=0.53).

Conclusions: Both FTC and TFV rapidly distributed to rectal tissues following vaginal gel dosing at concentrations 2-3 logs lower than those in vaginal tissues. These rectal drug levels were not sufficient to maintain the high efficacy observed vaginally. Further studies are warranted to determine whether improved vaginal gel formulations or drug combinations can be utilized to increase rectal drug exposures and efficacy.

941LB GSK1265744 Long-Acting Protects Macaques Against Repeated High-Dose Intravaginal Challenges

Chasity D. Andrews[1], William R. Spreen[2], Yun Lan Yueh[2], Agegnehu Gettie[1], Kasi Russell-Lodrigue[3], Hiroshi Mohri[1], Cecilia Cheng-Mayer[1], Zhi Hong[2], David D. Ho[1], Martin Markowitz[1]
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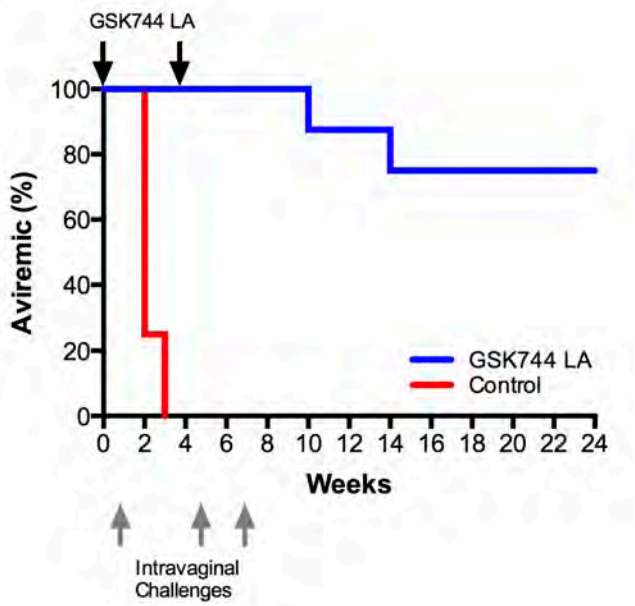
Background: GSK1265744 (GSK744) long-acting (LA) is a strand-transfer inhibitor of HIV/SIV integrase (InSTI) formulated as a 200 mg/mL injectable nanoparticle suspension. GSK744 LA is an effective pre-exposure prophylaxis (PrEP) agent against repeated low-dose intrarectal SHIV exposures in male rhesus macaques. This study was performed to evaluate the effectiveness of GSK744 LA as PrEP against high-dose intravaginal SHIV challenges.

Methodology: Twelve female rhesus macaques were injected intramuscularly (IM) with 30 mg Depo Provera on weeks -3 and 2 to synchronize the menstrual cycle and thin the cervicovaginal epithelium. Eight macaques were injected IM with 50 mg/kg GSK744 LA on weeks 0 and 4, and 4 macaques remained untreated as controls. All 12 macaques were challenged intravaginally with high dose SHIV162P3 (300 $TCID_{50}$) on week 1. GSK744 LA-treated macaques were further challenged with the same dose of virus at weeks 5 and 7. Infection status was monitored weekly by quantifying viral RNA (vRNA) in plasma. Plasma GSK744 concentrations were measured weekly by HPLC-MS/MS.

Results: All 4 control macaques became infected after a single high-dose challenge. Plasma vRNA was detected in control macaques 1 to 2 weeks after the first challenge (see figure). Of the 8 GSK744 LA-treated macaques, six remained aviremic through week 24 (p=0.0003, log-rank test). In the two GSK744 LA-treated macaques that became infected, plasma vRNA was detected 3 and 7 weeks after the last challenge. Consensus sequencing of the integrase-coding region showed breakthrough infections were initiated with wild-type virus, and no drug resistant mutation was identified. Drug concentrations at the time of vRNA detection were 0.15 or 0.37 µg/mL GSK744, respectively. Further investigation of the protective mechanism versus route of infection and virus titers may be warranted. In the aviremic macaques, GSK744 plasma levels fell below 1X protein-adjusted IC_{90} between weeks 9 and 16, suggesting late viral breakthrough is unlikely.



Conclusions: Using a stringent high-dose intravaginal SHIV challenge model where all control macaques became infected after one challenge, GSK744 LA administration protected 6 of 8 female macaques against three challenges. These results support further clinical development of GSK744 LA as PrEP in women at high risk for HIV-1 infection.

942 SHIV Infection Risk After Rectal Application of a Highly Osmolar Personal Lubricant

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Background: Personal lubricant use is common for anal sex. Some water-based products with high osmolality and low pH can damage rectal tissues. Additionally, the preservative polyquaternium 15 (PQ15) can enhance HIV replication in vitro. This has raised concerns that lubricants with such properties may increase STD/ HIV infection risk, although in-vivo evidence is scarce. In 2012, the WHO issued an interim advisory note to limit use of rectal lubricant formulations >1,200 mOsm/kg, with pH < 5.5, and containing PQ15. We use an animal model to test the hypothesis that a widely used, highly osmolar (>8,000 mOsm/kg), water-based lubricant with pH of 4.4, and containing PQ15 increases risk for HIV infection.

Methodology: To determine susceptibility to infection, we compared virus doses needed for infection in 20 lubricant- or control treated cynomolgus macaques. The macaques received six rectal, non-traumatic applications of lubricant or buffered saline during 3 weeks, followed by rectal virus exposures 30 minutes after the last lubricant application with escalating doses (1.25-25,000 tissue culture infectious doses [TCID-50] of SHIV SF162P3). We had previously observed an increase in rectal pro-inflammatory cytokines and epithelial tissue peeling after application of the lubricant. Uninfected macaques were rested for at least 6 weeks, and then re-exposed to higher doses until 47 exposures and 15 infections (controls=7, lubricant=8) had occurred. We calculated and compared animal infectious doses (AID-50) by modeling HIV infection as a function of the $\log_{10}$ TCID-50 using logistic regression.

Results: The estimated AID-50 was 2,990 TCID-50 (95% confidence interval [CI]: 200, 44750) in lubricant-treated macaques and 1,808 (CI: 728, 4495) in controls. The estimated AID-50 ratio of lubricant-treated macaques to controls of 1.65 (CI: 0.15, 17.9) was not statistically significant different (p = 0.72).

Conclusions: The tested lubricant did not increase susceptibility to infection. This indicates that neither the type and extent of inflammation induced by this lubricant, nor the presence of PQ15, affected infection risk in this model. Additional approaches could further clarify the effects of lubricant use on HIV risk by evaluating other products, vaginal and penile use, and by analyzing potential beneficial lubricant effects stemming from reduced condom breakage and tissue trauma during sex.

Session P-V3 Poster Session
Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Identifying and Reducing HIV Risk

943 Controlled Trial of an Internet-Based Risk Reduction Intervention in HIV+ Men Who Have Sex With Men

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Background: Improved programs to prevent and screen for sexually transmitted infections (STIs) and related risk behavior are needed among HIV-infected men who have sex with men (MSM). We piloted an internet-based safer sex intervention to reduce STIs, a biologic marker for high risk sexual activity, among HIV-infected MSM.

Methodology: Eligible subjects were HIV-infected MSM who reported recent unprotected sex or STIs. Participants at three Southern California HIV clinics were randomized (1:1) to either a monthly behavioral risk survey instrument alone or with tailored internet-based prevention messages based on their risk of HIV transmission (derived from self-reported risk behavior). The messages for the intervention arm targeted condom use, antiretroviral (ARV) use, disclosure of HIV status, and reducing substance use. STIs were assessed at baseline and then every three months, including for syphilis, gonorrhea and Chlamydia (latter two at urethra, anal and pharyngeal sites). The primary endpoint was any new STI event per subject over 12 month study period. Primary analysis was performed on a modified intention-to-treat (mITT) population (randomized subjects who completed a baseline visit) with a logistic regression model for the dichotomous outcome of any incident STI event that included treatment assignment, baseline STI status, ARV use, and methamphetamine use as predictors. A sensitivity analysis included those who completed ≥75% of their monthly visits.

Results: There were 181 MSM randomized, mean (SD) age 43.6 (11); 32.8% White, 31.7% Hispanic and 30.6% Black with 83.9% on ART with 35% having detectable viral load. Two did not complete their baseline visit resulting in a mITT sample of 179. There was no difference in attrition between the intervention (19%) and control (25%) groups (p=0.37). At baseline, 25 (28%) and 27 (30%) in the intervention and control arms, respectively, had a STI. Over the 12-month study period, 27 (30%) and 22 (27%) in the intervention and control arms, respectively, had at least one new STI. The multivariable logistic regression analysis on the mITT population showed no significant difference in the new STI event rates between the two arms (OR=0.74, 95% CI: 0.37-1.46, p=0.38). Limiting this analysis to those who completed ≥75% of monthly surveys (n=107) provided a similar result (OR=0.82, 95% CI: 0.32-2.11; p=0.68).

Conclusions: STIs were common in the HIV-infected MSM enrolled in this study. The internet-based risk reduction intervention showed no evidence for efficacy in reducing incident STIs among these subjects. Based on the primary endpoint, this study suggests that internet/computer-based safer sex programs such as the one utilized, are not effective for reducing high-risk sexual activity amongst HIV-infected MSM.

944 Changes in the Contribution (PAR%) of STIs To HIV Acquisition Among Kenyan FSWs From 1993 To 2012

Linnet Masese[1], Jared M. Baeten[1], Barbra A. Richardson[1], Susan M. Graham[1], Elizabeth Bukusi[2], Juma Shafi[3], Walter Jaoko[3], James Kiarie[3], R. Scott McClelland[1]
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Background: Genital infections including sexually transmitted infections (STIs) have been associated with an increased risk of HIV acquisition. Understanding how the contribution of different genital infections to HIV incidence has changed over the past two decades may be important for optimizing HIV prevention efforts. We assessed the population attributable risk percent (PAR%) of different genital tract infections, including STIs, to HIV acquisition in high-risk Kenyan women, from 1993 to 2012.

Methodology: We analyzed data from HIV-1-seronegative women in the Mombasa Cohort, a prospective cohort study of women reporting trading sex for cash or in-kind payment. Monthly HIV testing was performed using ELISA. We also performed monthly evaluation for genital tract infections including vaginal yeast, bacterial vaginosis (BV), Trichomonas vaginalis, Neisseria gonorrhoeae, non-specific cervicitis, and herpes simplex virus type 2 (HSV-2). We used Cox regression models to evaluate the association between different genital tract infections and HIV acquisition over 4 time periods (1993-1997, 1998-2002, 2003-2008 and 2008-2012). Each adjusted model addressed potential confounding factors including age, hormonal contraception, place of work, sexual risk behavior, and other genital tract infections. The resulting hazard ratios were used to calculate PAR%.

Results: Between 1993 and 2012, 2008 women contributed 6476 person-years of follow-up. The median age of participants at baseline was 28 years (interquartile range [IQR] 24-32). Most women worked in bars (N=1332, 66%), while the remainder worked in nightclubs (N=520, 26%) or at other venues (N=156, 8%). There were 325 incident HIV infections (incidence rate 5/100 person-years). In the overall adjusted analyses, vaginal yeast (HR 2.0; 95% confidence interval [CI] [1.6-2.6]; p=<0.001), BV (HR 1.5 95% CI [1.2-1.8], p=0.002), T. vaginalis (HR 1.5 95% CI [1.0-2.1], p=0.03), N. gonorrhoeae (HR 2.1 95% CI [1.4-3.1], p=0.001), and HSV-2 (HR 2.6 95% CI[1.5-4.3], p=<0.001) were significantly associated with increased likelihood of acquiring HIV. The overall PAR% for each infection was; vaginal yeast (6.3%), BV (10.4%), T. vaginalis (1.2%), N. gonorrhoeae (1.0%), and HSV-2 (54.6%). The PAR% for trichomoniasis and gonorrhea remained <3% and the PAR% for vaginal yeast remained <8% across the four time periods. The PAR% for BV (8.6%, 19.0%, 13.7%, 12.6%), and HSV-2 (46.0%, 70.8%, 51.2%, testing in progress for 2008-2012) were higher, but varied somewhat over time.

Conclusions: Bacterial vaginosis and HSV-2 have remained the largest contributors to PAR% for HIV acquisition over the past 20 years. Interventions that prevent these conditions could provide the greatest potential benefit in terms of reducing HIV risk in women.

945 Intervention To Reduce HIV/STI Among High-Risk Patients in China: Cluster Randomized Trial

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Background: China is experiencing growing HIV and STI epidemics. Interventions to train physicians in China on HIV and STI knowledge, diagnosis, treatment, and risk reduction counseling can reduce HIV/STI risk transmission among high-risk patients.

Methodology: Cluster randomized trial. We randomized 51 counties in two provinces in eastern China to intervention or delayed-control groups. Physicians (n=120) in the intervention group counties received structured HIV and STI training and opportunities to enhance their clinical and counseling skills; physicians (n=128) in delayed group counties received the training after 9 months. We recruited 1,124 STI patients (4-6 from each participating physician), treated baseline gonorrhea and Chlamydia infections, and measured 9-month incident gonorrhea and Chlamydia infections, condom use, HIV/STI-related knowledge and attitudes, and satisfaction with their physician. Statistical comparisons between patients in intervention and control counties used multi-level analyses to account for cluster effects.

Results: At 9-month follow-up, patients in intervention counties had significantly lower odds of combined gonorrhea or Chlamydia reinfection (AOR = 0.62, 95% CI 0.46 - 0.84), lower unprotected sex (AOR = 0.22, 95% CI 0.12 - 0.42), greater HIV knowledge (adj. beta = 2.13, 95% CI 1.53 - 2.73), more positive attitudes toward people living with HIV (adj. beta = 1.51, 95% CI 0.96 - 2.05), and more positive ratings of physicians (adj. beta = 0.22, 95% CI 0.15 - 0.30), compared with delayed-control county patients.

Conclusions: Integrating HIV and STI training into medical education in China can be a useful strategy in reducing the country's growing HIV and STI epidemics.

946 Validation of the Refined Denver HIV Risk Score Using a National HIV Testing Cohort

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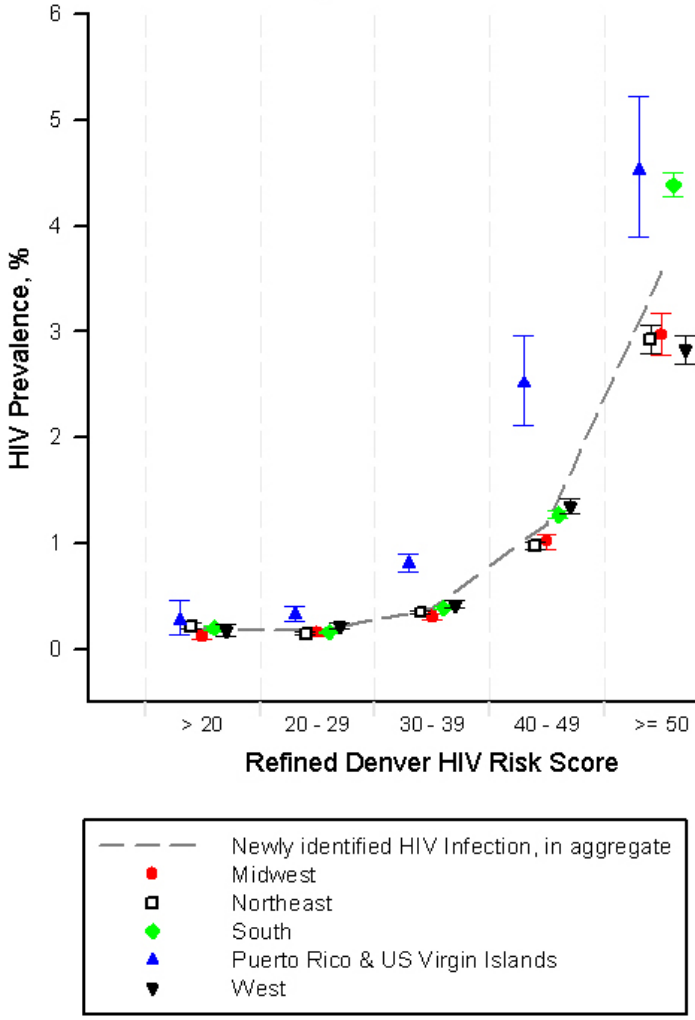
Background: The Centers for Disease Control and Prevention (CDC) and US Preventive Services Task Force recommend routine HIV screening for adolescents and adults. Recently, the Denver HIV Risk Score (DHRS) was developed as a clinical prediction instrument to guide HIV screening by providing estimates of HIV infection risk. The DHRS has been refined to include only patient demographics, sex with a male, injection drug use, and past HIV test, but has not been broadly validated across different geographic regions or HIV testing venues. Our purpose was to externally validate the refined DHRS in a national HIV testing cohort from the CDC.

Methodology: This was a secondary analysis of HIV testing data from the Program Evaluation and Monitoring System of the CDC's National HIV Prevention Program. Data from all CDC-funded HIV testing sites in the U.S. with the exception of Massachusetts, North Dakota, Ohio and Rhode Island were included. Individuals ≥13 years of age who underwent HIV testing from January 1, 2008 through December 31, 2010 were used with newly-diagnosed HIV infection as the outcome. All observations were assigned scores according to the refined DHRS and categorized into 5 mutually exclusive groups: < 20 (very low risk); 20-29 (low risk); 30-39 (moderate risk); 40-49 (high risk); and ≥50 (very high risk). Proportions and 95% CIs for each group are reported. Calibration is reported as predicted versus observed HIV prevalence and discrimination is reported using a ROC curve and the areas under the curve.

Figure. Prevalence of newly identified human immundeficiency virus (HIV) infection within each risk score category in the validation sample, stratified by geographical region, CDC PEMS data, 2008 - 2010. The refined Denver HIV Risk Score ranges from -4 to +73. Bars, 95% confidence interval.



Results: 4,830,941 testing events occurred, resulting in 30,080 (0.6%) newly-identified HIV infections. Of all visits, 432,674 (9%) were categorized as very low risk with an HIV prevalence of 0.20% (95% CI: 0.19%-0.21%), 1,312,427 (27%) were low risk with a prevalence of 0.17% (95% CI: 0.16%-0.17%), 2,003,857 (41%) were moderate risk with a prevalence of 0.39% (95% CI: 0.38%-0.40%), 811,501 (17%) were high risk with a prevalence of 1.19% (95% CI: 1.16%-1.21%), and 270,482 (6%) were very high risk with a prevalence of 3.57% (95% CI: 3.50%-3.64%). The DHRS demonstrated excellent calibration (regression slope = 1.09; R^2 = 0.99), good discrimination (ROC area = 0.77, 95% CI: 0.77 - 0.77), and similar accuracy across geographic regions.

Conclusions: The refined DHRS accurately categorized patients into significantly different HIV risk groups, regardless of geographic region. The refined DHRS is a relatively simple tool for quantifying HIV risk and may help identify individuals for HIV testing.

Session P-V4 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

PrEP, PEP, TasP

947 Cost Effectiveness of Antiretrovirals in HIV Control in Rural Zambia: A Stochastic League Approach

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Background: Earlier ART initiation and pre-exposure prophylaxis (PrEP) have both been demonstrated to effectively prevent new HIV infections. There is, however, limited funding available for HIV prevention. Choices must therefore be made when deciding on the optimal prevention strategy. The aim of this study was to compare the epidemiological impact, cost effectiveness and economic affordability of antiretroviral based prevention strategies.

Methodology: A deterministic mathematical model was made to predict the impact on the HIV-epidemic over 40 years of increasing the treatment initiation threshold to CD4 <500 cells/µl, and two hypothetical PrEP scenarios: prioritized to the most sexually active, and non-prioritized in the rural area of Macha, Zambia. We conducted a standard cost effectiveness analysis by calculating incremental cost effectiveness ratios (ICERs) (an ICER of <$3480 is defined as cost effective in Zambia). It is important, however, to determine what cost effective intervention is affordable given a budget. We therefore implemented an economic analysis, stochastic league tables, which enable the prediction of the optimal intervention per budget level to explore both cost effectiveness and affordability.

Results: Continuing treatment at CD4 <350 will strongly reduce the HIV prevalence over time: from 6.2% (interquartile range 5.8%-6.6%) in 2014 to 1.3% (0.9%-1.9%) in 2054. All other interventions will result in prevalence of around 1% after 40 years, but result in infections averted (between 16% [prioritized PrEP plus treatment at CD4<350] and 59% [non-prioritized PrEP plus treatment at CD4 <500]). The only strategy that was cost effective using standard cost effectiveness analysis was treating at CD4 <500, with an ICER of $62 ($46-$75). Non-prioritized PrEP plus treating at CD4 <500 was, however, borderline cost effective with an ICER of $5,861 ($3,959-$8,483). Based on current HIV treatment costs, it will cost on average $20 million to treat HIV at CD4 <350 over the coming 40 years in Macha. Initiating treatment at CD4 <500 would require a slight increase in budget up to $25 million, with a 96.7% probability of being the optimal intervention. Introduction of PrEP, however, is not included as an optimal intervention until the budget exceeds $180 million.

Conclusions: All prevention strategies avert new infections with a small impact on prevalence compared to baseline of treating at CD4<350. Following the WHO recommendation to start at a CD4 <500 would require only modest budget increases. While non-prioritized PrEP plus treatment at CD4 <500 is borderline cost effective, our stochastic league analysis shows that it is not economically feasible and should only be considered if there is a ten-fold increase in budget.

948 Darunavir(DRV)/r-Based PEP Versus Standard of Care (SOC) - the Randomized PEPDar Study

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Background: Post exposure prophylaxis (PEP) for 4 weeks is state-of-the-art following exposure to HIV with high risk of transmission. None of the recommended regimens has been studied in prospective randomized studies in this indication so far, discontinuations rates due to side effects are high. Darunavir/r has a favorable safety profile and high antiviral potency. It could therefore be an alternative to currently used drugs (mainly lopinavir (LPV)/r). This study was designed to generate data on safety and tolerability of DRV/r-based PEP compared to SOC-PEP.

Methodology: PEPDar was an open-label, randomized multicenter prospective noninferiority study enrolling patients following high risk exposure to HIV in Germany. Recommended SOC as per 2008 National Guidelines included 2 NRTIs plus LPV/r or EFV. Patients were stratified by risk of exposure (occupational [OE] vs. non-occupational [NOE]) to receive DRV/r + 2 NRTIs or SOC-PEP within 72 hours following high risk contact for 28-30 days. Primary endpoint was the early discontinuation rate (% subjects who discontinued HIV-PEP for >2 consecutive days prior to day 28) for any reason except documented negative HIV-status of the index person. The trial had 80% power to show noninferiority (overall significance level 5% [two-sided], non-inferiority margin 12%).

Results: Between 11/2011 and 05/2013 306 patients were enrolled at 22 centers. 82.7% were male (median age 33 years [range: 18-62]); 17.3 % were female (median age 31 years [range 18-55]). Median time between risk contact and start of PEP was 2 hours (range 0.1 - 22) after OE (n=62 [20.3%]) and 14 hours (range 0 -71.9) after NOE (n=244 [79.7%]). 155 patients received DRV/r + 2 NRTIs, 151 patients received SOC (LPV/r-based in all patients) + 2 NRTIs. 97% (n=298) received TDF/FTC as backbone. Early discontinuation rate was 5.8% (n=9) in the DRV/r-arm and 9.4% (n=14) in the SOC-arm showing non-inferiority (CI: -0.148; 0.078). Adverse events (AEs) related to DRV/r or SOC were reported in 106 DRV/r-patients (68.4%) and in 114 SOC-patients (75.5%) (p=0.203). Most common AEs (all grades) were diarrhoea (28 vs. 42 patients [p=0.056]), nausea (16 vs. 26 patients [p=0.097]) and fatigue (17 vs.22 [p=0.393]). SOC-patients experienced more sleep disorders (0 vs. 6 [p=0.014]). Rash was reported in 6 DRV/r- patients and 5 SOC-patients. No seroconversion was documented.

Conclusions: DRV/r showed noninferiority with regard to early discontinuation of PEP when compared to SOC (LPV/r in all SOC-patients). Both regimens were well tolerated. We conclude that DRV/r-based PEP is an alternative to SOC including LPV/r.

949 High Initiation of PrEP and ART in a Demonstration Project Among African HIV-Discordant Couples

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Background: PrEP and ART have demonstrated high efficacy for HIV prevention among African HIV serodiscordant couples. Assessing delivery, uptake of and adherence to antiretroviral strategies for HIV prevention outside of clinical trial settings is a priority.

Methodology: Enrollment into an open-label demonstration project of PrEP and ART among high-risk, research-naïve HIV serodiscordant couples from 4 sites in Kenya and Uganda began in November 2012. Couples are eligible if the HIV-infected partner is not on ART at enrollment. PrEP is offered as a bridge to ART initiation in the couple, in which ART is offered according to current national guidelines of Kenya and Uganda (CD4 ≤350 or symptomatic HIV disease). Tenofovir/emtricitabine PrEP is offered to couples in which the HIV-infected partner declines, delays, or is not eligible for ART, and during the first 6 months after the HIV-infected partner initiates ART, to allow time for achieving viral suppression. Couples are followed quarterly with counseling about HIV risk reduction strategies, ART benefits, ART and PrEP adherence counseling, and semiannual CD4 testing. ART adherence is assessed through biannual HIV RNA concentration measurements and PrEP adherence is assessed through medication event monitoring caps, pill counts, and tenofovir drug level testing.

Results: As of September 2013, 339 couples (70.2% in which the HIV-infected partner was female) were enrolled; with 96.6% of eligible couples enrolled. The median age is 29 years for HIV uninfected partners and 27 years for HIV infected partners. Most (94.4%) couples are married, 22.7% have no children, and the median number of children is 1. HIV-uninfected partners reported a median of 7 (IQR 3-12) sex acts with their study partner in the month prior to enrollment and 67.0% reported having unprotected sex. HIV-infected partners have a median CD4 count of 404 (IQR 256-595), median plasma viral load of 4.6 (IQR 4.0-5.0) log10 copies/mL, and 51.9% are eligible for ART. At enrollment, 97.3% of HIV uninfected partners initiated PrEP and 72.3% of ART eligible HIV infected partners initiated ART through on-site ART providers or accepted a referral to start ART at an off-site provider. Following the enrollment visit, only 2% of couples were not using PrEP or ART for prevention.

Conclusions: HIV serodiscordant couples from East Africa have high uptake of antiretroviral-based prevention and high rates of initiation of open-label PrEP and ART. Data from the ongoing study will be essential to guiding implementation and integration of antiretroviral-based prevention into policy.

950 PrEP Is Efficacious for HIV Prevention Among Women Using DMPA for Contraception

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Background: Pre-exposure prophylaxis (PrEP), using daily oral tenofovir disoproxil fumarate (TDF) or combination emtricitabine (FTC)/TDF, is a proven HIV prevention strategy. Observational studies have suggested that the injectable contraceptive depot medroxyprogesterone acetate (DMPA) may increase the risk for HIV acquisition among women. Whether PrEP is efficacious for HIV prevention among women using DMPA has not been evaluated previously.

Methodology: In a randomized, placebo-controlled trial of PrEP among Kenyan and Ugandan HIV serodiscordant couples (the Partners PrEP Study), we estimated the efficacy of PrEP (TDF or FTC/TDF) for HIV prevention among HIV uninfected women using DMPA. HIV uninfected members of the couples were seen monthly and study visits included HIV testing, study medication provision, and adherence counseling. Contraception was not required but women were counseled to delay pregnancy until after this PrEP safety and efficacy study, and a variety of contraceptives were offered on-site, free-of-charge.

Results: 1785 HIV uninfected women participated in the trial, of whom 901 (50.5%) used DMPA at some point during follow-up, including 486 who were using DMPA at enrollment and 415 who initiated DMPA during follow-up. During follow-up, 45 women acquired HIV, of whom 15 (33.3%) were using DMPA at the time of HIV acquisition. Among women using DMPA, HIV incidence was 1.24 per 100 person-years for women assigned to active TDF or FTC/TDF PrEP and 3.75 per 100 person-years among women assigned placebo, translating into a 72% reduction in the risk of HIV acquisition from PrEP among women using DMPA (hazard ratio 0.28, 95% confidence interval 0.10 - 0.83, p=0.02). Sensitivity analyses with varied definitions of DMPA use, including DMPA use as reported at enrollment and a prolonged effect of DMPA for 70 days after last reported use, had similar findings.

Conclusions: PrEP is efficacious for HIV prevention among women using DMPA, suggesting PrEP could mitigate the potential increased HIV acquisition risk that has been associated with DMPA use in some observational studies. Strategies to integrate PrEP use and family planning counseling should be prioritized for women at high risk of HIV infection.

951 PrEP Interest, Uptake, and Adherence Among Young Men Who Have Sex With Men (YMSM) in the United States

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Background: Young men who have sex with men, particularly racial minority YMSM, are the only group in the United States whose HIV infection rates continue to increase. Pre-exposure prophylaxis (PrEP), which has been shown to reduce the risk of HIV acquisition, may be an ideal prevention method for these young men. Data on interest in open label PrEP use among MSM from the iPrEx trial have been presented, yet YMSM in the United States were not included in those analyses. Understanding the interest, uptake, and adherence to PrEP among U.S. YMSM is critical for designing PrEP implementation programs domestically.

Methodology: All 68 YMSM previously enrolled in ATN 082, a randomized pilot trial of PrEP feasibility and acceptability, were eligible to enroll in the open label extension of the iPrEx trial (iPrEx OLE). All HIV-uninfected participants were offered daily PrEP (TDF/FTC) along with a comprehensive package of HIV/STI testing and integrated risk reduction/adherence counseling. All participants taking PrEP were tested for tenofovir levels via plasma. Participants completed detailed computer assisted self-interviews on reasons for study participation, knowledge of PrEP efficacy, PrEP adherence and sexual behavior. We compared rates of self-reported adherence, tenofovir drug levels, and sexual risk behavior between the ATN 082 and iPrEx OLE.

Results: Forty-six YMSM (68% of total eligible; mean age 21; 52% Black, 37% Latino) enrolled in iPrEx OLE. Of those, 69.6% chose to take PrEP. The most common reasons for study participation were to help fight the HIV epidemic (74%), to get tested for HIV (59%) and to protect against HIV (59%). Tenofovir detection during the first 12 weeks of iPrEX OLE was 58.3% - up from 45% during the same timeframe of ATN 082. Self-reported adherence (64.8%) was consistent with tenofovir detection. Most common reasons for missing doses were not having pills with them (28%), schedule changes (24%) and forgetting (22%). Perceptions of PrEP efficacy increased significantly (p<.001) across study visits, while number of recent sex partners and episodes of unprotected anal receptive sex decreased. Participants reported multiple social benefits from study participation and 70% stated they would take PrEP in the future if available.

Conclusions: When offered open label access to an efficacious product, the majority ATN 082 participants chose to enroll in iPrEx OLE and take PrEP. While adherence among this challenging population was not optimal, it improved from ATN 082 and was consistent with self-report. YMSM may find both medical and social benefits to participation in PrEP programs as well as develop skills to improve adherence and decrease sexual risk behavior. YMSM appear interested and willing to take PrEP now that efficacy has been established.

952 Early Adopters: Correlates of Chemoprophylaxis Use in an Online Sample of US Men Who Have Sex With Men

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Background: Although HIV pre-exposure prophylaxis (PrEP) use has been shown to decrease HIVincidence among men who have sex with men (MSM), uptake has not been widespread, and the demographics and behaviors of those who initiated PrEP outside of studies is not well known.

Methodology: In August 2013, members of the largest MSM sexual-partner seeking networking site in the US received an online invitation to complete a survey about their HIV prevention practices. Responses were analyzed using summary statistics. Multivariable logistic regression analyses were conducted to determine adjusted odds ratios to assess factors associated with having used PEP or PrEP.

Results: Of 9,179 MSM who responded to the survey, 18% used mobile technology. Participants' mean age was 26 years; 82% identified as homosexual or gay, 23.6% as bisexual, 2.4% as heterosexual, 0.4% as transgender and 1.1% as gender queer. Most of the respondents were white (85.7%), 3.9% Black, 7.5% Latino. Over 2/3 (68.4%) completed college. The sample was geographically diverse. More than ¼ (30.2%) reported a prior sexually transmitted infection (STI); 58.7% reported at least one episode of unprotected anal sex, and 7.5% reported substance use during sex in the prior 3 months. Although 84.0% reported that they had a primary care provider (PCP), only 53.9% reported that they felt comfortable discussing sex with their PCP. Only 3.2% of respondents reported prior PEP use, and 1.2% reported PrEP use. PEP users more often were younger, identified as gender queer (compared to homosexual or gay), had graduated college, had a prior STI diagnosis, engaged in recent unprotected anal sex, had used substances during sex, and were more comfortable talking about sex with their PCP compared to MSM who had not used PEP. PrEP users more often reported that they had graduated college, had a prior STI, and were more comfortable talking with their PCP about MSM sex compared to MSM who had not used PrEP. PrEP users had a 16-fold greater odds of having used PEP than PrEP-naïve MSM.

Conclusions: Although MSM in this online survey reported significant HIV risks, their experience with PEP and PrEP was limited. In order to increase PrEP uptake among MSM, PCPs need to be educated to provide culturally competent care, so that patients will be comfortable discussing HIV risks that could be decreased by PEP or PrEP.

953 Measuring Intermittent and Daily PrEP Adherence by Hair Levels, Self-Report and MEMS Caps Openings

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Background: Intermittent PrEP may facilitate adherence, reduce cost, and shows efficacy in simian models, but accurate measurement of adherence is critical for trial interpretation. Hair tenofovir (TFV) levels are strongly and linearly related to dose and predict HIV treatment responses, so may serve as objective markers of adherence. We compared TFV and emtricitabine (FTC) hair levels with traditional measures of adherence in two intermittent PrEP trials conducted in HIV serodiscordant couples in Uganda and men-who-have-sex-with-men (MSM) in Kenya.

Methodology: Each trial randomized HIV-negative individuals to daily versus intermittent (Mondays, Fridays, within 2 hours after sex other days) PrEP with FTC/TDF or placebo in a 2:2:1:1 ratio. Number of doses taken was assessed by self-report and medication event monitoring systems (MEMS); hair samples were collected and analyzed for TFV/FTC concentrations at weeks 8 and 16. Linear regression models with random intercepts analyzed relationships between logarithmically-transformed hair levels, MEMS and self-report.

Results: 172 hair samples from 88 volunteers randomized to daily or intermittent PrEP (active arms) were analyzed. Hair collection was highly acceptable (100% at week 8, 96% at week 16). Hair levels for those on daily doses averaged >2x (2.6x for FTC; 2.1x for TFV) those on intermittent dosing. Hair levels were rarely undetectable (<2.5%) at week 8, but were undetectable more frequently (with a significant difference for FTC) by week 16 (9.5% with undetectable FTC, p 0.008; 4.8% with undetectable TFV, p 0.35). Hair levels and MEMS counts were strongly associated: for every 10% increase in MEMS caps openings, TFV and FTC hair concentrations increased by 8% and 10%, respectively. Self-reported doses taken and TFV/FTC hair levels were weakly associated. Adjusting for other predictors (age, weight, height, hair color, gender, drug use, liver/renal function, dosing) did not substantially change estimated effects of MEMS counts on hair levels. MSM (Kenya) were estimated to have ~40% lower average TFV/FTC hair concentrations than heterosexual participants (Uganda), an observation only partially mediated by younger age.

Conclusions: In two intermittent PrEP trials in East Africa, hair collection was highly acceptable and feasible. Concentrations of TFV/FTC in hair were strongly associated with MEMS openings, but more weakly associated with self-report, likely reflecting biases of the latter. Hair levels in active arms were generally detectable, but there were more undetectable levels and fewer MEMS caps openings later in the trial. Hair concentrations were lower in MSM than heterosexual participants. Concentrations of TFV/FTC in hair should be investigated further as a promising measure of adherence in PrEP.

954 Implementation of PrEP in STD Clinics: High Uptake and Drug Detection Among MSM in the Demonstration Project

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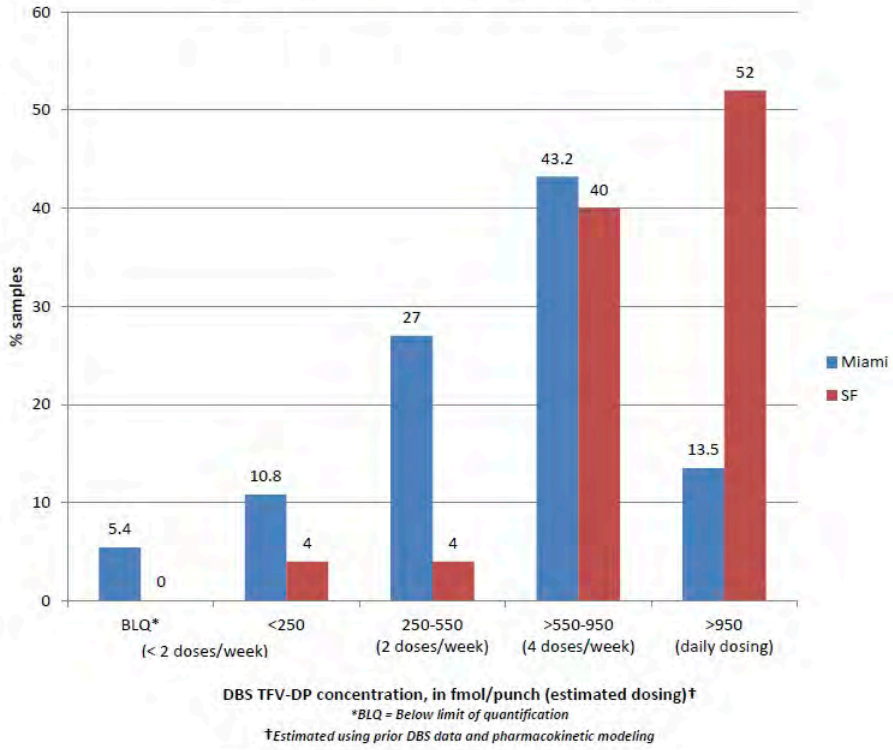
Background: Pre-exposure prophylaxis (PrEP) has been shown to be safe and efficacious in clinical trials. Demand for PrEP and levels of adherence in real world settings are unknown. We evaluated PrEP uptake and early drug detection among men who have sex with men (MSM) in the first year of a US PrEP Demonstration (Demo) Project.

Methodology: From 9/2012 to 9/2013, HIV-uninfected MSM and transgender women receiving services or requesting PrEP at STD clinics in San Francisco (SF) and Miami were offered the opportunity to screen for The Demo Project. Enrolled participants were offered up to 48 weeks of open-label emtricitabine/tenofovir. Predictors of PrEP uptake were assessed using multivariable logistic regression. Tenofovir diphosphate (TFV-DP) levels in dried blood spots (DBS) were assessed in a random sample of participants at the 4 week visit.

Results: Of 831 clients approached for participation in the Demo Project, 340 declined, 105 were ineligible based on behavioral or medical criteria, and 386 enrolled, for an overall uptake of 53% among potentially eligible clients (49% in SF vs. 64% in Miami). Mean age of enrolled participants was 35 years; 9% were African American, 35% Latino, and 46% white; 42% were uninsured and 73% had previously heard of PrEP. Participants in Miami were younger, more likely to be Latino or African-American, less likely to be insured, and less likely to report drug use or unprotected receptive anal sex in the prior 3 months (all $p<0.05$). In adjusted analyses, participants from Miami (AOR 6.5, 95% CI 2.9-14.8), with prior PrEP awareness (AOR 2.3, 95% CI 1.5-3.5), and those reporting unprotected anal sex with >5 partners (AOR 1.5, 95% CI 1.0-2.2) or >1 episode of anal sex with an HIV-infected partner (AOR 1.8, 95% CI 1.2-2.6) in the last 12 months were more likely to enroll in the Demo Project. In SF, higher risk perception (AOR 1.9, 95% CI 1.2-2.8) was also associated with enrollment. DBS samples from 87 participants at week 4 were tested: almost all had TFV-DP detected (100% in SF, 95% in Miami). Median TFV-DP levels were higher in SF than in Miami (975 vs. 658 fmol/punch, $p<0.001$), and a greater proportion of participants from SF had TFV-DP levels consistent with having taken at least 4 doses/week (92% vs. 57%, $p<0.001$) (Fig 1).

Conclusions: Demand for PrEP and rates of early drug detection are high among MSM in the first year of the Demo Project. Factors contributing to differences in PrEP uptake and adherence across sites warrant further investigation.

Figure 1: DBS TFV-DP levels, by site



955 High Medication Adherence Among HIV-1 Uninfected Women Experiencing Pregnancy in a PrEP Trial

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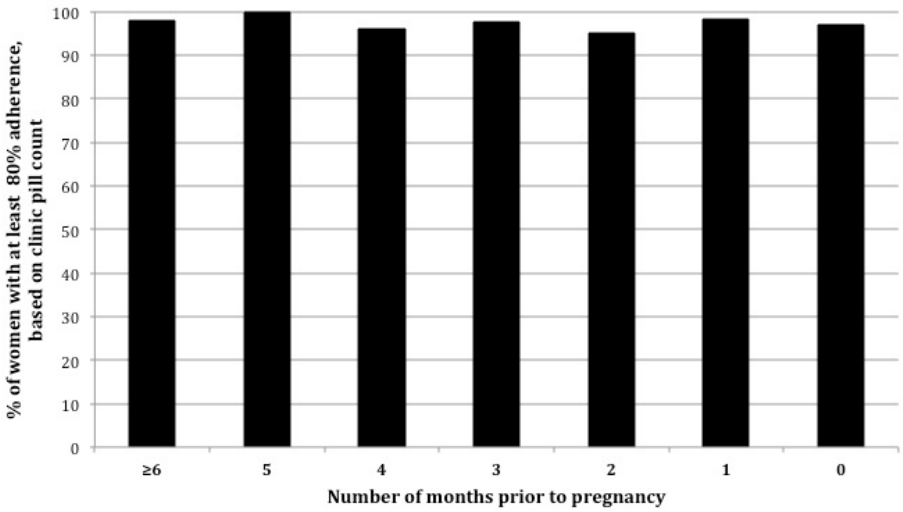
Background: Pre-exposure prophylaxis (PrEP) may be an important safer conception strategy for HIV-1 uninfected women with an HIV-1 infected partner. Identifying pregnancy predictors and medication adherence in this population may inform whether PrEP is a feasible safer conception strategy.

Methodology: We evaluated predictors of pregnancy and adherence to study medication among HIV-1 uninfected women enrolled in a randomized, placebo-controlled trial of oral, daily PrEP among African HIV-1 serodiscordant couples. Participants were counseled on HIV-1 risk reduction, contraception,

and PrEP adherence at monthly study visits. Monthly visits included pregnancy testing with urine β-hCG. Pill count adherence was calculated from monthly clinic counts of dispensed and returned study pills and stored plasma from selected study visits was tested for tenofovir drug concentrations.

Results: Among 1785 women whose median age was 33 years (IQR 28-38), pregnancy incidence was 10.2 per 100 person-years. Younger age, not using contraception, having an additional sexual partner, and reporting unprotected sex were associated with increased likelihood of pregnancy. PrEP adherence was high among women who became pregnant: monthly clinic pill counts of study medication demonstrated 98% of prescribed doses were taken and tenofovir was detected in 71% of plasma samples tested. Adherence was similarly high in the months prior to conception in comparison to prior periods (Figure 1).

Figure 1. Periconception adherence to study drug among HIV-uninfected women experiencing pregnancy in the Partners PrEP Study



Conclusions: HIV-1 uninfected women with known HIV-1 infected partners had 10% annual pregnancy incidence in a clinical trial with excellent access to effective contraception. Women who became pregnant had high medication adherence, suggesting that PrEP may be an acceptable and feasible safer conception strategy for HIV-1 uninfected women in an HIV-1 serodiscordant partnership.

956 Willingness To Use Pre-Exposure Prophylaxis Among Community-Recruited Injection Drug Users

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Background: Recent evidence indicates that using antiretrovirals as pre-exposure prophylaxis (PrEP) among injection drug users (IDUs) is effective in preventing HIV transmission. We examined the correlates of the willingness to use PrEP among community-recruited active IDUs in Washington, DC.

Methodology: Data from the IDU cycle (2012) of the National HIV Behavioral Surveillance system in DC were used. IDUs were recruited using respondent-driven sampling (RDS) and completed a detailed behavioral quantitative interview and underwent rapid testing for HIV. Data were limited to HIV-negative IDUs who reported on willingness to use PrEP and how it might affect their drug use and sexual behaviors. RDS-weighted proportions and correlates of self-reporting being very likely to use PrEP using unweighted multivariable analyses were reported. Potential correlates included demographic characteristics, sexual and drug use behaviors, institutional history, depressive symptoms, and utilization of needle exchange programs. Variables attaining a univariate p-value of ≤0.05 were included in the final model.

Results: Among 304 HIV-negative IDUs, 68.0% were male, and 82.7% were 50 or older, 97.2% were black, and 69.3% had a high school diploma or higher; the majority were unemployed or disabled. None had ever taken PrEP. 47.4% reported being very likely and 23.6% reported being somewhat likely to take PrEP if it were available and free, and 88.0% and 87.9% disagreed that they would no longer need to sterilize/clean needles or use condoms during sex if taking PrEP, respectively. Independent correlates of reporting being very likely to use PrEP included being younger (<50 years old; aOR: 2.68, 95% CI: 1.18, 6.11) and having two or more sex partners in the past 12 months compared to having none (aOR: 5.03; 95% CI: 1.82, 13.9).

Conclusions: A large proportion of active IDUs in Washington, DC reported being willing to use PrEP if it were available at no cost. IDUs who were younger and had more sex partners reported to be more willing to use PrEP, suggesting that these groups could be targeted first to explore the practicality of PrEP use in this population. Further research should be done to explore availability, uptake, and adherence of PrEP among IDUs.

957 PrEP Does Not Diminish the Pregnancy Prevention Effectiveness of Hormonal Contraception

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Background: Pre-exposure prophylaxis (PrEP) is highly effective for HIV-1 prevention. Some studies have suggested an antagonistic interaction between PrEP and hormonal contraception, with both biologic and behavioral mechanisms hypothesized. Evidence is needed to ensure PrEP and hormonal contraception can be effectively used together. We evaluated whether PrEP reduces hormonal contraceptive effectiveness for pregnancy prevention.

Methodology: In a clinical trial of PrEP (the Partners PrEP Study), 1785 HIV-1 uninfected women and their HIV-1 infected male partners were randomized to tenofovir or co-formulated tenofovir-emtricitabine PrEP or placebo and followed for up to 3 years. Contraception was not required for study participation, was offered on-site, and was recorded monthly; incident pregnancy was determined by monthly urine pregnancy testing. We estimated the contraceptive effectiveness of hormonal contraceptive methods (oral contraceptive pills, injectable contraception, and contraceptive implants) compared to no

contraception using the Andersen-Gill extension of Cox proportional hazards and compared contraceptive effectiveness for women assigned to PrEP versus placebo. Estimates were adjusted for age, number of children, partnership duration, sexually transmitted infections at enrollment, any unprotected sex, sexual frequency, and antiretroviral therapy use by HIV-1 infected partners.

Results: Among women reporting no contraceptive use, pregnancy incidence was 14.6% per year among women assigned PrEP and 17.4% per year among women assigned placebo (Table). Women reporting oral contraceptive use had similar pregnancy incidence compared to women using no contraception and this effect was similar for women assigned PrEP and placebo (interaction p=0.22). Women reporting injectable contraception had substantial protection from pregnancy which did not differ by randomization arm (PrEP: HR 0.3, p<0.001; placebo: HR 0.2, p<0.001; interaction p=0.45). Contraceptive efficacy was highest among women using contraceptive implants (incidence <1%/year).

Conclusions: PrEP had no adverse impact on contraceptive effectiveness for pregnancy prevention. As seen in prior studies in similar populations, oral contraceptive pills provided little reduction in pregnancy incidence, possibly due to poor adherence. A combination of injectable or implantable hormonal contraception plus PrEP provides effective prevention for pregnancy and HIV-1.

Contraceptive method	PrEP or placebo	Incidence per 100 person-years	Adjusted hazard ratio, vs. no contraception (95% CI)	p-value, vs. no contraception	p-value for difference in effect, PrEP vs. placebo
No contraception	PrEP	14.6	ref		
	Placebo	17.4	ref		
Oral pills	PrEP	17.7	1.0 (0.6 - 1.6)	0.86	0.24
	Placebo	10.1	0.6 (0.3 - 1.2)	0.13	
Injectable contraception	PrEP	5.1	0.3 (0.2 - 0.4)	<0.001	0.47
	Placebo	5.3	0.2 (0.1 - 0.4)	<0.001	
Contraceptive implant	PrEP	0.7	too few events for model to estimate		
	Placebo	0.0			

958 Uptake of Treatment as Prevention and Continuum of Care Among Men Who Have Sex With Men in Nigeria

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Background: Evidence has shown that treatment of HIV infection with antiretroviral therapy (ART) prevents heterosexual transmission of HIV to an uninfected partner. However, the "real world" application of this strategy to key populations such as men who have sex with men (MSM) has been limited. We report preliminary findings on acceptability of a treatment as prevention (TasP) strategy among HIV-infected MSM at a Trusted Community Center providing comprehensive HIV prevention and treatment to MSM in Abuja, Nigeria.

Methodology: Using respondent driven sampling (RDS), MSM who were >16 years old and have engaged in either receptive or insertive anal intercourse within the previous 12 months were recruited into a prospective combination HIV prevention and treatment study (TRUST). Two weeks after enrollment, HIV testing and counseling (HTC) was conducted. During every 3 month follow-up visits, all HIV-uninfected participants underwent repeat HTC; HIV-infected participants underwent clinical and laboratory evaluation, including CD4 count, plasma HIV viral load, immediate 3 weekly sessions of ART preparation, then ART initiation per TasP strategy irrespective of CD4 count. Reasons for not engaging in ART preparation and/or non-initiation of ART were documented. Characteristics associated with TasP engagement were determined using Chi-square; a double sided p-value <0.05 was considered significant.

Results: Within the first 6 months, a total of 413 participants were enrolled. Of the 413, 161 (38.9%) have completed visit 1 with 102 (63.3%) testing positive for HIV. Thirty eight (37.2%) HIV-infected participants were on ART at the time of recruitment while 64 (62.8%) were ART-naïve and referred for ART preparation. Of these 64, 17 (26.6%) did not complete the 1st session. Of the 47 who completed the 1st session, 23 (48.9%) and 3 (6.4%) did not complete the 2nd and 3rd session, respectively. Overall, of these 64, only 24 (37.5%) ART-naïve participants engaged in timely TasP. For participants who started ART, the median time from HTC to ART initiation was 26.5 days (range: 6 - 107 days). Compared to MSM who engaged in TasP, those who did not engage had significantly higher mean CD4 count (p=0.016), were more likely to be Muslims (p=0.024), younger (p=0.032), and of lower income status (p=0.028). Reasons given for lack of engagement in TasP included denial of HIV status, fear of medication side effects, perception of high CD4 count, and frequent travels.

Conclusions: Although, there was high acceptance of HTC among this MSM population, a high proportion did not engage in TasP, suggesting that customized treatment preparation for this high risk population may be necessary.

959LB FEM-PrEP: Participant Explanations for Non-Adherence

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Background: FEM-PrEP - a clinical trial of daily emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) for HIV prevention - was unable to determine the effectiveness of FTC/TDF among women in sub-Saharan Africa due to low study product adherence. We implemented a follow-up study to identify factors that influenced participants' non-adherence and reasons for participation.

Methodology: We conducted qualitative, semi-structured interviews (SSIs) (n=88) and quantitative audio computer-assisted self-interviews (ACASI) (n=224) with FEM-PrEP participants in Bondo, Kenya, and Pretoria, South Africa. SSI participants were purposefully sampled to represent a range of drug concentrations. The ACASI questionnaire was completed by most SSI participants (n=86), a randomly selected group of participants assigned placebo (n=50), and a separate group interviewed about risk perceptions (n=88). We used thematic analysis and descriptive statistics to analyze the qualitative and quantitative data, respectively. Ickovics' and Meisler's conceptual framework on adherence was used to better understand behavioral and contextual factors surrounding adherence.

Results: Table 1 lists factors influencing non-adherence, as reported in ACASI, for four of the five categories of the framework. Reasons for trial participation may be indirectly related to the fifth category - clinical setting (e.g., services): 93% of participants said they participated in FEM-PrEP because of indirect benefits (e.g., medical care). In the SSIs, participants frequently mentioned several individual and regimen-related factors as reasons other participants were non-adherent, including lack of support or discouragement from others, unknown effectiveness of FTC/TDF and unknown pill randomization, perceptions of low or variable HIV risk, large pill size, concerns about side effects, and the uncommon practice of taking pills when not sick.

Conclusions: Use of an investigational drug was a prominent concern among participants from both sites, although especially in Pretoria. Unacceptability of a daily pill as PrEP for some participants, particularly among women in Pretoria, and negative influences from others also influenced adherence within the context of a clinical trial. The trial's indirect benefits may have encouraged women who were not interested in taking the study product to enroll. Alternative study designs/procedures and enhanced community engagement paradigms may be needed in future studies.

Table 1: Factors influencing non-adherence

Category	Factor	Bondo (n=112)	Pretoria (n=112)	Overall (n=224)
Individual (e.g., social support, treatment satisfaction), n (%)	Forgot	18 (16)	46 (41)	64 (29)
	Felt at low risk of HIV	14 (13)	48 (42)	62 (28)
	Deterred by other participants' non-adherence	11 (10)	39 (35)	50 (22)
	Was traveling	26 (23)	22 (19)	48 (21)
	Used to taking pills only when sick	8 (7)	39 (35)	47 (21)
	Were told by someone not to take the pills	13 (12)	21 (19)	34 (15)
	Disliked taking pills	4 (4)	24 (21)	28 (13)
Study pill regimen (e.g., pill features), n (%)	Pill was investigational	29 (26)	77 (68)	106 (47)
	Daily pill taking was too difficult	11 (10)	60 (53)	71 (32)
	Perceived placebo assignment	19 (17)	42 (37)	61 (27)
	Pill was too big	12 (11)	48 (42)	60 (27)
	Feared side effects	11 (10)	48 (42)	59 (26)
	Had side effects	11 (10)	21 (19)	32 (14)
Patient-provider, n (%)	Poor treatment by staff	3 (3)	3 (3)	6 (3)
Disease (e.g., stigma), n (%)	Feared others would think she had HIV	8 (7)	14 (12)	22 (10)

960 Prevention of HIV Transmission With Post-Exposure Prophylaxis After Infected-Blood Transfusion

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Background: Without intervention, 90% of recipients transfused with HIV-infected blood are expected to become infected. While post-exposure prophylaxis (PEP) is commonly prescribed in the setting of non-occupational HIV exposures, there is very limited evidence documenting efficacy in this setting. We report the successful use of combination PEP following transfusion of HIV infected blood from a viremic donor source.

Methodology: A 12 year old girl with vaso-occlusive sickle cell crisis inadvertently received 1 unit of packed red blood cells from a donor subsequently found to be HIV-1 infected with plasma HIV RNA of 9740 copies/ml (not on antiretroviral therapy [ART]).Longitudinal testing of the patient's plasma and peripheral blood mononuclear cells (PBMCs) was performed by commercial laboratory tests and by highly sensitive research assays with thresholds of detection down to 0.07 DNA copies/106 PBMCs and 0.4 RNA copies/mL of plasma during directly observed combination anitretroviral therapy (cART) and up to 3 months after cessation of cART. Serial HIV-1 antibody measurements were also obtained.

Results: Approximately one day after the transfusion, the patient had a positive HIV ELISA and confirmatory western blot (WB), but was negative for HIV DNA by PCR. The reactive bands on WB were identical in the donor and the recipient (GP120, GP41, GP31, P24 and P17). After prompt recognition of the infected transfusion and referral to a local medical center, she was started on tenofovir, emtricitabine, ritonavir-boosted darunavir (subsequently changed to lopinavir), and raltegravir 22 hours after the start of transfusion. She demonstrated no signs or symptoms of acute HIV infection and received 13 weeks of cART in a tertiary care center under direct observation. Longitudinal testing of HIV-1 DNA and RNA by both commercial and highly sensitive research assays was negative during and 3 months after stopping cART. HIV antibody became undetectable 7 months after the exposure.

Conclusions: We demonstrate that PEP initiated shortly after infusion of HIV-1 infected blood products can prevent HIV-1 transmission, even when exposure leads to positive HIV-1 serologies. The observation that no HIV-1 DNA or RNA has been detected in blood after stopping cART and that antibody became undetectable over time strongly suggests that PEP prevented establishment of a viral reservoir. This case also cautions that the presence of positive screening antibody reactivity immediately following exposure to HIV-infected blood products may be difficult to interpret and highlights the potential use of ultra-sensitive HIV-1 assays to guide management in this setting.

961 Contingency Management Facilitates PEP Completion Among Stimulant-Using MSM

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Background: Post-exposure prophylaxis (PEP) is an emergency chemoprophylactic intervention after an exposure to viral inoculum. Stimulant-using (SU) MSM are at high risk of HIV acquisition, but are a challenging population in which to implement PEP. CM is a robust intervention that provides voucher-based incentives for stimulant-use abstinence, and has been shown to be a powerful and durable substance-use intervention. We previously reported that in a single-arm pilot intervention of PEP combined with CM in methamphetamine-using MSM, time to PEP initiation, adherence, and course completion rates were not different from historical non-SU populations.

Methodology: We conducted a prospective, randomized controlled trial of CM with PEP among SU MSM at a single site in Los Angeles, California. Participants enrolled in the study were randomized to CM or non-contingent (NC) control behavioral intervention and followed prospectively. Generalized linear models were used to estimate the effect of CM on likelihood of PEP course completion, rates of medication adherence, stimulant use and self-reported sexual risk behaviors. All analyses controlled for participant sexual identity, race/ethnicity, housing status, and income.

Results: Between June, 2010 and June, 2012, 140 MSM individuals were enrolled and randomized to CM (n=70) or a NC (n=70) behavioral intervention. The participants were 37% Caucasian, 37% African American, and 18% Latino. Mean age was 36.8 (SD 10.2) years, 61% had high school education or less, and 88.4% reported an annual income ≤$30,000. 45 participants (32%) initiated PEP after a high-risk sexual exposure during the study period, with a mean exposure-to-PEP time of 35.2 hours. 29 of the 45 had evaluable adherence data. PEP course completion was significantly greater in the CM arm compared to the NC arm (AOR 7.2, 95% CI 1.1-47.9), and there was a trend towards improved medication adherence by self-report in the CM arm (AOR 4.33, 95% CI 0.76-21.86). CM participants had a greater probability of stimulant-free urine specimens vs. NC participants (IRR 1.57, 95% CI 1.12-2.22), and a trend towards reduced episodes of UAI (IRR 0.34 [95% CI 0.11-1.08). One HIV seroconversion was observed in the context of repeat exposures, and is unlikely to represent PEP failure.

Conclusions: In a randomized, controlled trial of SU MSM, CM facilitated the use of PEP by increasing rates of course completion, and suggesting a trend toward improved adherence. Reductions in sexual risk afforded by the CM intervention are a prime example of HIV prevention synergy. Despite small numbers of individuals initiating PEP, findings suggest that CM may be a useful support mechanism for the use of PEP, and potentially other biomedical prophylactic strategies in stimulant-using MSM.

Session P-V5 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Circumcision

962 Male Circumcision: Association With HIV Prevalence, Knowledge, and Attitudes Among Women

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Background: Little is known on the impact of the current rollout of voluntary medicalized male circumcision (VMMC) in Africa among women. We studied the association of sexual partners' male circumcision (MC) status with HIV prevalence among women, and their knowledge and attitudes regarding MC. This ANRS-12126 study took place in the township of Orange Farm (110 000 adults), South Africa, where a VMMC rollout program was set up in 2008. In three years, MC prevalence increased from 12% to 53%, and HIV prevalence among circumcised men was 48% lower than among other men.

Methodology: Three random independent cross-sectional surveys were conducted in 2008, 2010 and 2012 among 5 561 women aged 15 to 49. Blood samples were tested for HIV. Background information and sexual behavior, reported sexual partners' MC status, and knowledge and attitudes regarding MC were collected. Prevalence rate ratios (PRR) and adjusted PRR (aPRR) were calculated using Poisson regressions.

Results: HIV prevalence was 30.1% (831/2 438), peaking at 47.8% (328/686) in the 30 to 34 age group. Among women ever having had sex, 30.0% (1 363/3 178) reported having had only circumcised partners. HIV prevalence among these women was lower than among other sexually active women 22.4% (305/1363; 95%CI: 20.3% to 24.9%) vs 36.6% (1 164/3 178; 95% CI: 35.0% to 38.2%), with PRR=0.72; 95%CI: 0.64 to 0.80; p<0.001, and aPRR=0.85; 95%CI: 0.76 to 0.95; p=0.004.

Among the reported 3 571 non-spousal sexual partnerships of the last 12 months, prevalence of consistent condom use was 37.5% (866/2 309) with circumcised partners and 38.6% (487/1 262) with uncircumcised partners (aPRR=1.00; 95%CI: 0.91 to 1.09; p=0.952).

Among the 2 200 women having had sex with circumcised and uncircumcised men, 74.4% (1 636) reported preferring circumcised partners, 3% (66) uncircumcised partners and 22.6% (498) had no preference.

Between 2008 and 2012, the proportion of women willing to have their male children circumcised increased from 83.0% (861/1 037) to 96.0% (2311/2 407) p<0.001.

In 2010 and 2012, among 3 496 women, 90.6% reported that circumcised men could become infected with HIV. About 1% believed that they were fully and 8.6% partially protected when having unprotected sex with a circumcised HIV positive partner. Moreover 55.1% asserted that condom use was easier for circumcised men, 20.4% that it was not, and 24.5% did not know.

Conclusions: The findings on the association of women's HIV prevalence with their sexual partners' MC status are probably due to the lower HIV prevalence rate among circumcised men. Data reveals women's satisfactory knowledge and attitudes regarding MC. This study is encouraging for the current rollout of VMMC. Incidence studies are needed to investigate the association of VMMC rollout with HIV among women.

963 Lower Odds of HIV Among Circumcised MSM in China and Interaction With Anal Sexual Role

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Background: Male circumcision reduces heterosexual acquisition of HIV, but evidence for its efficacy for preventing transmission among men who have sex with men (MSM) is unconvincing. We evaluated the association of male circumcision and odds of HIV and syphilis among Chinese MSM and the interaction between circumcision and anal sexual role on the relationship.

Methodology: During 2010-2011, we conducted a cross-sectional study among 1155 MSM who were living in Beijing, China. Each participant completed a standardized questionnaire to collection demographic/ sexual behavior information. Circumcision status was evaluated by both questionnaire self-reporting and by genital examination; and both HIV and syphilis infections were assessed with blood screening serology and confirmatory testing. We compared two methods for ascertaining circumcision; we performed both stratified analysis by anal sex role and multivariate logistic regression analysis for assessing the relationship of circumcision and HIV risk.

Results: Compared to uncircumcised men who practiced predominantly receptive or versatile anal sex, the adjusted risk of HIV among uncircumcised men practicing predominantly insertive anal sex was lower by 57% (adjusted odds ratio [aOR], 0.43; 95% confidence interval [CI], 0.32-0.59). Among circumcised men practicing predominantly receptive or versatile anal sex, it was lower by 52% (aOR, 0.48; 95% CI, 0.22-1.02), and among circumcised men practicing predominantly insertive anal sex was lower by 85% (aOR, 0.16; 95% CI, 0.04-0.65). After adjusting for demographic covariates and anal sex role, male circumcision was associated with a 54% lower odds of being HIV seropositive (aOR, 0.46; 95% CI, 0.24-0.89). Circumcision was not significantly associated with syphilis protection (aOR, 0.79; 95% CI, 0.45-1.42). The circumcision rate by self-report (10.4%) was higher than by genital exam (8.2%; *Kappa*=0.809, *P*<0.01). Prevalence of HIV in those MSM without prior known HIV infection was 5.3% (48/913). Syphilis prevalence in all MSM was 26.1% (298/1140).

Conclusions: Circumcised MSM were less likely to have acquired HIV, especially among men practicing predominantly insertive anal intercourse. Circumcision may be a more viable and efficacious global HIV prevention strategy for MSM that hitherto realized. Given methodological limitations in observational studies, a randomized clinical trial is needed to evaluate circumcision acceptability and efficacy among MSM in diverse settings.

964 Client Experiences of Odor Associated With PrePex™ Device Male Circumcision in Botswana

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Background: PrePex™ is a male circumcision device currently being studied for safety and acceptability. The foreskin tissue remains intact for the 7 days PrePexTM is worn, creating a mirobiome that favours anaerobic bacterial growth that can be malodorous. Some clients complain of malodor while wearing PrePex(TM), which might influence the acceptability of the device. We present preliminary results on PrePexTM client experiences, perceptions, and practices related to malodor, about which no detailed report exists in present literature.

Methodology: We surveyed 734 of the 805 target sample of men aged 18-49 years who enrolled in an on-going PrePexTM safety and acceptability study in Botswana between May and September 2013. On the device removal visit, participants were asked about odor experiences, including noticeability, effect on activities of daily living (ADL), and remedies to combat odor. The Wilcoxon Two-Sample Test was performed to assess statistical significance of differences in the responses.

Results: 734 men of median age 26 years (SD = 7.08) responded to odor survey questions. 688 (94%) men reported to have noticed an unpleasant odor while the PrePex device was in situ. Of these, 37.1% noticed it by day 2 post-placement. A total of 45.7% of clients who noticed an odor were not disturbed by it, while 40.1% reported "some discomfort," and 14.2% felt "very uncomfortable" from the odor. A total of 17.2% of clients reported that another person, mainly a partner or another family member, also noticed the odor. There was no association between family size and likelihood of another person to notice smell (p&gt0.05). Regarding ADLs, 69.8% of those reporting odor reported no disruptions, 4.9% reported "a lot" of disruption, and 7.4% forfeited an activity due to the odor. 25% of odor-reporters tried something to combat the odour, most commonly bathing or use of body perfumes. Of these, an equal proportion (23.3%) of clients felt remedies "helped a lot" as those who felt remedies "did not help". Clients with large family size were more likely to try

combating odor than those with smaller families (p &lt0.02). One participant self-removed the foreskin on day three post placement due to the odor, but suffered no clinical complications. 94.8% of clients who reported an unpleasant odor also reported that they would still recommend PrePexTM method to others.

Conclusions: The majority of clients in this study noticed an odor two days or later after device placement, but only a small proportion reported major disruption in routine activities. Odor may not be a major barrier to PrePexTM device circumcision in Botswana, but it merits attention. Research on measures to prevent or manage odor is needed. Meanwhile, a message on odor should be part of client counselling before the PrePexTM device procedure.

965 Penile Cytokines Correlate With HIV Target Cells and Decrease After Circumcision in Rakai, Uganda

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Background: Adult male circumcision (MC) reduces HIV acquisition by >50% in heterosexual men, but the mechanism of this protection is not completely understood. Recent evidence showed that MC reduces penile pro-inflammatory anaerobes; and since HIV preferentially infects activated CD4 T cells, this may represent one protective mechanism of MC. We hypothesized that MC reduces activated CD4 T cells in penile tissue; however, penile tissue cannot be biopsied post circumcision. We therefore first identified cytokines in penile swabs that correlate with the number of activated CD4 T cells in foreskin tissue. We measured these cytokines in swabs collected in a large, randomized trial of MC pre- and post-circumcision as a surrogate of changes in activated CD4 T cell density following circumcision.

Methodology: Foreskin tissue and coronal sulcus swabs were collected in a cross-sectional study of 89 men undergoing elective MC. Tissue density of HIV-target cells was determined with a combination of flow cytometry and immunofluorescence; levels of 14 cytokines and chemokines were measured in swabs with an electrochemiluminescent multiplex ELISA. We then measured cytokine and chemokine levels in swabs collected from 111 men randomized to circumcision and 107 uncircumcised controls during a clinical trial of MC in Rakai, Uganda. Swabs were collected at enrolment and at 6, 12 and 24 months, and cytokine levels were compared between control and intervention men using generalized linear modeling.

Results: In the cross-sectional study, we found that levels of IL-8 in coronal sulcus swabs correlated with the tissue density of highly HIV-susceptible CD4 T cells, including Th17, Th1 and CCR5+ CD4 T cells (all $p<0.05$), but not Tregs. In the longitudinal study, pre-circumcision cytokine levels were similar between control and intervention men, but after 6 months MC was associated with a reduction in IL-8 relative to controls (adjusted PRR 0.67, 95% CI: 0.52, 0.87), and this differential increased over the 2 years of follow-up. No cytokine changes were observed in uncircumcised men, and MC was not associated with changes in vaginal cytokines among female sexual partners.

Conclusions: Levels of IL-8 on the foreskin surface correlates with the density of highly HIV-susceptible CD4 T cell populations in the underlying foreskin tissue. Male circumcision is associated with reduced IL-8 on the coronal sulcus, suggesting reduced HIV acquisition after MC may be partly due to a reduction in penile inflammation, and thus HIV-susceptible cells, in remaining penile tissue.

966 HIV Shedding From Male Circumcision Wounds in Rakai, Uganda

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Background: A randomized controlled trial of circumcision of HIV-positive men reported increased HIV transmission to female partners among men who resumed sexual intercourse prior to wound healing. The effect of male circumcision (MC) on penile HIV wound shedding post-operatively is unknown. We conducted a prospective cohort study among men in Rakai, Uganda to assess HIV shedding post-MC.

Methodology: HIV shedding was evaluated among 189 HIV-infected men aged 12 years and above prior to MC, during surgery, and then for six weeks post-operatively in Rakai, Uganda. All men underwent dorsal slit MC. There were 60.5% (112/185) of men who had CD4 count ≥350 mm^3 and 39.5% (73/185) who had a CD4 <350 cells/mm^3. Weekly penile lavages of the MC surgical wounds were tested for HIV shedding and viral load using a real-time quantitative PCR assay (Abbott Molecular, Abbott Park, IL). Viral load was log_{10} transformed.

Results: HIV shedding was detected in 10.9% (20/184, 95%CI = 6.8%-16.3%) of men prior to MC and 60.1% (107/178, 95%CI = 52.5%-67.4%) of men during surgery immediately following foreskin removal. HIV shedding was detected in the post-surgical wound lavage at one or more follow-up visits in 41.3% of men (78/189). Compared to the pre-MC assessment, the probability of HIV shedding was significantly higher after MC at week one (17.9%, 30/168, 95%CI = 12.4%-24.5%), week two (30.2%, 49/162, 95%CI = 23.3%-37.9%) and week three (21.6%, 36/162, 95%CI = 15.5%-28.7%), and then declined at week four (6.5%, 11/168, 95%CI = 3.3%-11.4%) and week six (2.5%, 4/158, 95%CI = 0.7%-6.4%), Wilcoxon rank sum $p<0.001$. The median and interquartile range of log_{10} viral load among men with detectable viral shedding were: highest at week one (2.99, IQR = 2.59-3.45) and week two (3.20, IQR = 2.83-3.79), compared to week three (2.54, IQR = 2.27-2.94), week four (2.43, IQR = 2.24-3.73) and week six (2.46, IQR = 2.27-2.70). Plasma viral load did not change after MC and was not correlated with lavage viral load (R=0.07).

Conclusions: HIV shedding is increased from MC wounds, but returns to baseline approximately four weeks after surgery. Sexual abstinence and subsequent condom use are essential to reduce male-to-female HIV transmission following MC.

Session P-W1 Poster Session
Tuesday March 4, 2014, 2:30 PM–4:00 PM Exhibit Hall D
Cascade of Care and Testing

967 Finding Unawares: High Levels of Undiagnosed HIV Infection Among Moscow Men Who Have Sex With Men

Andrea L. Wirtz[1,2], Carla E. Zelaya[2], Noya Galai[3], Alena Peryshkina[4], Vladimir Moguilnyi[4], Petr Dzhigun[4], Irina Kostetskaya[4], Carl Latkin[5], **Chris Beyrer[2]**
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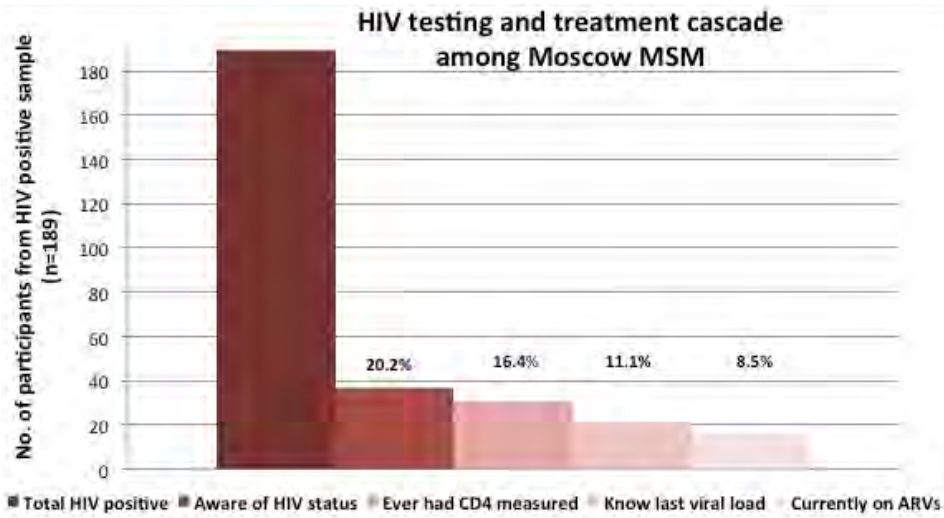
Background: Little is known about HIV testing behaviors of gay, bisexual and other MSM in Russia. Public sector testing is named based, and many MSM opt out of the system. New policies and laws may further restrict MSM from seeking HIV services. HIV prevalence, testing history, and correlates of undiagnosed HIV infection and risks were investigated in an anonymous MSM-friendly clinic in Moscow City.

Methodology: Participants were recruited via respondent driven sampling (RDS). Study activities included completion of an interviewer administered survey and biologic specimens for HIV testing. We examined the HIV testing/treatment cascade, socio-behavioral factors, and sexual identity characteristics. HIV prevalence was adjusted for participants' network sizes. The proportion of previously undiagnosed HIV infections and correlates undiagnosed HIV infection were explored.

Results: 1433 MSM living in Moscow were recruited via RDS methods. Among this predominantly Russian born (85.0%), young population (median age 29 yrs.), most men self-identified as gay (55.0%) or bisexual (42.9%). Median age of first sex with a man was 18 years. Reported sexual risk practices in the last 12 months were high: 50.1% reported five or more anal sex partners (last 12mo.), 18.5% reported offering money/drugs in exchange for sex, 19.9% received money/drugs in exchange for sex, and 80.7% reported alcohol and/or drugs prior to sex. Men reported having only male partners (64.2%) or both male and female partners in the last 12mo. (35.1%). The majority of participants reported a lifetime history of HIV testing (85.5%) and 91.6% of those had received the result. The adjusted HIV prevalence among participants providing samples (n=1171) for HIV testing was is 12.4 (95% CI: 9.3 - 16.1; unadjusted prevalence was 15.6%). Of participants testing positive or previously tested, 79.8% (n=146/183) had a previously undiagnosed HIV infection. Only 8.5% (16/189) of MSM with HIV infection were receiving ART. Among MSM living with HIV who self-identified as gay, 72.4% had undiagnosed infection, compared to 89.9% of bisexual men living with HIV infection (p=0.013).



Conclusions: This newly described population understands the importance of and utilizes HIV testing services, yet high risk practices and a high level of undiagnosed and untreated HIV infection persist. Moscow MSM will seek and use anonymous and safe HIV testing, and urgently need it. These findings have implications for public health programming and clinical care.

968 Increases in HIV Testing Among MSM: US National HIV Behavioral Surveillance System, 2008-2011

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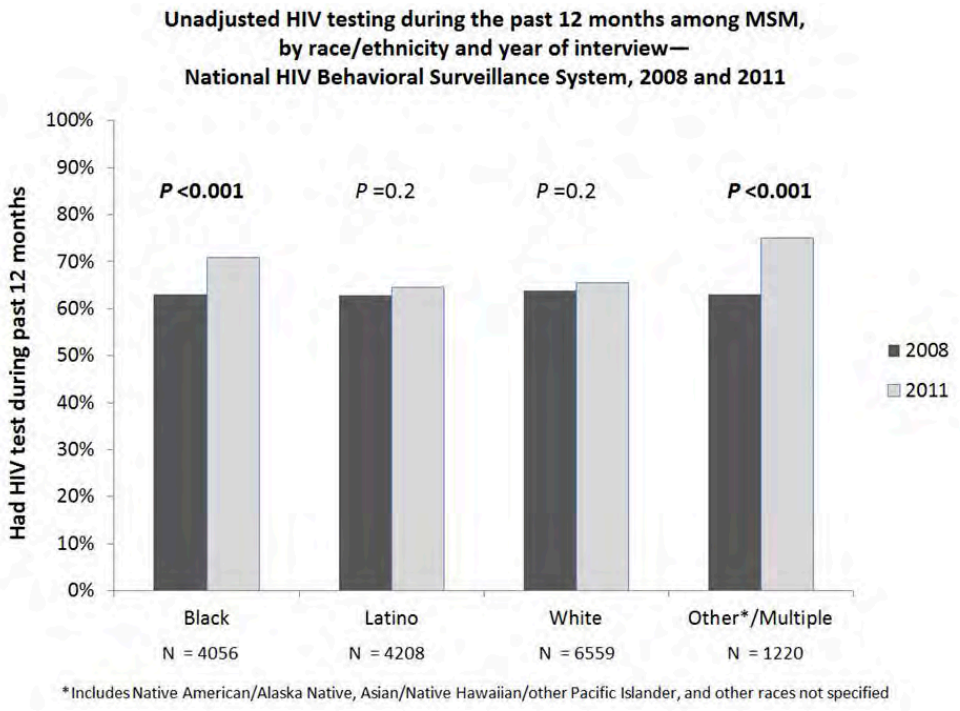
Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, Atlanta, GA, United States

Background: In 2010, 66% of new HIV infections in the United States occurred among men who have sex with men (MSM, including men who inject drugs); 35% of these MSM were black. HIV testing is an essential first step in HIV care and treatment for HIV-positive individuals. CDC began expanded HIV testing initiatives in 2007, focusing initially on blacks. A second focus, on MSM of all races, was added in 2010. We assessed changes in HIV testing behavior among MSM from 2008 to 2011.

Methodology: We analyzed data from the National HIV Behavioral Surveillance System. Men included in the analysis sample were recruited and interviewed in 2008 and 2011 at venues in 20 metropolitan statistical areas (MSAs), were ≥18 years old, reported at least one male sex partner in the past 12 months, and did not report a positive HIV test result more than 12 months prior to interview. We compared the proportions tested recently (past 12 months) from 2008 and 2011, using chi-square analysis, overall and by race/ethnicity. To determine if interview year was associated with recent HIV testing, we used a Poisson model with robust standard error to calculate adjusted prevalence ratios [APR] and 95% confidence intervals [CI]. The model was adjusted for race/ethnicity, age, education, income, and MSA; to see if temporal changes in recent HIV testing varied by race/ethnicity or age, we included interaction terms for interview year by race/ethnicity and age.

Results: We included 16,069 MSM (2008: 7,943; 2011: 8,126). In unadjusted analyses, recent testing increased from 63.3% in 2008 to 67.4% in 2011 overall ($P<0.001$) and from 63.0% to 70.9% among black MSM ($P<0.001$; see figure). MSM of other or multiple races also experienced an increase, from 63.1% to 75.1% ($P<0.001$). Model results indicated an overall increase in recent testing (APR=1.09, CI=1.06-1.12) and that the increase varied significantly by race/ethnicity (the interaction of year with age was not significant). Increases were largest for black MSM (APR=1.12, CI=1.07-1.17) and MSM of other or multiple races (APR=1.20, CI=1.11-1.30). The proportions tested did not change significantly for Latino MSM (APR=1.02, CI=0.98-1.08) or white MSM (APR=1.03, CI=0.98-1.07).



Conclusions: HIV testing increased among black MSM and MSM of other or multiple races from 2008 to 2011. Despite gains in testing, improved coverage is still needed, consistent with CDC recommendations. Increasing the number of MSM tested and linked to care will improve health outcomes and may reduce transmission of HIV.

969 Feasibility of HIV Self-Test Vouchers To Raise Community-Level Serostatus Awareness, Los Angeles

Robert Marlin[1], Sean Young[1], Greg Wilson[2], Jeffrey P. Rodriguez[3], Joe Montes[4], Jose Ortiz[5], Rhea Mathew[5], Zoe Glick[6], Jeffrey D. Klausner[1]

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Background: About 25% of HIV-infected individuals are unaware of their status and may cause up to half of all new HIV cases. In particular, men who have sex with men (MSM) and minorities are at high risk for being sero-unaware and would benefit from increased testing. The FDA recently approved the OraQuick® In-Home HIV Test, a new method to increase HIV serostatus awareness and testing. While past studies show that the test is highly acceptable, none have determined how to best promote it to high-risk groups. We examined the feasibility of implementing a voucher program for free OraQuick® In-Home HIV Test kits targeting high-risk MSM in Los Angeles.

Methodology: The following measures were used to determine feasibility: (1) the creation of a user-friendly voucher describing the OraQuick® test and where and how to redeem the voucher, (2) the establishment of a redemption and third-party payment system with a retail location, (3) the formation of relationships with community based organizations (CBOs) and other groups for dissemination, and (4) the use of social media such as Facebook® to promote the voucher. In addition, we determined the feasibility of recruiting and enrolling voucher users for interviews by: (1) the attachment of a survey recruitment flyer to the voucher, (2) the establishment of an anonymous call-in survey system, and (3) the willingness of voucher users to answer questions on their HIV testing behaviors and results. Analyses were done with Microsoft Excel® to calculate descriptive statistics and Facebook Ads Manager® to measure Facebook® use.

Results: We created a paper voucher for free OraQuick® kits and partnered with Walgreens® to develop a trackable redemption and payment system. Walgreens was chosen as a retail partner based on the location of its stores. Our Facebook® ads reached 28,910 users from July 25 through September 27 2013. Between July 19 and October 8 2013, we supplied 641 vouchers to 3 CBOs, 3 student distributors, and one clinic. Distributors reported dispensing 196 (30.6%) of the 641 supplied vouchers to clients and 44 (22.4%) clients redeemed their vouchers. Twenty-eight (63.6%) of the 44 who redeemed their vouchers participated in our survey, one of whom newly tested HIV-positive and was linked to care.

Conclusions: Our findings suggest that the development of a voucher system to promote HIV self-testing kits is feasible. It is also feasible to track voucher use, collect information anonymously from voucher users, and identify new HIV cases. Our methods could be used to assess whether a self-testing promotion system enhances the community level of serostatus awareness. Continued work should be done to expand the voucher program and compare it with other methods of self-testing promotion and traditional HIV testing.

970 Availability, Accessibility, Price of Rapid HIV Self-Tests, New York City Pharmacies, Summer 2013

Julie E. Myers[1,2], Olivia El-Sadr Davis[3], Elliott R. Weinstein[3], Molly Remch[3], Amy L. Edelstein[4], Blayne H. Cutler[1], Julia A. Schillinger[5,6]

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Background: The US FDA recently approved an over-the-counter, rapid HIV self-test for personal use. Since October 2012, kits have been available in US pharmacies (manufacturer's suggested retail price, or MSRP, $39.99). We conducted a survey of NYC pharmacies to assess the availability, accessibility, and price of rapid HIV self-tests.

Methodology: All NYC pharmacies (n=2568) were stratified into tertiles using the HIV diagnosis rate of the neighborhood in which the pharmacy was located using surveillance data. A random sample of 250 pharmacies was taken from the first (high morbidity neighborhood [HighMN]) and third (low morbidity neighborhood [LowMN]) tertiles, since we were primarily interested in disparities in neighborhood access to the self-test kit associated with the burden of new HIV infections. Pharmacies were excluded if: closed during business hours, non-retail, or >10 minute walk from a subway station (except for Staten Island) by online mapping. Project staff visited the pharmacy, observed whether it was an independent or major chain pharmacy (>50 locations in NYC), asked a pharmacist/pharmacy technician about the kit's availability/location, visually inspected the pharmacy for kits, and determined price. Handheld devices were used for data collection. We conducted bivariate analyses using the chi-square test for dichotomous variables and the *t*-test for continuous variables.

Results: There were 361 pharmacies in the final sample (161 from LowMN and 200 from HighMN). Overall, kits were available in 27% of pharmacies [30% of LowMN and 24% of HighMN (p=0.13)]. Kits were available in 84% of chain pharmacies (which made up only 24% of pharmacies surveyed) compared to only 9% of independent pharmacies (p<0.01). There was no difference in aisle display location, but kits were more often kept behind the pharmacy counter in HighMN (77%) vs. LowMN (55%, P<0.03). In pharmacies that had kits available (n=97), 80% of pharmacists correctly stated kit availability, and 88% of those pharmacists correctly identified ≥1 kit location. Median kit price was US$42.99 (range: US$32.99-50.00); 66% of pharmacies set kit price above MSRP. There was no price difference by neighborhood tertile.

Conclusions: Approximately 1 year after FDA approval, rapid HIV self-test kits were available in less than a third of pharmacies in LowMN and HighMN in NYC but in most chain pharmacies. Pharmacies in areas of greatest need for HIV prevention were more likely to require interaction with the pharmacist to obtain the kit - a potential obstacle to purchase. Price was often set above MSRP and did not differ by neighborhood disease burden. To make the self-test kit a viable method for low-threshold testing in HighMN, efforts are needed to encourage more pharmacies to carry them and display them more openly.

971 Acceptability & Affordability of Self HIV Testing in an Urban Neighborhood With 3% Seroprevalencee

Amy Nunn[1], Philip Chan[1], Caitlin Towey[1], Joanna Poceta[1], Sophie Feller[2], Stacey Trooksin[3]

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Background: The USFDA recently approved the "OraQuick® In-Home HIV Test," the first over-the-counter self test for HIV, which retails for approximately US $40. Little is known about the self test's acceptability, accessibility and affordability in the United States' most heavily impacted neighborhoods and among individuals at highest risk for acquiring HIV.

Methodology: We explored acceptability, accessibility and affordability of self testing among 994 community residents participating in a community-based HIV and HCV testing, treatment and linkage to care program called "Do One Thing". Do One Thing takes place in a Philadelphia zipcode with 3% HIV seroprevalence and limited HIV testing and treatment services. We conducted a survey about HIV risk behaviors, demographics and attitudes related to self HIV testing, including willingness to use and pay for self tests, and whether individuals would seek medical care if they were to test positive.

Results: HIV seropositivity among this population was 1.2%. Participants reported high-risk behaviors; 23% were engaged in concurrent sexual partnerships, 24% believed their partners were engaged in concurrent partnerships and 15% reported injection drug use or cocaine use. Eleven percent were men who have sex with men and 88% were African American. Participants also reported socioeconomic factors frequently correlated with HIV infection; 39% were uninsured, 56% lived below the poverty line, and 37% had incarceration histories. Participants had very positive attitudes about self HIV testing and linkage to care (Figure 1). The overwhelming majority was willing to self test (91%) and also believed their families, friends or loved ones would be willing to self test (78%). Almost all participants reported they would seek medical care if they were to test HIV-positive (96%). Although most were willing to pay for the test (57%), only 26% of participants were willing to pay more than $20 and only 14% were willing to pay the current market price.

Conclusions: Self-testing was highly acceptable in this neighborhood with high rates of HIV infection and most respondents reported they would seek medical care if they tested positive. The self test is an important tool for expanding access to testing in heavily impacted neighborhoods but its price may be prohibitively expensive for the highest risk populations. Public health programs should consider financing self-testing and linkage to care programs in heavily impacted neighborhoods.

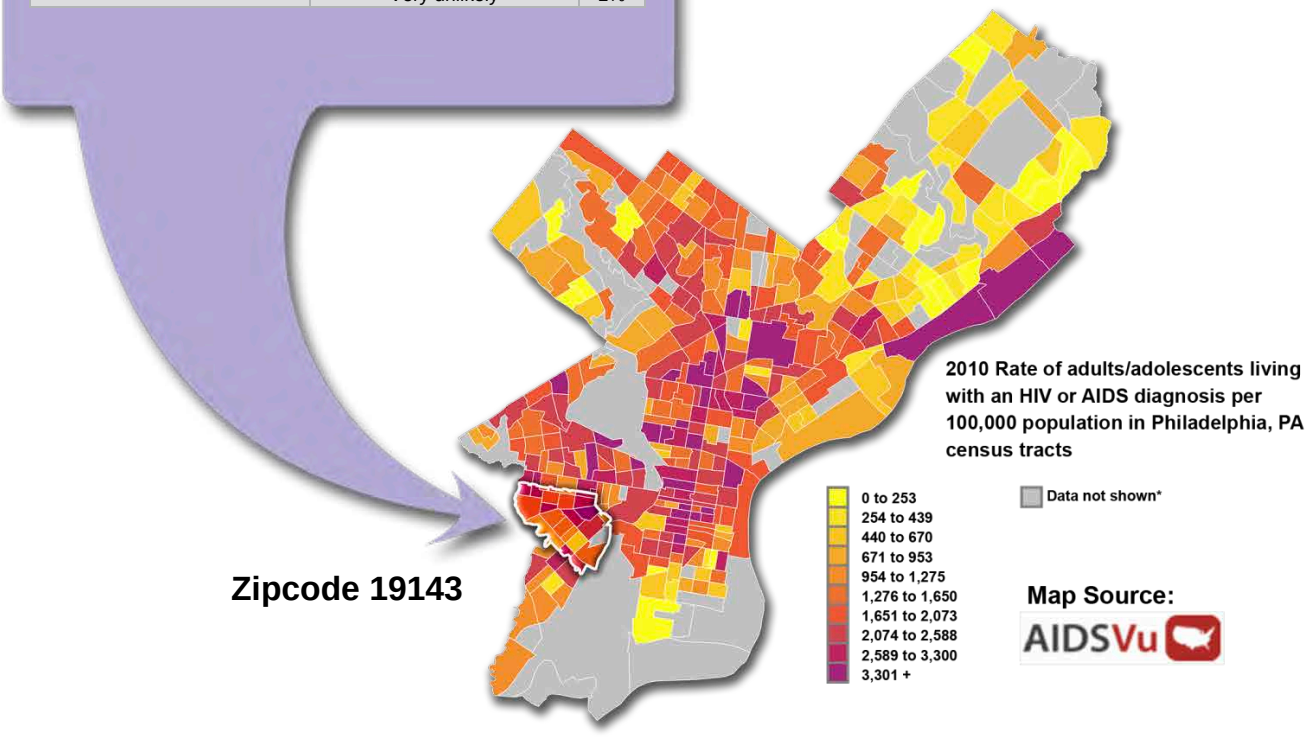
Figure 1. Attitudes about self HIV testing in a Philadelphia neighborhood with high rates of HIV infection (N=994)

Attitudes about home-based testing

	Answer	%
If we provided your friends, family, or loved ones with a free, home-based HIV test kit, how likely would they be to take the test?	Very likely	43%
	Likely	35%
	Neutral	8%
	Unlikely	12%
	Very unlikely	2%
If we provided you with a free, home-based HIV test kit, how likely would you be to take the test?	Very likely	60%
	Likely	31%
	Neutral	2%
	Unlikely	6%
	Very unlikely	1%
How likely would you be to buy a home-based HIV test kit at your local pharmacy?	Very likely	22%
	Likely	35%
	Neutral	8%
	Unlikely	20%
	Very unlikely	15%
How much would you be willing to pay for a home-based HIV test at your local pharmacy?	Not interested in buying a home-based HIV test kit	29%
	$0-10	18%
	$11-20	27%
	$21-30	10%
	$31-40	2%
	$41-49	4%
	More than $50	10%
If you took a home-based HIV test and tested positive, how likely would you be to go to the doctor afterwards?	Very likely	90%
	Likely	6%
	Neutral	2%
	Unlikely	1%
	Very unlikely	1%

Demographics

	Answer	%
Gender	Male	52%
	Female	48%
Self-identified sexual orientation	Heterosexual	89%
	Gay/Lesbian	5%
	Bisexual	6%
Race	African American	88%
	African	3%
	White	4%
	American Indian or Alaska Native	1%
	Asian	1%
	Bi-racial or multi-racial	1%
	Other	2%
Household income	Less than $14,999	56%
	$15,000 to $29,999	15%
	$30,000 or more	16%
	Decline to Answer	13%
Health insurance status	Insured	61%
	Uninsured	39%



972 Getting To Zero: HIV Testing and Counselling in Kenya - Results From a Population-Based Survey

Anne Nganga[1], Wanjiru Waruiru[2], Carol Ngare[1], Victor Ssempijja[3], Patricia Oluoch[4], Inviolata Njoroge[5], Thomas Gachuki[6], William Maina[1], Rex Mpazanje[7], Andrea A. Kim[3]
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Background: HIV testing and counselling (HTC) is a gateway into HIV prevention and treatment programs. In 2007, only 36% of persons had ever been tested for HIV. The universal access target for HIV testing in is 80% of the population. Nationally-representative data on HIV testing are important to evaluate Kenya's progress towards reaching the universal target.

Methodology: In 2012, Kenya conducted a national household survey among persons aged 18 months-64 years. Respondents aged 15-64 years were administered a questionnaire and provided blood for centralized testing. Home-based testing and counselling (HBTC), using rapid HIV testing kits based on the national HIV testing algorithm was offered to participants to learn their HIV status. Point-of-care CD4 T-cell count testing was conducted among persons testing HIV+ in HBTC. Data were weighted to account for sampling probability and adjusted for for non-response. We describe HIV testing among survey respondents aged 15-64 years. Results from HBTC are based on a subset of participants that accepted HBTC.

Results: Of 13,720 adults interviewed, 71.6% (80.4% women, 62.5% men) had ever been tested for HIV. Among those, 56.1% had been tested in the past year, 69.3% had been tested more than once, and 37.2% had been tested with a sexual partner. Fifty-three percent of HIV-infected persons did not have correct knowledge of their HIV status. Incorrect knowledge of HIV positive status was higher among men [62.0%; 95% confidence interval (CI) 53.4-70.5] compared to women (47.8%; 95% CI 42.1-53.4), youth aged 15-24 years (81.0%; 95% CI 72.3-91.7) compared to persons aged 25-34 years (58.9%; 95% CI 50.5-67.4), and persons who did not use condoms with their most recent sexual partner in the past 12 months (67.7%; 95% CI 60.3-75.1 vs. 37.1%; 95% CI 29.1-45.2). Overall, 9,874 (72.0%) participants accepted HBTC. Among those, 361 (4.1%; 95% CI 3.3-4.9) tested HIV+, and of those, 94% accepted POC CD4+ T-cell count testing. Of those, the median CD4+ T-cell count was 423 cells/mm^3 (interquartile range: 250-573), and 40.3% (95% CI 30.8-49.6) of those who were antiretroviral therapy (ART) naïve were eligible for ART based on current national guidelines (CD4≤350 cells/mm^3).

Conclusions: HIV testing has improved over the last five years, nearly reaching the universal access target in Kenya. However, correct knowledge of HIV status among HIV-infected persons remains low. HTC should be expanded to reach more men and youth, and strategies are needed to increase repeat testing for persons at risk. HBTC for HIV can be successfully integrated into population-based surveys as a tool to identify persons in need of treatment. However, HIV prevalence data from HBTC will be an under-representation of national prevalence due to selective participation.

973 Counselor Based Versus Integrated Routine HIV Screening in an Urban Emergency Department

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Background: Since 2006, St. Luke's-Roosevelt (SLR) Hospital has offered Emergency Department (ED) patients free HIV testing. Starting in July 2010, the Spencer Cox Center for Health partnered with the ED to move from a counselor-based to a routine, integrated model of oral rapid HIV testing in the hospitals' two EDs in New York City (NYC). Under this integrated model and in compliance with the 2010 New York State (NYS) HIV Testing Law, all ED patients aged 13-64 years old were routinely offered rapid HIV testing at triage; and result notification, counseling, and testing was performed by teams of medical providers and nursing. The aim of this study is to describe the demographic population profile of patients who underwent HIV rapid testing and to analyze any significant differences in the populations reached by HIV testing in the ED before and after the implementation of routine HIV testing.

Methodology: Data was collected from 5/2006 to 6/2013 of all adolescent and adult patients who underwent HIV rapid testing (RT) unless they declined or were ineligible [Level I or II trauma, <13 years old]. After verbal consent, HIV testing (OraQuick® Advance Rapid HIV-1/2 Antibody test) was performed. Confirmatory labs were performed following preliminary positive results. All demographic characteristics of patients who underwent HIV testing between 5/2006-6/2010 (counselor-based) were compared to those patients testing between 7/2010-6/2013 (routine testing), using Fisher Exact and Wilcoxon tests. Factors associated with testing positive on the rapid oral test were analyzed in multivariate logistic regression.

Results: 48274 HIV tests were conducted. Majority of patients were female (54%; N=26216) and insured (71%; N=34371) with a median age of 34 yrs (range=13-99 yrs). 87% of testing occurred during the routine testing period (N=42198), showing a 7-fold increase in testing volume after transition to an integrated model (1,453 in 2009 vs 11,443 in 2010). There were no significant differences in race, gender, insurance status, and age between patients who underwent HIV testing in the ED using the both models. 328 (0.7%) patients tested HIV positive; 258 (79%) during the routine testing period. In multivariate analysis, significant predictors of testing HIV positive were male gender ($p<0.001$), Medicaid ($p<0.001$), uninsured ($p<0.001$), Hispanic ($p=0.018$), and Black ($p<0.001$).

Conclusions: Routine HIV testing in the ED was feasible and allowed for significant increases in patient access to HIV testing and in identification of HIV infections. Patients who tested HIV positive were more likely to be male, uninsured, and non-White; highlighting the importance of having free and routine HIV testing in the EDs of large urban hospital centers.

974 Low Feasibiliy Rate of Self Testing With a Finger-Stick Whole Blood Test

Guillaume Gras[1], Pascal Le Bret[2], Jean Francois Dailloux[2], Gwenael Le Moal[3], Aurelia Raoult[4], Gaelle Fajole[5], Penelope Hodges[5], Claire Poirier[1], Frédéric Bastides[1], Louis Bernard[1]

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Background: Self HIV testing would contribute measurably to public health by helping more infected individuals become aware of their HIV status and therefore reducing HIV transmission. In 2012, the FDA approved the OraQuick In-Home test with oral (saliva) swab. INSTI HIV1/HIV2®, a finger-stick whole blood test, used for years by healthcare professionals, more sensitive, provides a test result in 5 minutes and could be an alternative. Little is known about the feasibility of self-testing with finger-stick whole blood tests.

Methodology: We conducted a prospective monocentric study (September 2013). Eligibility requirements included: > 18, HIV positive patient without mental or physical handicap. After agreement, patients performed self testing with INSTI HIV1/HIV2® with a detailed notice. The test was considered as correct if patient performed all steps alone with a correct interpretation of the results.

Results: Forty patients (mean age = 45.8, sex ratio M/F = 3.4) were included with primary education (13), secondary education (14), tertiary education (13). Viral load was < 1,6 log for 25 patients (62.5%). Five (12.5%) patients did not able to complete all steps of the test. Of the remaining 35 HIV positive patients, 25 had a positive test result (sensitivity=71.4%), 1 negative (patient with undetectable viral load), 2 invalid, 7 non-reactive. Mean time to perform testing was 6 minutes 40 s (min = 3 min 20s, max = 13 min 30s): mean time for blood collection = 3 min 50 s and for mixing and reading = 3 min 20 s. The test was correctly performed by 19 patients (47,5%). Main reasons for failure were lack of blood (11), wrong lancet utilization (4), and in the mixing of the samples (3). Factors associated with success were: age (40.4 vs 50.8, p=0.02) and tertiary education (53% vs 14%, p = 0.01). The pain was low for 21 (52.5%) patients and 19 (47.5%) patients declared no pain. The notice was considered as adapted for 27 patients and relatively adapted for 13. Performing the test was considered very easy for 22 patients and quiet easy for 18. Thirty four (85%) patients would recommend this test to a friend. Because of low rate of feasibility, the study was stopped.

Conclusions: Feasibility of self testing with INSTI VIH1/VIH2® appears to be low in our study. The main reason for failure was blood collection. However a finger-stick whole blood test does not appear to be a barrier to self testing. An improvement in the technique of whole blood collection should be made.

975 Estimating the Size of the Undiagnosed HIV Population in the Netherlands by Disease Stage

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Background: Previous studies showed that a large proportion of HIV-infected individuals in the Netherlands are unaware of their infection. As recent estimates of the size of this group are not available, we sought to estimate the number and proportion of undiagnosed individuals stratified by risk group and by CD4 cell count stratum.

Methodology: Using a newly developed adaptation of a previously published back-calculation method, we estimated the annual number of new HIV infections over calendar time as well as CD4 count stratum-specific rates of diagnosis by fitting a model of disease progression to observed data from the ATHENA national observational HIV cohort on HIV and AIDS diagnoses and CD4 counts at the time of diagnosis. The model incorporated different stages of HIV infection characterised by CD4 counts and described disease progression in the absence of antiretroviral treatment from the time of infection to HIV diagnosis or onset of AIDS. Rates of progression between the different disease stages were based on historical cohort data on untreated HIV-infected patients. We considered men who have sex with men (MSM), injection drug users (IDU), and heterosexual men (HET-M) and women (HET-W) originating from the Netherlands, i.e., groups consisting mostly of non-migrants. Bootstrap techniques were used to calculate 95% confidence intervals (CI).

Results: By the end of 2011, a cumulative number of 19,761 HIV infections - 15,152 in MSM, 1170 in IDU, 1189 in HET-W, and 2250 in HET-M - were estimated to have occurred since the start of the epidemic in the 1980s (see Table). Altogether, 2938 (15%) of all infections were still undiagnosed: 2207 (15%) MSM, 16 (1%) IDU, 134 (11%) HET-W, and 581 (26%) HET-M. Amongst the undiagnosed individuals, 1142 (52%) MSM, 4 (28%) IDU, 53 (40%) HET-W, and 240 (41%) HET-M were estimated to have a CD4 cell count ≥500 cells/mm^3. The number of undiagnosed individuals with CD4 counts below 350 cells/mm^3 was 600 (27%) for MSM, 8 (51%) for IDU, 51 (38%) for HET-W, and 217 (37%) for HET-M.

Conclusions: Although MSM formed the largest group of HIV-infected individuals unaware of their infection, the estimated CD4 distribution suggested that approximately half of them were in an early stage of infection and had been infected only recently. Approximately 30% of the undiagnosed individuals were already in immediate need of treatment. This proportion was even higher in groups other than MSM although absolute numbers of undiagnosed individuals in these groups were much smaller.

Number and percentage of (undiagnosed) infections, overall and by disease stage				
	MSM	IDU	HET-W	HET-M
Cumulative number of infections by the end of 2011	15152 [14926-15441]	1170 [1110-1241]	1189 [1074-1238]	2250 [2088-2351]
Undiagnosed, Overall, N	2207 [2090-2393]	16 [12-25]	134 [94-180]	581 [470-662]
Undiagnosed, Overall, %	15 [14-16]	1 [1-2]	11 [8-15]	26 [21-29]
Undiagnosed, CD4 ≥500 cells/mm^3, N	1142 [1067-1267]	4 [2-9]	53 [38-75]	240 [178-274]
Undiagnosed, CD4 ≥500 cells/mm^3, % of all undiagnosed	52 [50-54]	28 [16-41]	40 [34-45]	41 [38-43]
Undiagnosed, CD4 ^{3}, N	600 [564-628]	8 [6-11]	51 [36-65]	217 [186-247]
Undiagnosed, CD4 ^{3}, % of all undiagnosed	27 [26-29]	51 [38-63]	38 [33-42]	37 [36-41]
Number of infections in 2011	642 [558-743]	7 [0-23]	46 [31-74]	72 [32-138]
MSM: men who have sex with men; IDU: injection drug users; HET-W: heterosexual women; HET-M: heterosexual men; []: 95% confidence interval				

976 Prenatal HIV Testing Coverage of Medicaid-Insured Women – United States, 2009–2010

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Background: Prenatal screening for maternal HIV infection is a critical step in the prevention of mother-to-child transmission of HIV. The U.S. Centers for Disease Control and Prevention (CDC) recommends universal HIV screening of all pregnant women, and since 2006, has recommended an opt-out model to increase HIV testing uptake and coverage. CDC also recommends universal prenatal screening for syphilis and hepatitis B. We estimated prenatal testing coverage for syphilis, hepatitis B, and HIV in a large Medicaid-insured population in the United States during 2009–2010.

Methodology: We analyzed Medicaid claims data from a large administrative database to estimate testing coverage for syphilis, hepatitis B, and HIV among pregnant women aged 15–44 by age group and by race and ethnicity. We used procedural and diagnostic codes to identify pregnant women with a live birth in 2010, and included those who were continuously enrolled in Medicaid ≥210 days prior to the date of delivery. Procedural codes were used to identify syphilis,hepatitis B, and HIV screening tests, and Rh and ABO blood typing. Maternal blood typing is performed as part of routine obstetric care and was used to estimate the proportion of women who had received prenatal care.

Results: Among 113,943 pregnant women, 87% (98,709) had claims for Rh and ABO blood typing. Among women with Rh and ABO blood typing, 98% (96,735) were tested for syphilis, 97% (95,748) for hepatitis B, and 84% (82,916) for HIV. Prenatal testing coverage for all three diseases decreased with age. The greatest difference in testing coverage by age was observed for HIV: it was 87% for women 15–19 years and 79% for women >35 years. Testing coverage for syphilis was 92% for Hispanic women, 98% for white women, and 100% for black women; for hepatitis B it was 91% for Hispanic women, 97% for white women, and 98% for black women. HIV testing coverage did not differ by race and ethnicity.

Conclusions: Among women with Rh and ABO blood typing, prenatal testing for syphilis and hepatitis B was nearly universal. However, prenatal testing for HIV was suboptimal, indicating that barriers to HIV testing still exist. Interventions are needed to facilitate the routinization of prenatal HIV testing.

977 Measuring Late HIV Diagnosis Among Men Who Have Sex With Men: AIDS Diagnosis vs. Testing Frequency

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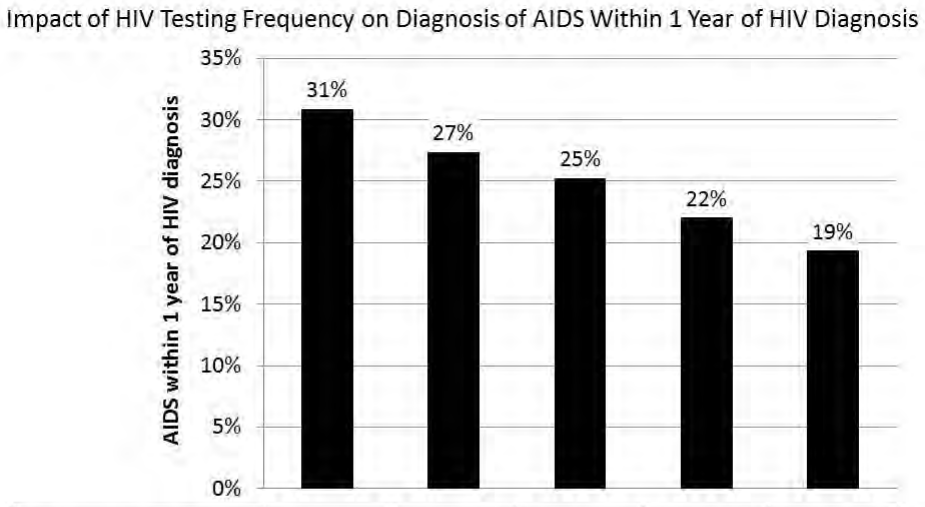
Background: HIV surveillance in the U.S. monitors the occurrence of AIDS within one year of HIV diagnosis as a surrogate measure for late HIV diagnosis. The validity of this approach, particularly in populations with high levels of testing, is uncertain.

Methodology: We examined the relationship between AIDS diagnosis within 1 year of HIV diagnosis and time from last negative to first positive HIV test (intertest interval, ITI) using HIV surveillance and partner services data. Public health staff routinely assessed dates of last negative tests through partner services interviews or medical record review. We categorized ITIs as ≤12, 13-24, 25-36, 37-48, 49-60, >60 months, or never tested, then calculated the proportion of AIDS ≤1 year from HIV diagnosis within each ITI category (ITI AIDS risk). We modeled hypothetical changes in population-level testing frequency by sequentially moving 50% of persons in each ITI category into the next higher or lower category. For each new distribution of ITIs, we estimated the proportion of persons with AIDS ≤1 year from HIV diagnosis by applying our ITI AIDS risk data. When calculating median ITIs, men who never tested negative were assigned the maximum observed ITI.

Results: From 1/1/2010-8/30/2012, 583 cases of HIV were diagnosed among MSM in King County, WA. Among 547 (94%) MSM with testing history data, the median ITI was 16 months (IQR: 6-48), and 326 (60%) and 430 (79%) had tested within 2 and 5 years of diagnosis, respectively. 138 (25%) were diagnosed with AIDS within 1 year of HIV diagnosis, of whom 40 (29%) and 81 (59%) had tested within 2 and 5 years of HIV diagnosis, respectively. The figure shows estimates of the proportion of MSM diagnosed with AIDS within 1 year of HIV diagnosis at varying population testing frequencies. Decreasing the median ITI from 16 to 9 months - which involves 58% of newly diagnosed MSM testing negative ≤1 year prior to diagnosis - decreased the proportion of AIDS ≤1 year after HIV diagnosis from 25 to 19%. Increasing the median ITI to 31 months increased this proportion to 31%.



ITI in months: Median (IQR)	31 (19-60)	23 (13-51)	16 (6-48)	11 (5-43)	9 (4-36)
Tested in 2 years prior to HIV diagnosis	37%	52%	60%	65%	69%
Tested in 5 years prior to HIV diagnosis	75%	77%	79%	86%	89%

Conclusions: Population estimates and individual-level classification of late HIV diagnosis differed based on how late diagnosis was defined. Even large changes in HIV testing frequency among MSM may have limited impact on the proportion of persons with AIDS within 1 year of HIV diagnosis, suggesting that the measure may have limited utility in monitoring the success of HIV case-finding efforts. Efforts to monitor trends in late diagnosis should include the ITI.

Session P-W2 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Cascade of Care, Linkage, and Retention

978 Using HIV Surveillance Registry Data To Re-Link Patients To Care: The RSVP Project in San Francisco

Kate A. Buchacz[1], Miao-Jung Chen[2], Maree Kay Parisi[2], Maya Yoshida[2], Erin Antunez[2], Viva Delgado[2], Nicholas J. Moss[3], Susan Scheer[2]

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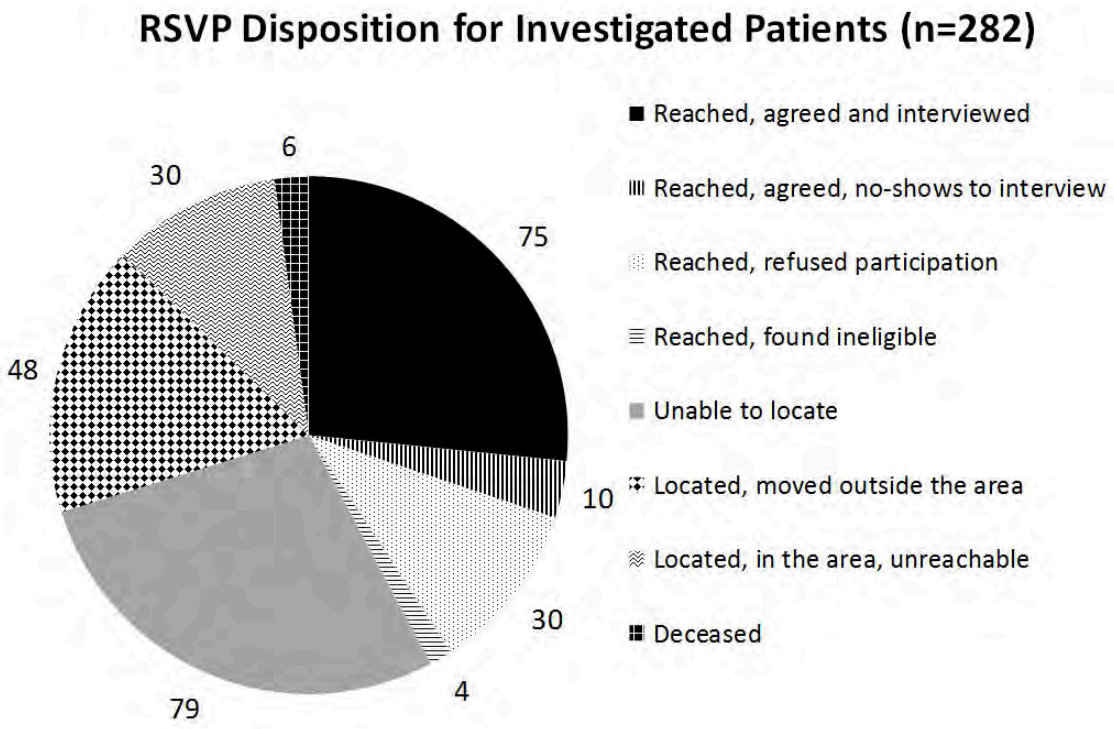
Background: Patients with unsuppressed HIV viral load (VL) who fall out of care may experience poor clinical outcomes and potentially transmit HIV. We assessed the feasibility and yield of using the San Francisco Department of Public Health (SFDPH) enhanced HIV surveillance system (eHARS) to identify such persons and re-engage them in care.

Methodology: Using SFDPH eHARS data as of 4/20/2012, we selected HIV-infected adults who had a VL >200 copies/mL in blood samples drawn 9-15 months earlier and had no subsequent reported VL or CD4 laboratory results (a proxy for being "out-of-care"). We prioritized cases presumed alive and residing in the Greater San Francisco Bay Area (GBA) for outreach. We used information from eHARS and medical and public health databases to contact cases for interview and referral to the SFDPH linkage services (LINCS). We then repeated our original eHARS case selection through 4/20/2012, this time matching with eHARS data current as of 4/20/2013, to assess how reporting delays of HIV laboratory results affected original eligibility, and what percentage of cases had any subsequent HIV laboratory results reported between 4/20/2012 and 4/20/2103.

Results: Of 476 selected cases, 42 (9%) were deceased and 152 (32%) were living outside the GBA per SFDPH eHARS on 4/20/2012. Among the remaining 282 cases, after extensive search and outreach efforts, 75 (27%) were interviewed (Figure). Fifty-eight (77%) of these cases reported seeing an HIV provider in the prior year and 54 (72%) accepted referral to LINCS. Of those referred, 28 needed re-linkage and 26 accepted other services. Rerunning our original match one year later, of the 282 cases originally prioritized for outreach, 213 (76%) still met the original eligibility criteria, of whom 130 (61%) had a subsequent reported HIV laboratory result between 4/20/2012 and 4/20/2013. Delayed HIV laboratory reporting from counties outside of SF was the most common reason cases were re-classified as ineligible when we repeated the original match one year later.

Conclusions: Among HIV cases identified as out-of-care and prioritized for RSVP outreach, about one-quarter were interviewed and offered re-linkage to HIV care, demonstrating the feasibility but limited yield of our project. Most patients had some HIV care regardless of contact through the RSVP Project. Verifying patients' HIV care status with medical providers and improving HIV laboratory reporting mechanisms may aid future similar efforts.



979 Disentangling Roles of Internalized Stigma and Depression in Women's Linkage To Care

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Background: Linkage of HIV-positive pregnant and postpartum women to HIV care and treatment programs is essential for long-lasting maternal and child health. Internalized HIV-related stigma, defined as self-devaluation and/or shame due to one's HIV status, has been suggested as an important barrier to engagement in HIV care. However, it remains unclear if the effect of stigma is mainly due to depression, which is also an impediment to use of health services and is highly correlated with internalized stigma. In order to understand how to support women's linkage to HIV care, it is crucial that we disentangle the unique roles of stigma and depression.

Methodology: Women were recruited at nine antenatal clinics in Kenya. Of 239 pregnant women newly diagnosed with HIV and interviewed during pregnancy, 165 (70%) participated in follow-up interviews six weeks after delivery. Data on women's linkage to HIV care during the follow-up period were obtained from medical records. We examined relationships between a measure of internalized stigma, postnatal depression scores (Edinburgh Postnatal Depression Scale, EPDS), and linkage to HIV care using logistic regression, accounting for clustering by clinic.

Results: Six weeks after delivery only 56% of the women had linked with HIV care. Of the women who participated in follow-up interviews, half reported experiencing internalized HIV-related stigma, and 23% had an EPDS score ≥13 indicating depression. Those who reported any internalized stigma had significantly higher odds of depression (OR=4.10, 95%CI=1.70-9.92). In bivariable analyses, internalized stigma was significantly associated with reduced odds of linkage to care (OR=0.56, 95%CI=0.38-0.82) and depression was marginally significant (OR=0.46, 95%CI=0.19-1.13). After adjusting for depression and other predictors, internalized stigma remained significantly associated with reduced linkage to care (adjusted OR=0.56, 95%CI=0.35-0.88), while postnatal depression was not (p=0.63).

Conclusions: Our results suggest that HIV-related stigma and depression have negative effects on linkage to HIV care among pregnant and postpartum women, and that stigma has a significant effect independent of depression. These findings indicate that in addition to depression interventions, services for this population need to incorporate specific HIV-related stigma reduction and coping strategies.

980 Longitudinal Treatment Outcomes in HIV-Infected Prisoners and Influence of Re-Incarceration

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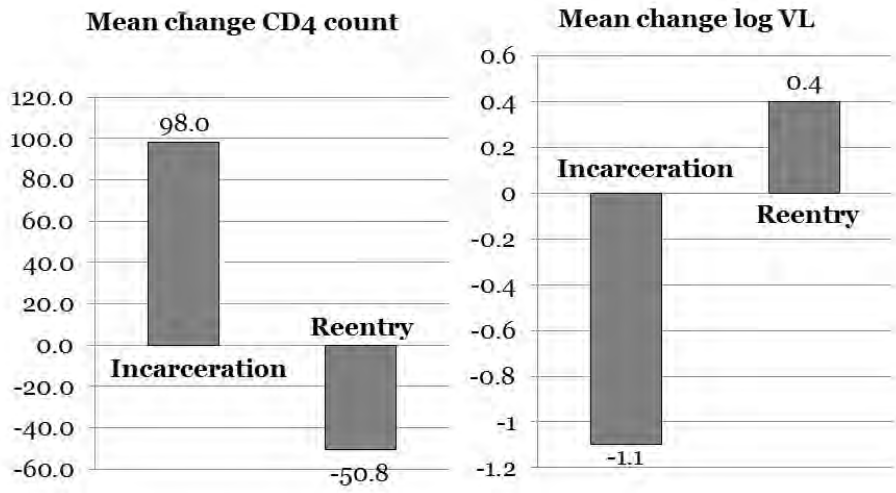
Background: One-sixth of PLWHA transition through prison or jail annually but treatment outcomes during and following incarceration have not been systematically evaluated in over a decade.

Methodology: A retrospective cohort study of HIV+ prisoners on ART (2005-2012) examined treatment outcomes using longitudinally linked correctional, pharmacy, and laboratory databases. Viral suppression (VS) on release, defined as HIV-1 RNA<400, was the primary outcome; secondary outcomes were

mean change in log-transformed HIV-1 RNA and CD4 count during incarceration. Correctional characteristics, ART type, directly observed therapy (DOT), and other characteristics were analyzed as correlates of VS. In a sub-sample of recidivists with ≥90 days in the community, we examined VS on reentry.

Results: Among 882 HIV+ prisoners (1,185 incarceration periods), proportion achieving VS was significantly higher on release compared to entry (70.0% vs 29.8%; p<0.001). VS on release correlated with female gender (AOR=1.81, 95%CI 1.26-2.59) and lower psychiatric severity (AOR 1.50, 95%CI 1.12-1.19), but not race/ethnicity, incarceration duration, ART regimen type, or DOT. During incarceration, only 36.8% of prisoners switched ART regimen, primarily from nNRTI- to PI-based regimens. For 497 recidivists (934 incarceration periods), after a median 329 days in the community, VS was significantly lower than on last release (31.3% vs. 52.2%; p<0.001). VS on reentry correlated with increasing age (AOR=1.04, 95%CI 1.02-1.07), receiving an nNRTI based regimen (AOR=1.93, 95%CI 1.42-2.63) or being prescribed an antidepressant (AOR=1.40, 95%CI 1.01-1.95), and negatively with being Black (AOR=0.66, 95%CI 0.45-0.98).

Conclusions: From the largest contemporary systematic evaluation of HIV treatment outcomes among prisoners on ART, the majority achieved VS, confirming that ART can be optimized during incarceration when appropriate resources are provided. Compared to an earlier cohort (1997-2002), more achieved VS on release with fewer ART changes and VS was more often sustained through reentry, likely due to ART regimens with lower pill burden and fewer adverse side effects. The decrease in VS between release and reentry suggests that more effective transitional care and services are still needed to improve individual and societal health and reduce onward HIV transmission post-release.



981 Imprisonment Among a Large US Clinical Cohort of HIV-Positive Outpatients

David L. Rosen[1], Carol E. Golin[2], Catherine A. Grodensky[3], Samuel Stinnette[1], Becky L. White[4], Sonia Napravnik[1], David A. Wohl[4]

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Background: Retention in HIV care is critical to good outcomes but can be interrupted by incarceration: an estimated 14% of all HIV-positive(HIV+) individuals in the US pass through a prison or jail annually. A greater understanding of the characteristics of HIV+ patients who become incarcerated and the resulting lapse in clinical care between community and correctional settings could inform interventions to improve their health outcomes and reduce transmission.

Methodology: We deterministically matched and linked records from the UNC Center for AIDS Research HIV Clinical Cohort (UCHCC) with records from the NC state prison system. For January 2000 to May 2011, we examined the proportion of UCHCC patients who became imprisoned, UNC clinic visits prior to imprisonment, the time lapse between clinical care and prison entry, most recent viral load (VL) prior to incarceration, and the covariate-adjusted associations between patient demographic and clinical characteristics and a subsequent incarceration.

Results: From January 2000 to May 2011, 3,258 UCHCC patients attended at least one clinical HIV visit; 71.1% male, 70.6% non-White. During the same period, 5.2% (n=170) were imprisoned a total of 180 times. The median time of follow-up at UNC prior to imprisonment, number of HIV clinic visits before incarceration, and time from last UNC visit to prison entry were, respectively, 1.5 (inter-quartile range [IQR] 0.1-3.8) years, 5 (IQR: 2-14) visits, and 11.7 (IQR: 3.4 - 32.9) months. For 63% (n=106), the most recent VL prior to imprisonment was detectable (i.e. ≥400 copies/mL). Injection drug use history, detectable VL, Black race, and male gender were associated with subsequent incarceration (Table 1).

Conclusions: In a large outpatient HIV+ cohort of patients, one in twenty were imprisoned. For nearly half of those who became incarcerated the period between last clinic visit and prison entry was over a year, and these patients' most recent pre-incarceration VL was commonly detectable, suggesting that in the time leading up to imprisonment, many of these patients are out of care and at risk for HIV transmission and poor health outcomes. However, these patients had a high frequency of visits prior to imprisonment. These results highlight the individual and clinical factors associated with risk of incarceration and opportunities to detect and intervene prior to imprisonment.

982 A Surveillance-Based Risk-Scoring Tool To Prioritize Cases for HIV Care Re-Linkage Efforts

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Background: HIV laboratory surveillance data (reported CD4 count and viral load results) are often used to identify persons living with HIV/AIDS (PLWHA) who are out of HIV care, but many health departments lack resources to investigate all cases missing recent data. A risk scoring tool could identify cases most likely to benefit from HIV care re-linkage efforts.

Methodology: We derived and internally validated a risk scoring tool using data from public health investigations of HIV cases in King County, WA that had no lab results reported to our health department for ≥12 months prior to 4/30/2012. We separately derived and validated risk scores for 1) out-migration or death ("Gone") and 2) currently residing in area and contactable ("In Area, Contactable"). The investigation protocol included queries to a governmental records database, medical records searches, calls to HIV medical and social service providers, and calls and letters to PLWHA. We randomly divided the dataset in half, and used one dataset for risk score development and the other for validation.

Results: Among 5,708 diagnosed PLWHA in King County, 1128 (20%) had no lab reported for ≥12 months prior to 4/30/2012. Of these, 413 (37%) were determined through case investigation to have out-migrated or died, 219 (19%) were in the area and successfully contacted, 168 (15%) were in the area but were not contacted because new lab results were reported before contact was attempted, and 328 (29%) were not conclusively determined to be out of area and were not contactable. The final model for each risk score included 3 variables: years since last laboratory report (<5, 5-9, >9), county of residence at the time of HIV diagnosis (King or not), and years of age at the time of ascertainment of gap in laboratory results (≤40, 41-65, >65). The "Gone" score had modest discriminatory accuracy [area under the receiver-operator characteristic (ROC) curve = 0.65] as did the "In Area, Contactable" score (AUC=0.72). Internal validation demonstrated similar predictive ability of both risk scores in the validation group.

Conclusions: We found that a combination of 3 variables available in standard HIV surveillance predicted the likelihood that a PLWHA was residing locally and contactable. Although the accuracy of this score requires external validation, choosing not to investigate cases with "In Area, Contactable" scores of <3 would allow health departments to avoid approximately one-third of all investigations while missing only 5% of contactable persons.

Risk Score Interpretation						
	"Gone" Risk Score			"In Are, Contactable" Risk Score		
Case Investigation Priority Tier	% Cases in Each Priority Tier	Score	% Moved or Died (for Each Score Value)	% Cases in Each Priority Tier	Score	% In Area, Contactable (for Each Score Value)
HIGH	45%	0	22%	47%	5	41%
		1	25%		4	40%
MEDIUM	45%	2	38%	20%	3	14%
		3	44%			
LOW	9%	4	59%	33%	2	4%
		5	75%		1	2%
		6	78%		0	0%

983 Beyond Core Indicators of Retention in HIV Care: Added Prognostic Value of Missed Clinic Visits

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Background: The Institute of Medicine (IOM) and Department of Health and Human Services (DHHS) have released core indicators of retention in HIV care calculated based upon attended clinic visits (2 visits at defined intervals per 12 month period). Recent research suggests missed clinic visits may capture distinct aspects of retention from measures based upon attended visits. We evaluated associations between the IOM and DHHS retention measures and all-cause mortality, and further assessed the added prognostic value of missed visits when used in conjunction with these core indicators.

Methodology: HIV-infected patients initiating ART at 5 CNICS sites from 2000-11 were included. Retention in care over 24-months (mos) following ART start was measured using the IOM (HRSA HAB measure) and DHHS core indicators, and as a count of missed (no show) clinic visits. Separate Cox models evaluated the relationship between retention measures and all-cause mortality with follow-up time starting at 24 mos. Next, separate Cox models evaluated the association between missed visits and all-cause mortality among the subset of patients classified as retained according to the IOM and DHHS core indicators. Models controlled for age, race, gender, site, baseline CD4 and VL.

Results: Among 3926 patients (mean age 38, 81% male, 54% white, 47% CD4<200, 42% VL>100K), 64% and 59% met the IOM and DHHS retention core indicators, respectively, and 32% had zero missed visits over 24-mos following ART start. Subsequently, 333 patients (8.5%) died during 17841 person-years follow-up. In separate multivariable Cox models, failure to achieve the IOM indicator (HR=2.2; 95%CI=1.8-2.8), the DHHS indicator (2.4; 1.9-3.0), and missed clinic visits at 24-mos (1-2 no shows: 2.0; 1.5-2.8, >2 no shows: 3.2; 2.4-4.5) were all associated with increased long-term mortality. Roughly two-thirds of patients classified as retained by the IOM and DHHS core indicators had one or more no show clinic visits in the 24-mos following ART start. Separate multivariable Cox models restricted to patients classified as retained by the IOM and DHHS core indicators demonstrated increased mortality risk among patients with more missed clinic visits (IOM: 1-2 no shows 1.8; 1.2-2.7, >2 no shows: 3.7; 2.4-5.6 and DHHS: 1-2 no shows 1.7; 1.1-2.6, >2 no shows: 3.7; 2.3-5.8).

Conclusions: These data are among the first to provide empirical validation of the IOM and DHHS core indicators of retention in care with clinical outcomes. Both measures were strongly associated with long-term mortality among ART initiators. However, study findings suggest assessment of missed clinic visits, in conjunction with these core indicators, can meaningfully enhance prognostic value for all-cause mortality, with implications for health care policy and clinical care.

984 National ART Monitoring System Enables Robust Transfer-Adjusted Retention Analyses in Namibia

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Background: Previous antiretroviral treatment (ART) program outcome evaluations have shown trends of declining retention with advancing initiation cohort year, corresponding to ART scale up and decentralization of service delivery. However, most ART data systems have limited ability to follow transfer patients (TP) between health facilities, leading to misclassification of loss to follow up and artificially low retention estimates. Namibia's electronic patient management system (ePMS) captures longitudinal data from all patients receiving ART in the public sector and can track both official and unofficial TP using unique codes assigned to patients at ART initiation. We present a retention analysis of Namibia's ART program, both crude and adjusted for inter-facility transfer (IFT).

Methodology: We evaluated all HIV-infected adults initiating ART in all 213 public health facilities in Namibia from January 2003 to December 2013. We used Kaplan-Meier analysis to estimate trends in retention, unadjusted and adjusted for IFT through de-duplication of TP from the cumulative cohort. Retention was defined as visiting a health facility within 90 days of the next scheduled follow-up visit.

Results: Before adjusting for IFT, 167,484 adult patients initiated ART from 2003 to 2012. After adjusting for IFT, only 140,224 patients initiated ART; of these, 59.6% were female and median age at initiation was 35 years (IQR: 30 to 42). Unadjusted and adjusted retention proportions at 12, 24, 36, and 48 months were: 0.88/0.86, 0.85/0.83, 0.83/0.81 and 0.81/0.79 in the 2004 initiation cohort; 0.93/0.91, 0.89/0.88, 0.85/0.84 and 0.81/0.81 in 2006; 0.89/0.88, 0.83/0.84, 0.77/0.80 and 0.70/0.75 in 2008; 0.87/0.88, 0.77/0.81, 0.68/0.73 and not available (NA) in 2010 and; 0.81/0.82, NA, NA and NA in 2012. 10,725 (25%) of 43,028 patients classified as lost in the unadjusted analysis were identified as being retained at a different facility after adjustment for IFT.

Conclusions: Evaluation of ART patient outcomes in resource-limited settings is essential to understanding program quality and impact. Heterogeneous data systems may have led to underestimation of retention and other longitudinal outcomes. Consistent with previous reports from other countries this unadjusted analysis shows trends of declining retention, corresponding to service scale-up and decentralization. However, ART retention in later cohorts improved after adjustment for IFT. This analytic approach allows for robust determination of ART program outputs by de-duplicating TP from cumulative cohort analyses. National standardized ART monitoring systems like Namibia's may be a best practice for other countries as routine tracking and quantification of TP enables more robust retention analysis and program monitoring.

985 Migration After HIV Diagnosis, United States

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Background: Early diagnosis, prompt linkage to care, and retention in ongoing care benefit the health of people living with HIV and can reduce the onward transmission of HIV. However, continuing care may be affected by people relocating to seek better social or medical support, and local jurisdictions need accurate information on patient populations for care planning and public health intervention. Very few studies have reported on U.S. migration among persons diagnosed with HIV.

Methodology: Using data from the National HIV Surveillance System (NHSS) reported through March 2013, we assessed migration to another state among persons diagnosed with HIV in the United States through 2009. Persons living with HIV infection may move from state to state; therefore, may be reported to CDC from more than one state. CDC provides information on potential duplicate reporting to state health departments based on information CDC receives, and state health departments collaborate to determine whether these potential duplicative reports are the same person or not. Using information from the de-duplication process, CDC determines inter-state migration. Migration was assessed from HIV diagnosis through 2010 overall (ever) and within 12 months after HIV diagnosis. We defined area of residence as urban (metropolitan area ≥500,000 population), suburban (metropolitan area of 50,000-499,999 population), or rural (nonmetropolitan population). We calculated prevalence ratios (PR) and 95% confidence intervals (CI) to determine factors associated with migration.

Results: Of 1,503,778 persons diagnosed with HIV in the United States through 2009, 9.9% ever migrated to another state and 2.5% migrated within 12 months of diagnosis. A higher percentage of females ever migrated compared with males (PR =1.30, 95% CI 1.28, 1.31). Compared with whites, fewer blacks ever migrated (PR=0.94, 95% CI 0.92, 0.95) while more Hispanics migrated (PR=2.38, 95% CI 2.34, 2.43). Compared to persons living in the Northeast at time of HIV diagnosis, a higher percentage of persons living in the South migrated (PR=6.95, 95% CI 6.32, 7.64).

Persons in suburban (PR=1.35, 95% CI 1.33, 1.37) and rural (PR=1.32, 95% CI 1.29, 1.34) areas of residence migrated more than persons in urban areas. Results were similar for persons who migrated within 12 months of HIV diagnosis.

Conclusions: Higher geographic mobility among persons after a diagnosis with HIV was observed among women, Hispanics and persons living in the South. Local jurisdictions should consider the impact of migration while planning prevention, linkage to care, and retention in care programs. HIV interventions can be tailored to the characteristics and needs of these populations.

986 Early Linkage To HIV Care and Antiretroviral Therapy Use Among MSM — 20 US Cities, 2008 and 2011

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Background: Over half of HIV infections in the United States occur among men who have sex with men (MSM). Antiretroviral therapy (ART) is now recommended for all infected persons to improve health and prevent HIV transmission. Timely linkage to care is a key step for initiation of ART. We analyzed data from MSM in the National HIV Behavioral Surveillance system (NHBS) to determine the prevalence of early linkage to care and ART use by key characteristics and evaluate changes in prevalence from 2008 to 2011.

Methodology: Venue-based, time-space sampling was used to recruit men for interviews and HIV testing in 20 cities participating in NHBS in 2008 and 2011. Early linkage to care was defined as a self-reported clinic visit for HIV care within 3 months of diagnosis and current ART use was defined as use at the time of interview. Self-reported HIV-positive MSM who had ≥ 1 partner in the past 12 months were included in the analyses. Early linkage models were further restricted to those diagnosed with HIV ≥ 3 months prior to interview. We used linear mixed models clustered on city to examine differences in the two outcomes between 2008 and 2011. To explore whether temporal changes in the outcomes varied by demographics, interaction terms were included in the models.

Results: Prevalence of early linkage to care was 75% (599/802) in 2008 and 79% (757/964) in 2011 ($P = .09$). In both years, early linkage was highest among those with higher education and income, gay-identified vs. bisexual- or heterosexual-identified, and at older age at diagnosis (≥ 30). In a multivariable model adjusted for race/ethnicity, age at diagnosis, and region, prevalence of early linkage did not change significantly between years overall ($P = .17$) and only changed significantly for Hispanic ethnicity (75% in 2008 vs. 84% in 2011, $P = .04$). Prevalence of ART use was 66% (567/854) in 2008 and 77% (791/1,030) in 2011 (P = .0001). Higher ART use was observed among whites, older age groups, men with higher education and income, and gay-identified MSM in both years. In a multivariable model adjusted for race/ethnicity, current age, income, sexual identity, and region, ART use significantly increased from 2008 to 2011 (P = .02). ART use also increased significantly among most races/ethnicities, younger age groups (< 30), men with higher income, bisexual- or heterosexual-identified MSM, and men interviewed in Western cities.

Conclusions: While the prevalence of early linkage among MSM did not increase significantly between 2008 and 2011, the prevalence of ART use increased among most demographic groups. These findings demonstrate that progress is being made in getting people on HIV treatment, but that more efforts are needed to link patients to clinical care within 3 months of diagnosis and improve coverage of ART.

987 The Impact of Opioid Substitution Treatment On Highly Active Antiretroviral Treatment Adherence

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Background: Opioid substitution treatment (OST) has been associated with enhanced uptake and adherence to highly active antiretroviral therapy (HAART), however standard methods for estimating the causal effect of a time-varying treatment on the mean of a repeated measures outcome may be biased when there are time-dependent variables that are simultaneously confounders of the effect of interest and are predicted by previous treatment. In our context, previous HAART adherence is hypothesized to be a time-dependent confounder for the effect of OST on future HAART adherence. Our objective was to determine the impact of OST exposure on adherence to HAART among HIV-positive opioid dependent individuals.

Methodology: We selected all HAART-eligible HIV-positive individuals ever accessing opioid substitution treatment between January 1st, 1996 and March 31st 2010 within a linked population-level database for British Columbia, Canada, after meeting the criteria for HAART initiation. A marginal structural model was estimated using monthly-updated inverse probability of treatment weights (IPTW). The primary outcome measure was 95% HAART adherence, according to pharmacy refill compliance records. Exposure to OST was defined as at least 21 days of OST receipt in a calendar month. We controlled for fixed and time-varying covariates, including age, gender, ethnicity, health authority of residence, calendar year, OST history at HAART eligibility, AIDS status, CD4 and prior HAART exposure in estimated IPTW.

Results: Among 12,349 HIV-positive individuals observed in BC between 1996 and 2010, 1,811 (14.7%) accessed OST, and 1,347 (10.9%) were selected for the study. Subjects were 39% female, were of median age 35 (interquartile range: 29-41) at HAART eligibility, and had a median of 6.6 years (2.8-10.9) of follow-up. During OST, individuals spent a median 55% (20%-85%) of the time on HAART, while out of OST individuals spent only 26% (7%-58%) of the time on HAART. The unadjusted odds of HAART adherence during OST exposure was 2.26 (95% confidence interval: 2.01-2.54), while the adjusted odds, estimated within the marginal structural model, was 2.17 (1.90, 2.49).

Conclusions: Our results demonstrate that access to OST more than doubles the odds of HAART adherence among opioid-dependent individuals with HIV. This study informs funding decisions for OST and strategies to increase access to HAART.

988 Correlation Between Community Variables and HIV Linkage To Care and Viral Suppression, Atlanta, GA

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Background: Linkage and retention in care are central to reducing morbidity and mortality for HIV-infected persons. The Centers for Disease Control and Prevention recommends linkage to care within three months of diagnosis, but 33% fail to link within this period. An HIV-infected person's residence may be critical to his potential for linkage and retention in care after diagnosis. We hypothesize that within metro Atlanta, low "community linkage to care" and "community viral suppression" may correlate with neighborhood-level variables at the zip code level, including high levels of poverty and income inequality, low educational attainment, high proportion vacant houses, and poor public transportation access.

Methodology: We used data from the Georgia Department of Public Health, U.S. Census Bureau American Community Survey, and the Atlanta Regional Commission to examine distributions of neighborhood-level variables and statistical correlations with community linkage to care (average percent linked to care within three months) and community viral suppression (average percent with reported viral load below 200 cells/mL), by zip code tabulation areas (ZCTAs). The analysis included persons living in six Georgia counties comprising the metro Atlanta area with a new HIV diagnosis reported through Georgia's Electronic HIV/AIDS Reporting System from January 1, 2006 through December 31, 2010. With zip codes as observations, we evaluated correlations between neighborhood-level variables and two primary HIV outcomes, community linkage to care and community viral suppression. Pearson's and Spearman's correlations were used to evaluate associations between zip code level variables and primary outcomes.

Results: In the 123 included ZCTAs, median HIV incidence was 203 per 100,000 persons. Overall, 53% of people diagnosed with HIV linked to care within three months of diagnosis and 45% achieved viral suppression. 16% of the population was living below the poverty line, and 88% had at least a high school diploma equivalent. Income inequality was not prominent (mean Gini coefficient 0.44). On average, 3% of occupied houses lacked telephone service, and 13% of houses were vacant. There was a median of 54 public bus stops in each zip code. Areas of high poverty and greater number of bus stops correlated with poor linkage to care and lower levels of viral suppression. Higher educational attainment and low proportion vacant houses correlated with greater community virologic suppression.

Conclusions: Certain neighborhood-level variables may correlate with community-level linkage to care and viral suppression for HIV-infected persons. Bus stop density may be a marker of high poverty, in addition to an indicator of transportation access, in the linkage and retention in care paradigm.

Session P-W3 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Cascade of Care, Community Viral Load, and Viral Suppression

989 Viral Suppression Among Foreign-Born HIV-Infected Persons in the United States

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Background: Few national-level data exist on the characteristics of and clinical outcomes among foreign-born HIV-infected persons. Using data from the Medical Monitoring Project (MMP), a nationally representative survey of HIV-infected adults receiving medical care in the United States, we report on the characteristics of and clinical outcomes among foreign-born HIV-infected adults.

Methodology: We used data from the 2009 MMP cycle collected from 461 outpatient HIV care facilities in 16 states and Puerto Rico on 4217 adult participants. Participants were classified as foreign-born if they listed a country or territory of birth other than the United States or Puerto Rico during interview. Receipt of antiretroviral therapy (ART) was defined as documented ART prescription in the medical record in the past 12 months. Viral suppression was defined as documented most recent viral load measurement of ≤200 copies/mL in the medical record. We used multivariable logistic regression to assess the independent association between foreign-born status and ART prescription and viral suppression after adjusting for confounding. All analyses account for clustering, unequal selection probabilities and non-response.

Results: In all, 529 participants (13.1%) self-identified as foreign-born; the majority (61.2%) was from either Central America or the Caribbean. Over 90% of foreign-born persons were diagnosed with HIV after entry into the United States. Foreign-born persons were more likely to be young, male, Hispanic, living at or below the poverty level, and uninsured compared to native-born persons. Adjusting for potential confounders including age and language, there was no association between foreign-born status and ART prescription (adjusted odds ratio aOR 0.81; p 0.30) or viral suppression (aOR 1.10; p 0.55). However, in multivariable modeling assessing foreign-born status and region of birth, foreign-born persons from the Caribbean were less likely to be prescribed ART (aOR 0.43; p 0.005) and to achieve viral suppression (aOR 0.51; p 0.011) than native-born persons.

Conclusions: In this nationally representative sample of HIV-infected persons receiving medical care, foreign-born persons overall were equally likely to be prescribed ART and achieve viral suppression compared to native-born persons. However, significant disparities among foreign-born persons exist, with persons from the Caribbean being less likely to be prescribed ART and achieve viral suppression. Efforts to improve clinical outcomes among HIV-infected foreign-born persons should be strengthened, especially for migrants from the Caribbean.

990 Mapping Community Viral Load and Transmission Potential Prevalence of HIV Among MSM in New York City

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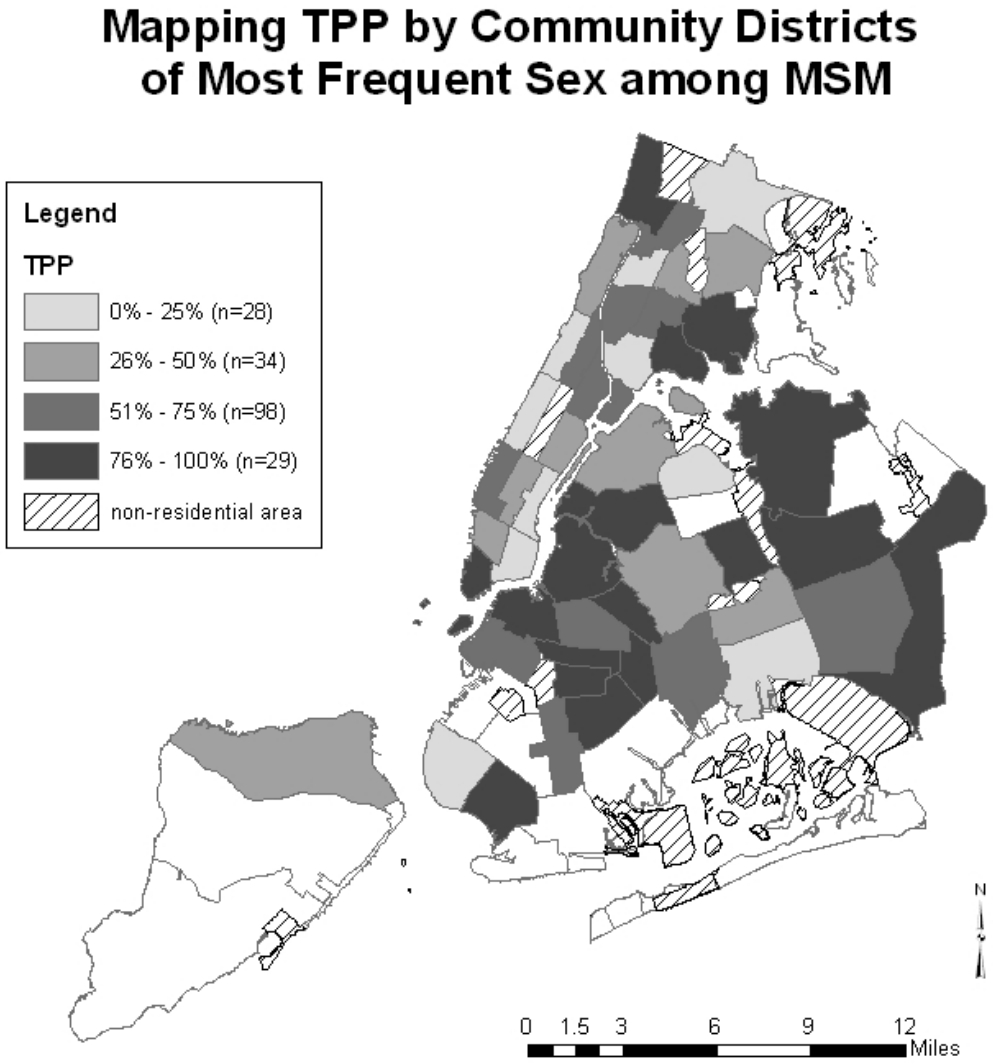
Background: Community viral load (CVL) and transmission potential prevalence (TPP) are aggregate biological markers used to monitor population-level HIV transmission. Lower CVL and TPP have been shown to be associated with decreased HIV incidence or new diagnosis. Previous studies of CVL and TPP have been based on place of residence. Data on CVL and TPP based on where MSM have sex can provide a more nuanced assessment of potential transmission.

Methodology: The NYC M2M study recruited MSM in NYC via modified time-space, venue-based sampling and web-based recruitment from 2010-12. Participants identified the neighborhood where they most frequently had sex in the last 3 mos. using Google Earth, and completed an ACASI questionnaire and a sexual network inventory. They received HIV testing and, if HIV+, CD4 and viral load (VL) testing. For geographic analysis, CVL was calculated as median VL of HIV+ men. TPP was defined as the percent of the sample with VL>20 copies/mL. ArcGIS was used to visualize median CVL and TPP by

community districts of most frequent sex among HIV+ men. For comparisons by sociodemographics and risk behaviors, median VL and TPP were used and compared using Kruskal-Wallis and chi-square tests.

Results: Of total 1,458 men, 327 (22%) reported being HIV+; 195 HIV+ men (60%) agreed to CD4 and VL testing. 84 men (43%) had undetectable VL; median CVL was 2,201 copies/mL among those with detectable VL. Overall median CD4 was 545 cells/mL. Maps of CVL and TPP by geographic areas of most frequent sex are shown. Median VL and TPP were significantly higher for men who were Black or Hispanic, newly HIV diagnosed, had no prior HIV treatment, last engaged in medical care >6 mos. ago, and had low HIV treatment adherence self-perception. Higher median VL was also associated with recent drug use; higher TPP was also associated with age <30 years, lower education level, and no unprotected anal sex (UAS) in last 3 mos.

Conclusions: The distribution of TPP by most frequent sex geographic areas provided a slightly different picture of potential HIV transmission than CVL among MSM in NYC. Both VL and TPP were higher among Blacks and Hispanics, newly HIV diagnosed, and those infrequently engaged in medical care. The finding of no recent UAS among those with higher TPP is encouraging.



991 HIV Care and Viral Suppression Among Persons Living With HIV/AIDS, New York City 2006-2010

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Background: New York City (NYC) has measured its baseline and will monitor its progress toward meeting the care and viral suppression goals of the National HIV/AIDS Strategy.

Methodology: Using the city's population-based HIV/AIDS surveillance registry we measured trends in retention in care (≥1 visit/year), engagement in care (≥2 visits/year, 3 months apart), and viral suppression (<400 copies/mL) in persons diagnosed and presumed to be living with HIV/AIDS (PLWHA) in NYC during 2006-2010. We compared results obtained with the crude denominator most frequently used for national estimates (persons diagnosed and reported in NYC and not known to be dead) against a denominator that was adjusted to reflect a more accurate count of PLWHA in the city during the

analysis period. We did this by removing all those with no HIV-related laboratory tests (WB, CD4, viral load of genotype) reported in NYC in the five years preceding the year of analysis on the premise that previously diagnosed persons for whom no data existed for such a long period of time, the majority of whom would have needed care due to advancing disease, were not likely to be living in NYC . The adjusted PLWHA population (N=84,146) for 2010 was used to describe the outcome measures by demographic characteristics, transmission risk and clinical status, and to estimate adjusted prevalence ratios (PRs) and 95% confidence intervals (CIs).

Results: The percentage of persons retained and engaged in care was stable in both populations. In the crude population, retention was 64.7% in 2006 and 64.1% in 2010; engagement was 52.9% in 2006 and 53.7% in 2010. Using the adjusted population, retention was 82.5% in 2006 and 81.8% in 2010; engagement was 67.5% in 2006 and 68.5% in 2010. In contrast, viral suppression increased from 34.7% in 2006 to 46.4% in 2010 in the crude population and 44.3% to 59.1% in the adjusted population. Blacks were least likely to have a suppressed viral load (PR=0.89, 95% CI: 0.87, 0.90), and PLWHA at both ends of life (age <13 and age ≥50) did better at viral suppression than those in the middle age brackets (PR=1.58 [95% CI: 1.43, 1.76] and PR=1.61 (PR 1.56, 1.65), respectively).

Conclusions: NYC experienced stable rates of retention and engagement in care but significant increases in viral suppression during 2006-2010. Higher proportions retained, engaged and virally suppressed than published national estimates may reflect a combination of the more accurate case counting that is available at the local level, comprehensive reporting of HIV-related laboratory test results, the widely accessible, affordable HIV care that is available in NYC, and early adoption of early ART by local clinicians.

992LB Low Incidence and High Population Viral Suppression in Malawi: The Chiradzulu HIV Incidence Study

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Background: The rural district of Chiradzulu, in Malawi, was the site of the first antiretroviral (ART) program implemented in sub-Saharan Africa by Médecins Sans Frontières (MSF) together with the Ministry of Health. ART became available there in early 2001, decentralization of care was completed in 2003, and task shifting allowing nurses to initiate ART started in 2006. By the end of June 2013, 27,000 patients (within a district of 280,000 inhabitants in total) were receiving ART. Here we present findings of the Chiradzulu HIV Impact in Population Study (CHIPS), which directly measured HIV Incidence, population viral load and coverage at each step within the cascade of care in early 2013, after 15 years of a district-wide program. This is one of the first population-level studies incorporating these specific metrics, which WHO recently identified as the most relevant for evaluating and optimizing both the therapeutic benefit of HIV treatment to individuals and the public health effectiveness of "treatment as prevention" strategies.

Methodology: Cross-sectional population-based survey . The study was conducted between February and May 2013. Using a multistage cluster sampling method, we recruited all individuals age 15 to 59 living in 4,125 selected households. Each individual who agreed to participate was interviewed and tested for HIV at home. All participants who tested positive also had their CD4 count and viral load measured. The Lag and Biorad Avidity assays were used to distinguish recent from long-term infection.

Results: Of 8,271 individuals eligible for the study 7,269 agreed to participate and were tested for HIV (94.1% inclusion for women and 80.3% for men). Overall HIV prevalence was 17.0% (95%CI 16.1 - 17.8). Based on the LAg and Biorad avidity assays results, overall incidence was 0.39 (95%CI 0.0-0.77) and 0.34 (95%CI 0-0.72) new cases per 100 Person-Years respectively. Incidence was higher among women compared to men (0.57 vs 0.18 new cases per 100PY)

Coverage at steps along the HIV care cascade was found to be as follows. Among the total HIV-infected population, 76.7% (95%CI 74.4 - 79.1) had been previously diagnosed, 71.2% (95%CI 68.6-73.6) were in care, 65.8% (95%CI 62.8-68.2) were on ART and 61.8% (95%CI 59.0-64.5) had a viral load below 1,000 copies. Proportion of population viral suppression (VL<1,000copies/ml) was higher in women compare with men (65.3% vs 53.9%, p<0.001)

Conclusions: This population incidence study suggests that high levels of population viral suppression and low incidence can be achieved in high-prevalence settings in sub-Saharan Africa. However, no causal relation between population viral suppression and low incidence can be made from this cross-sectional study.

993 Disparities in Viral Suppression Among a Large Cohort of HIV-Infected Persons in Washington, DC

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Background: Although achieving viral suppression (VS) is the ultimate goal of the HIV care continuum, it is well known that disparities exist among particular subpopulations with regard to treatment access. Accordingly, one of the goals of the National HIV AIDS Strategy is to reduce HIV-related health disparities. We sought to identify potential disparities in VS among an urban cohort of HIV-infected persons in care.

Methodology: Data from the DC Cohort, a longitudinal observational cohort study of HIV-infected persons in care in Washington, DC were used for this analysis. Data were abstracted from participants' electronic medical record data and through manual data abstraction from 13 participating clinical sites. VS was defined as a viral load (VL) <200 copies/ml at the time of enrollment or at the most recent VL measurement. Descriptive statistics, bi- and multivariate logistic regression analyses were performed to identify factors associated with achieving VS.

Results: Among the first 3,589 participants, most were black (75%), male (75%), were a median age of 47 years at enrollment, and 40% were infected through male-to-male sexual contact. At enrollment, 3,303 (92%) participants were prescribed antiretrovirals with a mean treatment duration of 5.1 years, and 74.2% were virally suppressed (VS). Unadjusted logistic regression analysis found that those not VS were significantly more likely to be black, female, younger, have temporary housing, public insurance, unemployed, have co-morbid alcohol or substance abuse conditions and be treatment experienced. After multivariable adjustment including for HAART therapy, blacks (aOR:0.48; 95%CI:0.30, 0.78); younger participants (aOR:1.18; 95%CI:1.10, 1.26 per 5 year increase); and treatment inexperienced participants remained significantly less likely to be VS. Viral suppression was not significantly associated with insurance status, employment, duration of HIV infection or co-morbid medical conditions including hepatitis B, C, depression, or diabetes. Among participants who were not VS, 16.9% had VL ≥100,000 copies/ml at enrollment. Longitudinal analysis among 361 participants from consent date forward found that after 373 person-years of follow-up, 88.6% of participants remained VS; the median VL among unsuppressed participants was 1,430 copies/ml.

Conclusions: Among a large urban cohort of HIV-infected persons, the majority of persons were able to achieve and maintain viral suppression; however, disparities in viral suppression exist with regard to race, sex, social and economic factors. Efforts to identify these populations with disparate outcomes will allow for appropriate targeting of resources to improve viral suppression and achieve national goals.

994 Community Viral Load and HIV Incidence: A Multi-City Study of High-Risk Populations in India

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Background: Community viral load (CVL) has been proposed as a barometer of HIV transmission risk within populations. However, there are different ways in which CVL may be measured and few data are available comparing methods with HIV incidence in representative samples from high-risk populations.

Methodology: We recruited men who have sex with men (MSM) from 12 cities and injection drug users (IDU) from 10 cities across India (only 1 city overlapped) for HIV counseling and testing (target recruitment of 1000 per site) using respondent-driven sampling, a method that produces unbiased estimates in `hidden' populations. We constructed 4 measures of CVL: 1) average $\log_{10}$ HIV RNA in those aware of their HIV-positive status (CVL-aware), 2) average $\log_{10}$ HIV RNA in all HIV-infected (CVL-positive), 3) HIV prevalence, and 4) prevalence of infected individuals with HIV RNA >1000 c/mL (viremia prevalence). CVL-aware reflects HIV RNA among people accessing care, but does not consider the contribution of undiagnosed individuals. CVL-positive includes data from both diagnosed and undiagnosed individuals. Viremia prevalence reflects both the HIV prevalence and the proportion with non-suppressed HIV RNA in a community. We estimated HIV incidence in each community with a validated multi-assay algorithm that used HIV RNA, CD4, BED, and avidity in HIV seropositive participants. We used Spearman correlation coefficients and Poisson regression to assess the associations between site-level HIV incidence estimates and the 4 CVL measures. HIV prevalence and viremia prevalence were $\log_e$-transformed, and all CVL indices were expressed per standard deviation (SD) to facilitate comparisons.

Results: A total of 21 495 participants were recruited across 22 sites (12 022 MSM and 9473 IDU). The median (range) site-level CVL measures were 3.0 $\log_{10}$ c/mL (2.5, 4.2) for CVL-aware, 3.8 $\log_{10}$ c/mL (2.6, 4.4) for CVL-positive, 10.7% (1.9, 47.2) for HIV prevalence, and 5.3% (1.6, 26.4) for viremia prevalence. The median (range) site-level HIV-incidence was 0.5% per year (0, 3.4). The Table shows correlations (rho) and incidence rate ratios per SD increase in each of the 4 CVL indices, the latter adjusted for MSM vs. IDU site. Patterns were similar in the MSM and IDU strata.

Associations between CVL indices and HIV incidence among MSM and IDU in 22 Indian cities		
Community viral load index	Rho (P value)	Incidence rate ratio (95% confidence interval)
CVL-aware	0.36 (0.11)	1.54 (1.17, 2.03)
CVL-positive	0.19 (0.40)	1.59 (1.17, 2.16)
HIV prevalence	0.56 (0.007)	1.61 (1.04, 2.55)
Viremia prevalence	0.72 (<0.001)	2.05 (1.35, 3.12

Conclusions: Among the CVL indices evaluated, the prevalence of viremic individuals was the most strongly associated with current HIV incidence in a multicity study of MSM and IDU in India.

995 Declines in Community Viral Load in the Context of Population Prevention Strategies in the Bronx

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Background: Multiple HIV prevention strategies involving expanded HIV testing and implementation of expanded treatment guidelines, both population-wide and institutionally, have been recently instituted in the catchment area of the Montefiore Medical Center clinical network (MMC), the largest provider of HIV care in the Bronx, New York. We aimed to examine the association between the introduction of these initiatives and improvements in community viral load between 2007 and 2012.

Methodology: We used data from the Einstein-Montefiore Center for AIDS Research (CFAR) HIV Integrated Clinical Database, which combines electronic medical records, laboratory test results, prescription data, and clinical intake information. Inclusion criteria included HIV infection, intake at an outpatient clinic affiliated with MMC, age 13+, and at least one HIV-1 viral load (VL) measure obtained during the study period. We described community viral load based on the geometric mean of the last recorded VL per individual in each year, including both those in regular care and those in sporadic care. We examined calendar-year trends in VL suppression (<200 copies/mL) in the population overall and among prespecified subgroups. We assessed disparities in VL suppression by age, sex, race/ethnicity, and transmission risk using Poisson regression with generalized estimating equations.

Results: We analyzed 6,998 HIV-infected individuals receiving outpatient care at MMC between 2007 and 2012 (median age 48, interquartile range 41-55, 47% Hispanic, 45% black). The median HIV-1 VL throughout this period was <200 copies/mL. We identified a significant decrease in the geometric mean VL, from 567 copies/mL in 2007 to 90 copies/mL in 2012, and a corresponding increase in the percent of individuals with a suppressed VL, from 57% to 75% (both $p_{trend}<0.0001$). Population groups significantly less likely to have a suppressed VL were younger individuals, those of black race or Hispanic ethnicity, men who have sex with men [92% of whom were black or Hispanic], and perinatally-infected individuals. In adjusted analyses, only age and race/ethnicity remained as significant barriers to suppression. Increases in VL suppression occurred across most subgroups, including those traditionally believed to be less engaged in care such as injection drug users, but were less consistent among those age 13-24 ($p_{interaction}=0.05$).

Conclusions: In this high HIV prevalence area, population-wide HIV prevention strategies, including implementation of expanded treatment guidelines, coincided with improvement in community viral load among most groups. More attention is needed to address continued disparities in the care continuum in the Bronx, particularly among young people.

Session P-W4 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Cascade of Care

996 New Epidemiological Indicator To Estimate the Gap Between WHO Eligibility ART Criteria and Reality

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Background: Many HIV-infected persons initiate antiretroviral therapy (ART) late. CD4 count distribution at ART initiation is used to assess the timeliness of ART. We propose a new additional indicator to estimate the gap between the WHO recommended and the actual timing of ART initiation: the lost time in starting ART (LTISA). Here, we estimated LTISA in Cameroon over time.

Methodology: LTISA was calculated by subtracting the mean time from HIV seroconversion to ART eligibility threshold to the mean time from HIV seroconversion to ART initiation. We estimated the time from seroconversion to CD4 cell count thresholds <350 and <200 cells/mm3 using data from the ANRS 1220 Primo-CI cohort of HIV seroconverters. CD4 cell count declines were analyzed by fitting a mixed linear model. From this model, we derived an equation for the time it takes for an HIV-infected person to reach a given CD4 threshold, which depended on the estimated CD4 count at seroconversion and CD4 cell count slope. To estimate the time from seroconversion to ART initiation in Cameroon we conducted a survey in a nationally representative sample of HIV facilities. Medical records of adult HIV patients who initiated ART in these facilities in the month of October over the period 2007-10 were reviewed to collect sociodemographic and CD4 cell counts at ART initiation data. We then assessed how many CD4 counts were lost from seroconversion to ART initiation, and convert these losses into time using the aforementioned equation.

Results: 3037 CD4 count measurements from 350 seroconverters of the Primo-CI cohort were used in the mixed model. Mean CD4 cell counts at seroconversion was 550/mm3 (95% confidence intervals (CI): 526-574) and mean CD4 cell counts decline during the first year after seroconversion was 47 cells/mm3 (95% CI: 46-48). We estimated that median times from seroconversion to CD4 cell counts <350 and <200 cell/mm3 were, respectively, 4.4 years (inter-quartile range (IQR): 2.0-7.6) and 8.1 years (IQR: 5.2-11.3). Median CD4 cell counts at ART initiation among 4154 Cameroonese patients was 144/mm3 (IQR: 67-223). We found that median times from seroconversion to ART initiation ranged from 9.1 to 11.0 years, depending significantly on gender, age and period of ART initiation. Median time from seroconversion to ART initiation was shorter after than before the adoption of 2010 WHO eligibility ART criteria (9.3 versus 10.2 years). Despite this decrease, LTISA in Cameroon increased from 2.9 to 5.4 years over the same period because the CD4 threshold for ART eligibility was increased from 200 to 350 cells/mm3.

Conclusions: LTISA could provide useful information to monitor progress made by countries in reducing gaps between the WHO eligibility ART criteria and the actual timing of ART initiation.

997 Trends in Cascade of Care in the Eastern European Country of Georgia: 2008-2012

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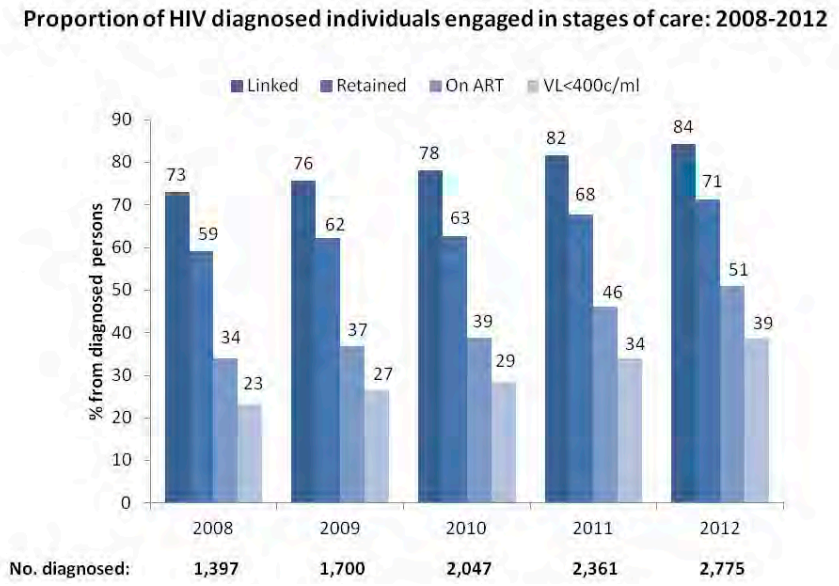
Background: The HIV epidemic is rapidly evolving in the Eastern Europe. There is limited information about the patterns of engagement in HIV care in this region. We aimed to assess trends in cascade of care in the country of Georgia over the period of 2008-2012.

Methodology: The analysis included all adult (age ≥18 years) HIV patients diagnosed in Georgia from 1989 through 2012. Data was extracted from the national HIV/AIDS database. The proportions of patients linked to care, retained in care, receiving antiretroviral therapy (ART) and with viral load <400 copies/ml were calculated from the total number of diagnosed HIV patients known to be alive at the end of each calendar year.

Results: A total of 3,554 adult persons were diagnosed with HIV in Georgia and 779 of them died by the end of 2012. Among diagnosed patients 74% were men and 55% had history of injection drug use (IDU). Linkage to care increased from 73% to 84% (p<0.0001), with the most notable improvement seen among persons with history of IDU (68% vs. 80%, p<0.0001). The proportion of patients retained in care increased from 59% to 71% (p<0.0001). However, retention among those linked to care did not vary significantly over the study period. Phased implementation of ART initiation criteria of CD4 count <350 cells/mm3 led to marked increase in ART coverage and proportion of virally suppressed patients. Average CD4 cell count at ART initiation increased from 133 cells/mm3 to 194 cells/mm3 (p<0.0001). Compared to non-IDUs, persons with history of IDU were less likely to engage in various stages of care at any studied year.



Conclusions: Our analysis demonstrates that engagement in the continuum of HIV care in Georgia has been improving over time. IDUs are at higher risk of suboptimal engagement. Additional efforts are needed to increase retention in care and earlier initiation of ART.

998 Use of National Standards To Monitor HIV Care and Treatment in a High Prevalence City – Washington, DC

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Background: The United States Department of Health and Human Services (DHHS) recently identified a set of seven core indicators for monitoring the provision of HIV prevention, care and treatment services. Additionally, the Institute of Medicine (IOM) has also put standard measures in place to assess HIV-related core indicators and quality of care outcomes. With the availability of these measures, population-based outcomes related to HIV care and treatment can more easily be monitored. We sought to examine outcomes along the care continuum among a cohort of HIV-infected persons in care in Washington, DC, a city with one of the highest HIV prevalence estimates in the U.S.

Methodology: The DC Cohort is a longitudinal observational cohort study of HIV-infected persons receiving outpatient care at 13 clinics in Washington, DC. Baseline and longitudinal data on participants enrolled between 1/1/11 and 8/15/13 in the DC Cohort were obtained through electronic medical record abstraction and manual data entry and used to measure select DHHS and IOM measures.

Results: With respect to the DHHS measures, during the period from enrollment to 12-months, 61% of Cohort participants were retained in medical care, 89% were on antiretrovirals (ARVs), 73% were virally suppressed and 8% were homeless or unstably housed. Upon review of the IOM core indicators for HIV care and quality measures, 52% were in continuous care per the IOM definition, 40% were routinely monitored using CD4 counts and 81% of those in continuous care had a CD4≥350 cells/µl. Only 3% of participants with CD4 counts less than 500 cells/µl had not been started on ARVs and viral load monitoring was routinely performed among 52% of participants. With respect to STD screenings, 5% of participants had been screened for gonorrhea and chlamydia, and 15% were screened for syphilis.

Conclusions: Assessment of these standard HIV care indicators show that although retention in care and routine immunologic and virologic monitoring were moderate, high proportions of participants were receiving antiretroviral therapy with good outcomes as measured by CD4 counts and viral loads. Continued longitudinal analysis will assist in identifying areas for improvement in the quality of HIV clinical care.

U.S. DHHS and IOM Quality of Care Indicators among DC Cohort Participants		
U.S. DHHS Measures for Monitoring HIV Prevention, Treatment, and Care Services		
Retention in medical care (n=742)	Number of persons with HIV who had ≥1 HIV medical care visit in each 6 month period of the 24 month measurement period, with a minimum of 60 days between the first medical visit in the prior 6 month period and the last medical visit in the subsequent 6 month period	455 (61.3)
ARV therapy among persons in HIV medical care (n=455)	Number of persons with HIV who are prescribed ART in the 12-month measurement period	403 (88.6)
Viral load suppression among persons in care (n=455)	Number of persons with HIV with a viral load	332 (73.0)
Housing status at baseline (n=4,053)	Number of persons with HIV who were homeless or unstably housed in the 12-month measurement period	311 (7.6)

IOM Core Indicators for HIV Care and Quality Measures		
Proportion in continuous HIV care (n=742)	Proportion of people with HIV who are in continuous care (≥2 routine HIV medical care visits in the preceding 12 months ≥ 3 months apart)	388 (52.3)
Regular CD4 testing for monitoring immune function (n=1,021)	Proportion of people with HIV who received ≥2CD4 tests in the preceding 12 months	408 (40.0)
Regular viral load monitoring for clinical progression (n=768)	Proportion receiving ≥2 VL tests in 12 months from baseline	396 (51.6)
Maintenance of immune function to reduce risk of OIs and cancer (n=388)	Proportion of people with HIV in continuous care for 12 or more months and with a CD4+ cell count ≥350 cells/mm3	314 (80.9)
Appropriate initiation of ART (n=3,976)	Proportion of people with HIV and a measured CD4+ cell count	105 (2.6)
Screening for sexually transmitted infections (n=4,053)	GC and Chlamydia screening at least once; Syphilis screening annually	GC: 214 (5.2) Chlamydia: 213 (5.2) Syphilis: 607 (15.0)

999 Potential Impact of Viral Load On ART Eligibility Criteria in Swaziland

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Background: Antiretroviral therapy (ART) programs implementing "treatment as prevention" need to target not only those who need ART for their own health but also those likely to transmit HIV. Observational studies suggest that HIV transmission risk differs depending on whether the viral load (VL) is above or below 10,000 copies/ml. We describe an assessment of the additional persons who would need ART if VL criteria were added to current CD4 count eligibility criteria in Swaziland.

Methodology: In the Swaziland HIV Incidence Measurement Survey, a nationally representative sample of 18,172 men and women, age 18-49, underwent household-based counselling and rapid HIV testing and provided clinical/demographic information in 2010-11. Among 5802 HIV+ individuals identified during the survey, 1000 were randomly selected to participate in a follow-up visit, with collection of blood for CD4 enumeration via automated flow cytometry and viral load using Roche CAPTAQ HIV-1 Test, V2.0.

Results: Among 949 HIV+ individuals who participated in this sub-study, complete CD4 and VL data were available on 927; in unweighted analysis, 456 of these (49%, 95% CI: 46-52%) did not report ART use. Based on current Swaziland guidelines of ART initiation at CD4 threshold of 10,000 copies/ ml were added as a separate ART initiation criterion, the number eligible for ART at CD4<350 would increase by 193 (63%, 95% CI: 57-68%) of the 308 currently ineligible individuals not on ART, an additional 42% (95% CI: 38-47%) of the 456 of the untreated HIV+ sample, and 21% (95% CI: 18-24%) of the entire HIV+ sample.

Conclusions: We provide an estimate of the proportion of additional HIV+ adults who would be ART eligible if a VL threshold were added to CD4 eligibility criteria. Almost one-third of untreated HIV+ persons in our sample are already eligible for ART based on current national CD4 count criteria; effective linkage to ART for them is a program priority. The addition of VL > 10,000 copies/ ml to the initiation criteria would increase the ART-eligible proportion of untreated HIV+ adults in our sample by 42%, to almost 75%. These results indicate that the addition of VL to eligibility criteria could modestly increase demand on Swaziland's ART program. These targeted increases in coverage would be expected to lead to notable reductions in transmission.

VL distribution by CD4 count among HIV+ adults reporting no ART use						
		CD4 Count (cells/ml^3)				
		TOTAL	0-199	200-349	350-499	>500
Viral Load (copies/ml)	TOTAL	456	63	85	110	198
	<1000	42	3	6	5	28
	1,000-9,999	90	1	7	19	63
	10,000-99,999	226	33	38	66	89
	>100,000	98	26	34	20	18

1000 Health Insurance for PLWH: Establishing a Baseline To Monitor the Impact of the Affordable Care Act

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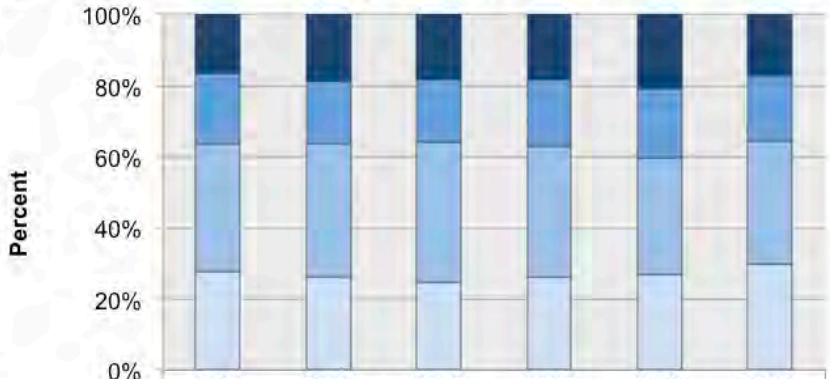
Background: The Affordable Care Act (ACA) will expand Medicaid coverage in most states to include all people with incomes up to 133% of the federal poverty level and will facilitate the purchase of private coverage through health insurance marketplaces. These changes will increase access to care for many people living with HIV (PLWH). Baseline data are needed to monitor the impact of the ACA on access to HIV care. This study examines trends in health insurance coverage (2006-2011) among HIV-infected adults at 13 geographically diverse clinics in the HIV Research Network.

Methodology: Health insurance coverage in each year was categorized as private, Medicaid, Medicare (including dual Medicare/Medicaid), and uninsured/Ryan White. We used multinomial logistic regression to determine if the proportion of patients with each insurance type changed over time, adjusting for age, sex, race/ethnicity, HIV transmission risk, and CD4 count.

Results: Between 2006 and 2011, 37,749 HIV-infected adults were followed for a total of 120,464 person-years. Overall, there were slight fluctuations in the proportion of patients with each insurance type, with no clear trends over time. The proportions of patients with private insurance, Medicare, Medicaid, and uninsured/Ryan White in each year ranged between 17-21%, 18-20%, 33-40%, and 25-30%, respectively. (Figure)

Significant ($p<0.01$) associations with insurance type were as follows. Private insurance was more common among whites (30%) than Blacks (15%) or Hispanics (10%), and among persons with MSM (26%) than heterosexual (13%) or IDU (10%) risk. Medicare was highest among those ≥65 years old, and lowest among 18-24 year olds (5%). Medicaid was more common among women (50%) than men (31%), and among persons with IDU (53%) than MSM (24%) or heterosexual (42%) risk. Hispanics were more likely to be uninsured (36%) than whites (27%) or Blacks (23%). Similarly, young adults (18-24 year olds) were more often uninsured (51%) than persons aged 65 years or older (7%).

Figure: Health Insurance Coverage for PLWH, 2006-2011



	2006	2007	2008	2009	2010	2011
Private	17	19	18	18	21	17
Medicare	20	18	18	19	19	18
Medicaid	36	38	40	37	33	35
Uninsured/RW	28	26	25	26	27	30

Conclusions: Health insurance coverage was stable between 2006 and 2011, providing a firm baseline for assessing the impact of the ACA. Disparities in health insurance coverage exist, particularly for racial/ethnic minorities and younger adults. Monitoring how health insurance coverage changes will be critical to ensuring that PLWH benefit from health reform and for defining the future role of the Ryan White Program.

Session P-W5 Poster Session
Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Acute Infection

1001 Atypical Clinical Presentations Occur in One Third of 293 Patients With a Primary HIV-1 Infection

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Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, Zurich, Switzerland

Background: Proportion and disease-spectrum of atypical clinical presentations in primary HIV-Infection (PHI) has not systematically been studied. Unusual presentation of PHI may lead to delayed diagnosis with impact on transmission.

Methodology: Between January 2002 and June 2012 we prospectively enrolled 293 individuals with a well-documented PHI in the Zurich Primary HIV Infection Study, which is an open label, non-randomized, observational, single-center study. PHI was classified as "acute" (acquisition of infection during the last 3 months) or "recent" (acquisition during the last 6 months). At the first visit, a detailed history of symptoms and clinical signs of PHI, a physical examination and standard and specific HIV laboratory parameters were obtained. "Typical" ARS was determined in case of documented or reported fever (temperature > 38° Celsius) plus at least one symptom OR ≥ 2 symptoms (in absence of fever) considered as ARS symptoms in literature. "Atypical presentation" was determined by study-physicians based on patient's medical history, review of medical chart, lack of any ARS symptoms OR a single symptom only. The date of infection (EDI) for each patient was estimated integrating all available clinical and laboratory data. Time to diagnosis was calculated based on EDI and date of first positive screening test.

Results: We analysed 293 individuals with PHI, including 271 males. PHI was classified in 245 (84%) individuals as "acute" and in 48 (16%) as "recent". PHI manifested as typical ARS in 203 (69%) of 293 patients. Overall, PHI presented atypically or with an opportunistic infection (OI) in 90 (31%) of 293

patients, 16 (18%) of them were fully asymptomatic. Patients with atypical PHI presented with a broad spectrum of diseases (table 1). Gastrointestinal tract and central nervous system were the most prevalent organ systems for atypical PHI and OI's. Atypical presentation did not lead to a significantly delayed diagnosis (median time EDI to first positive test without symptoms: 42 days [95% Bootstrap confidence interval 18.4, 65.6]; atypical presentation: 32 days [25.8, 38.2], typical ARS: 29 days [24.8, 33.2]; p= 0.13), but a surgical intervention was required in 6 (6.5%) of 90 patients.

Conclusions: Atypical presentations and OI's occur in a substantial proportion of patients with PHI, however, did not result in delayed diagnosis. This may be explained by the severe clinical presentation of these patients leading to a low treshold for HIV testing.

Table 1: Atypical clinical presentations in 90 (of 293) patients with a primary HIV-1 infection

Type of presentation	Number (%)	Acute infection (%)	Baseline CD4[^] (percentage)	Baseline viruslcad log_{10}RNA	Inpatient (%)	Outcome
Opportunistic infections*						
Soor-stomatitis/oesophagitis	13 (14)	12 (92)	346 (26)	6.7	8 (62)	survived
CMV colitis	1 (1)	-	164 (22)	6.5	1 (100)	intervention
CMV gastritis	1 (1)	1 (100)	427 (26)	6.1	-	survived
CMV hepatitis	2 (2)	2 (100)	432 (24)	6.7	2 (100)	
Multisegmental herpes zoster	1(1)	1 (100)	305 (21)	5.4	-	survived
Autoimmune thrombocytopenia[*]	1 (1)	1 (100)	165 (24)	6.4	1 (100)	survived
Peripheral polyradiculoneuritis	1 (1)	1 (100)	215 (9)	6.0	-	survived
Severe diarrhea > 30days	1 (1)	1 (100)	343 (28)	6.0	2 (50)	survived
Total:	21 (23)	19 (90)	299 (23)	6.2	14 (67)	
Central nervous system						
Severe encephalitis	2 (2)	2 (100)	480 (35)	6.5	2 (100)	survived
Herpes simplex 1 meningitis	1 (1)	1 (100)	585 (35)	6.3	1 (100)	survived
Paresis (e.g. cranial nerves)	3 (3)	2 (66)	460 (16)	6.8	2 (66)	survived
Prolonged vertigo	1 (1)	1 (100)	222 (33)	6.6	1 (100)	survived
Acute psychiatric disorder	3 (3)	1 (33)	466 (19)	6.5	1 (33)	survived
Distal paresthesia	1 (1)	1 (100)	589 (18)	4.8	-	survived
Total:	11 (12)	8 (73)	483 (26)	6.2	7 (64)	
Ocular						
Herpes keratitis	1 (1)	1 (100)	470 (18)	5.6	-	survived
Gastrointestinal tract						
Tonsilitis	6 (7)	4 (66)	364 (29)	6.9	3 (50)	survived
HSV-1 stomatitis/oesophagitis	1 (1)	1 (100)	389 (38)	6.9	1 (100)	survived
Gastritis with gastric bleeding	1 (1)	1 (100)	503 (36)	8.0	1 (100)	intervention
Diarrhea only	1 (1)	1 (100)	502 (34)	3.4	-	
Acalculous cholecystitis	1 (1)	1 (100)	643 (29)	7.0	1 (100)	intervention
Appendicitis	1 (1)	1 (100)	840 (35)	4.2	1 (100)	intervention
Anal abscess with *E. faecium*[*]	1 (1)	1 (100)	277 (18)	6.2	1 (100)	intervention
Anitis	1 (1)	-	378 (25)	6.7	-	survived
Total:	13 (14)	10 (77)	499 (31)	6.1	8 (62)	
Respiratory tract						
Pneumonia (e.g. *P. aeruginosa*)	3 (3)	3 (100)	260 (15)	6.1	1 (33)	survived
Cough only	2 (2)	2 (100)	257 (25)	5.0	-	survived
Total	5 (6)	5 (100)	258 (20)	5.6	1 (20)	
Heart						
Acute atrial fibrillation	1 (1)	1 (100)	329 (17)	6.6	-	survived
Urogenital tract						
Acute renal failure	1 (1)	1 (100)	355 (43)	5.0	1 (100)	survived
Prostatitis	1 (1)	-	990 (38)	3.8	-	survived
Epididymitis	1 (1)	1 (100)	196 (21)	3.7	1 (100)	intervention
Total:	3 (3)	2 (66)	514 (34)	4.1	2 (66)	
Skin and soft tissue						
Impetigo contagiosa	1 (1)	1 (100)	432 (35)	5.4	-	survived
S. aureus folliculitis	1 (1)	1 (100)	542 (29)	6.1	-	survived
Sternal pyodermia	1 (1)	1 (100)	477 (36)	4.2	1 (100)	survived
Mastitis	1 (1)	1 (100)	664 (31)	4.5	1 (100)	survived
Gluteal mycosis	1 (1)	1 (100)	237 (8)	5.9	-	survived
Hair loss	1 (1)	-	698 (40)	4.9	-	survived
Severe dermatitis	2 (2)	1 (50)	774 (26)	5.9	-	survived
Total:	8 (9)	6 (75)	546 (29)	5.2	2 (25)	
Blood system						
Severe pancytopenia[*]	3 (3)	3 (100)	329 (29)	6.7	3 (100)	survived
Thrombophlebitis	1 (1)	1 (100)	127 (12)	5.8	-	survived
Severe electrolyte disturbance	1 (1)	1 (100)	560 (20)	4.2	1 (100)	survived
Total:	5 (6)	5 (100)	338 (20)	5.6	4 (80)	
Constitutional symptoms						
Weight loss and/or night sweat	7 (8)	7 (100)	476 (26)	5.2	-	
Total	**74 (82)**	**64 (71)**	**421 (24)**	**5.0**	**38 (41)**	
Asymptomatic atypical PHI	**16 (18)**	**7 (8)**	**499 (30)**	**4.4**	**-**	**survived**
TOTAL	**90 (100)**	**71 (79)**	**460 (27)**	**5.1**	**38 (41)**	

* According to Center for Disease Control classificaton state B or C
[^] in 2 cases together with severe neurological symptoms
[*] together with generalized herpes simplex 1 skin-infection
[*] leading to rectostomy; in addition bilateral *P. aeruginosa* pneumonia, arthritis of the left knee, acute renal insufficiency
[*] in 1 case together with *E. faecalis* bacteremia, pneumonia, skin abscesses, retinal hemorrhagia

1002 Evaluating New Definitions of Acute and Early HIV Infection From HIV Surveillance Data

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Background: The Centers for Disease Control and Prevention plans adding acute (Stage 0) infection (AHI) to the HIV staging system. We evaluated our ability to categorize early and AHI using Public Health - Seattle & King County surveillance data.

Methodology: Cases of AHI were identified by pooled nucleic acid amplification testing (NAAT), conducted for men who have sex with men (MSM) with negative antibody tests at King County testing sites since 2003. We calculated inter-test intervals (time from last negative to first positive test) and interpretations of "recent" from the serologic algorithm for recent HIV seroconversion (STARHS) to create surveillance definitions of early and AHI: AHI included inter-test intervals of zero days and 0-30 days; early HIV diagnoses were inter-test intervals of 0-180 days or a STARHS recent result. Last negative HIV tests were lab reports to the HIV/AIDS Reporting System (eHARS) or patient/provider data collected for HIV Incidence Surveillance. Sensitivity was calculated as the proportion of cases correctly identified as early or AHI by surveillance definitions relative to the gold standard of AHI defined by NAAT.

Results: Between 2005 and 2011 2,156 individuals were diagnosed with HIV in King County, including 1,556 (72%) MSM. Of 1,223 individuals with a known testing history (57% of all diagnoses), 377 (31%) tested negative for HIV within six months of their HIV diagnosis. Among 1,104 with STARHS results (51% of new cases), 39% were STARHS recent. Of the 47 MSM with AHI identified by NAAT, 33 (70%; 95% CI=55-82%) had an inter-test interval of six months or less (Table). Over one third (36%) of the 47 AHI cases had documentation of their negative antibody test on the same day in eHARS. Four of these were documented lab test results and 13 came from other sources. Of the 47, 18 (38%) AHI cases had STARHS testing. Of these, 94% (95% CI = 70-100%) were STARHS recent; the single non-recent result was from a four month post-diagnosis specimen.

Conclusions: Early and AHI cases were frequently missed in eHARS because negative antibody tests weren't reported. Similarly, STARHS results were not available for half of all recently diagnosed individuals and a larger proportion of AHI diagnoses. Successful implementation of the revisions to the HIV staging system will require that laboratories report negative HIV tests obtained concurrently with reactive HIV tests.

Acute HIV (AHI) identification sensitivity for inter-test intervals & STARHS; King County 2005 - 2011

Inter-test intervals:	AHI cases identified N (sensitivity)	AHI cases missed N (%)	(95 % CI)
Same day	17 (36%)	30 (64%)	(23-52%)
Acute (0-30) days	28 (60%)	19 (40%)	(44-73%)
Early (0-180) days	33 (70%)	14 (30%)	(55-82%)
STARHS (Serologic algorithm for recent HIV seroconversion) category:			
STARHS recent	17 (36%)	30 (66%)	(23-52%)
STARHS recent limited to those with STARHS results	17 (94%)	1 (6%)	(70-100%)

1003 Association Between Number of Acute Retroviral Symptoms and Extended High Viremia by HIV-1 Subtype

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Background: Prompt identification of persons with acute HIV infection, particularly those likely to have high viral loads after acute HIV, presents important transmission prevention opportunities. In a large study of HIV-1 seroconverters across 9 sites in Africa, we sought to determine whether the number of signs and symptoms of acute retroviral syndrome (ARS) predicted extended high viremia (mean viral load >= 5 log10 copies/ml 130-330 days after infection) in HIV-1 subtypes A, C, and D.

Methodology: Adults who acquired HIV-1 infection in a multicenter HIV-1 incidence study were enrolled in a sub-study assessing ARS, immune progression, and viral load dynamics. 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. ARS signs and symptoms were assessed at sub-study enrollment, and viral load was assessed monthly for 3 months post-EDI and quarterly thereafter. "Extended high viremia" was defined as mean pre-ART viral load >=5 log10 copies/ml

130-330 days post-EDI. We used log-binomial regression to examine associations by subtype between the number of ARS symptoms and extended high viremia, controlling for sex.

Results: Among the 130 volunteers (38%) with pol-derived subtype A infection, extended high viremia prevalence increased linearly with the number of ARS signs/symptoms; those with 2-7 and >=8 symptoms were 1.9 (95% confidence interval: 1.4, 2.8) and 3.7 (1.8, 7.7) times as likely to have extended high viremia vs. those with 0-1 symptom (p=0.03 and 0.003, respectively; Figure). Among the 153 subtype-C volunteers (45%), those with 2-7 symptoms were 2.1 (1.3, 3.4) times as likely to have extended high viremia vs. those with 0-1 symptom (p=0.02; Figure). Among the 59 subtype-D volunteers (17%), extended high viremia prevalence was similar in those with 2-7 vs. 0-1 symptom (p=0.93). In subtypes C and D, 0% of those with >=8 symptoms had extended high viremia (Figure); however, measures were imprecise because few subtype-C and D volunteers reported extreme numbers of symptoms.

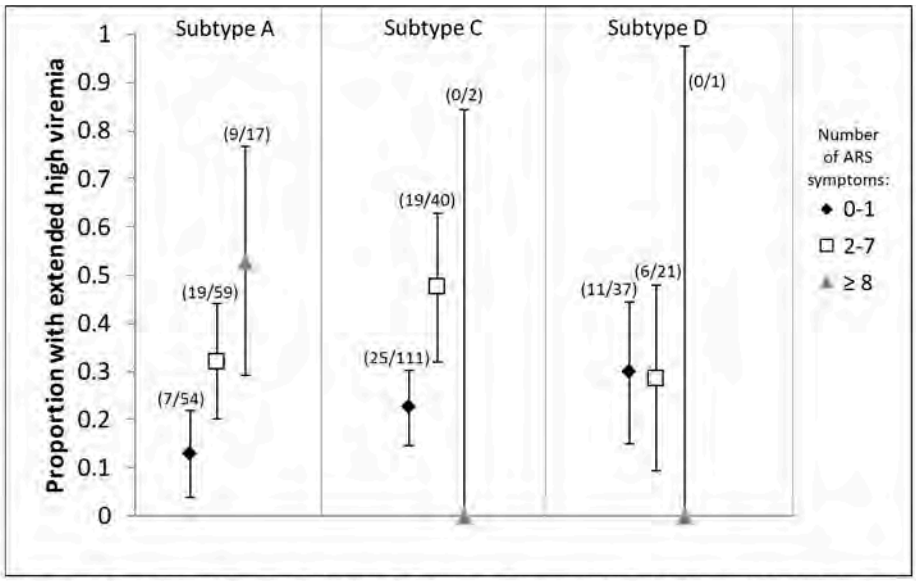

Figure. Prevalence of extended high viremia (mean $\log_{10}$ viral load ≥5 $\log_{10}$ 130-330 days after the estimated date of infection) by subtype and number of acute retroviral syndrome (ARS) symptoms. Numerator and denominator for each proportion are shown in parentheses.

Conclusions: In this multi-site African cohort, the relationship between number of ARS signs/symptoms and extended high viremia varied appreciably across subtypes, suggesting potential differences by subtype in pathogenicity, immune response, and the predictive power of number of symptoms in identifying newly infected persons who likely will have extended high viremia.

1004 Targeted Screening of Young Adults for Acute HIV-1 Infection at Care Seeking in Kenya

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Background: Up to 40% of new HIV-1 infections derive from sexual contact with patients with acute HIV-1 infection (AHI) who frequently seek care for symptoms prior to seroconversion. We assessed whether AHI could be detected in young adults seeking urgent care at pharmacies (PR) and health facilities (HF) in Coastal Kenya.

Methodology: Young adults (<30 years of age) meeting one of four predetermined AHI risk criteria: (1) fever (≥37.5 °C axillary), (2) sexually transmitted disease symptoms (STD), (3) diarrhoea, or (4) body pains and multiple partners in the last 2 months were referred from 5 PR and identified at 5 HF. Prevalent HIV-1 was determined by nationally recommended serial HIV-1 testing (2 rapid tests) in all patients assessed for AHI-criteria. HIV-1-negative or -discordant patients who accepted p24 antigen testing were randomized to reminders or no reminders and invited for repeat rapid testing 2-4 weeks following enrollment (Clinicaltrials.gov, NCT01876199). AHI was diagnosed by a positive p24 antigen test and subsequent seroconversion. Febrile HIV-1-negative patients were also screened for malaria using a rapid test, with PCR confirmation of positives.

Results: Of 6527 young adult outpatients, 3602 (55.2%) were screened for AHI risk criteria and tested for prevalent HIV-1.Overall, 139 (3.9%) patients had undiagnosed prevalent HIV-1, of whom 36 (25.9%) had never tested, 100 (71.9%) were previously negative, and 3 (2.2%) had an unknown status. The prevalence of undiagnosed HIV-1 among patients meeting AHI risk criteria was 7.6% (68/896) vs. 2.6% (71/2706) among those who did not (p<0.001). This finding did not differ by source of referral (PR vs. HF). AHI was diagnosed in 6 of 507 HIV-1-negative or -discordant patients (prevalence 1.2%, 95% confidence interval (CI): 0.4%-2.6%), including 2 patients referred from PR. Of these 6 AHI cases, 4 were diagnosed among the 242 patients with fever (prevalence 1.7%, 95% CI: 0.5%-4.2%), vs. 2 among 265 non-febrile patients (prevalence 0.7%, 95% CI: 0.0%-2.7%). Malaria was diagnosed in 4 of the 242 febrile patients (prevalence 1.7%). No additional HIV-1 seroconversions were detected at repeat HIV-1 testing of 243 (47.9%) participants who returned for repeat rapid testing. Return rates were higher among patients who received reminders (58.5% vs. 41.1%, p<0.001).

Conclusions: We found a high burden of undiagnosed prevalent and acute HIV-1 in young adults seeking urgent care at PR and HF in an area endemic for malaria. Reminding patients about follow-up testing was modestly efficacious. AHI prevalence was highest among young febrile adults. An AHI detection strategy targeting febrile young adults seeking care at PR and HF is feasible and could potentially be used to target Treatment as Prevention programs.

Session P-W6 Poster Session
Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**
Incidence Assays

1005 Independent Evaluation of Predicate Incidence Assays for HIV Surveillance

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Background: Accurate estimates of HIV incidence are needed to assess epidemics, calibrate models, and design and evaluate interventions. The cross-sectional use of biomarker-based Tests for Recent HIV Infection (TRIs) in principle offers affordable, low-bias options for incidence estimation. To date, there has been no independent, directly comparative benchmarking of candidate TRIs.

Methodology: A repository was assembled comprising replicate plasma samples from 5641 specimens representing 2007 subjects from studies in Africa, Brazil and the United States, with suitably characterized longitudinal subject information (estimated exposure dates, detailed treatment and clinical history, viral load, CD4 counts). Five TRIs (BED, Limiting Antigen (LAg), Detuned Vitros, Vitros Avidity and Biorad Avidity), previously assessed on a 250 sample 'Qualification Panel', were evaluated using a clade diverse 2500 member 'Evaluation Panel'. Using developers' previously published recent/non-recent discrimination criteria, frequency estimation and regression yielded estimates of the Mean Duration of Recent Infection (MDRI - mean time, within one year post estimated exposure, that subjects return recent results), False-Recent Rate (FRR - proportion of recent test results among patients at least one year post infection) and assay reproducibility (CoV - coefficient of variation of assay reading). FRR was calculated by time since infection for untreated patients, and separately by ARV treatment status.

Results: Table 1 shows primary performance characteristics of the incidence assays. FRR is reported by treatment status and in a hypothetical population with 30% of positives ART suppressed. Treated versus untreated FRR differences all have $p<0.001$.

Conclusions: This is the first independent evaluation of predicate incidence assays. According to developers' published protocols, none appears suitable, in stand-alone form, as a widely applicable incidence surveillance tool. As viral suppression drives false recent results, optimized use of serologic assays, using low viral load as indicative of non-recent infection, could yield practical TRIs. Work is on-going to 1) evaluate additional assays, 2) optimise multiple biomarker algorithms, 3) estimate FRR with realistic population representative distributions of clinical stages, and 4) maintain and expand the repository to support new work including biomarker discovery.

Table 1: Primary Performance Characteristics of Tests

Assay	Mean Duration of Recent Infection (days) [1]	False Recent Rate			Assay Reproducibility (CoV) [5]
		Untreated [2]	ART Suppressed [3]	Population [4]	
LAg	180 (161-197)	1.1%	30.2%	9.9%	15%
BED	246 (227-264)	6.7%	46.9%	18.7%	9%
LS-Vitros	230 (209-248)	8.8%	58.3%	23.6%	8%
BioRad Avidity	265 (247-280)	6.4%	35.4%	15.1%	21%
Vitros Avidity	238 (218-258)	7.2%	52.1%	20.7%	3%

[1] Mean time under recent/non recent threshold, estimated from 815 observations on 246 seroconverters
[2] 1126 specimens. Mean time post infection 10 years. Standard deviation 2.5 years
[3] 96 specimens from patients with VL below 75 copies per ml, initiated more than 6 months post exposure
[4] Weighted averaging of preceding two columns, assuming 30% viral suppression in positive population
[5] Based on at least 25 aliquots of a specimen with mean assay result near recent/non recent threshold

1006 Performance of the Limiting Antigen-Avidity EIA for Use With Dried Blood Spot Specimens

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Background: The Limiting Antigen-Avidity EIA (LAg-Avidity EIA) is a newly developed HIV-1 incidence assay that was recently validated for plasma specimens for estimation of HIV-1 incidence, a critical end-point measurement to determine the impact of HIV programs. The LAg-Avidity EIA was developed for global use and is available as a kit for use with serum/plasma from two manufacturers. Collection of liquid specimen, processing, storage, and transport are challenging in resource-limited countries and dried blood spots (DBS) are the specimen of choice for surveillance activities. Thus, there is an urgent need for the development and qualification of a LAg-Avidity EIA for use with DBS specimens. Here, we present the evaluation of the Maxim LAg-Avidity DBS EIA for use specifically with DBS specimens.

Methodology: A total of 447 matched plasma and DBS specimens were used for this evaluation. Of these, 133 plasma units were purchased from Boca Biolistics (Coconut Creek, FL) and 90 were from Seracare Life Sciences (Milford, MA). Matched DBS were prepared by spotting 100 µl of mock blood (plasma mixed 1:1 with packed red blood cells) onto Whatman 903 filter paper (Whatman plc, United Kingdom). The remaining 224 specimens were collected as unlinked remnant whole blood specimens from HIV-positive patients at an Atlanta-based clinic and matched DBS and plasma were prepared by spotting whole blood onto Whatman 903 filter paper followed by plasma separation. For DBS specimens, 500 µl of specimen diluent was used to elute antibodies overnight from a single 6 mm punch and 100 µl was added to the assay plate. DBS controls were used when testing DBS specimens. All other assay steps remained the same. All plasma and DBS specimens were tested independently by two operators using the Maxim HIV-1 LAg-Avidity EIA (Maxim Biomedical, Rockville, MD) according to the manufacturer's instructions.

Results: Correlation between the DBS and plasma specimens was excellent (R^2=0.94) with 85 specimens classifying as recent and 362 as long-term infections with both specimen types (overall agreement 98.6%, kappa=0.956). DBS kit controls were highly reproducible across 26 runs performed by two operators with inter- and intra-run coefficients of variation (%CV) for the low positive control (LPC) and high positive control (HPC) <10%, similar to plasma controls. Inter-operator normalized optical density (ODn) variability between two operators was <10%.

Conclusions: This evaluation demonstrates the Maxim LAg-Avidity EIA performs similarly with the DBS or serum/plasma specimens, allowing DBS specimens to be used in surveillance activities for the estimation of HIV incidence. This comprehensive evaluation will further facilitate implementation of LAg-Avidity EIA for cross-sectional incidence estimates.

1007 The Impact of HIV Subtype On Specificity of Cross-Sectional HIV Incidence Assays in Rakai, Uganda

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Background: We compared the impact of viral subtype on the specificity of three cross-sectional incidence assays by testing samples from Ugandan individuals infected 2+ years.

Methodology: Samples were obtained from 510 adults (212 subtype A, 298 subtype D) enrolled in the 2008-2009 Rakai Community Cohort Study (RCCS) who were infected for 2.2 to 14.5 years (median 5.4 years). These individuals were not virally suppressed and were antiretroviral drug treatment-naïve. The samples were tested with three assays: (1) the LAg-Avidity enzyme immunoassay (LAg-Avidity, reported as normalized optical density [OD-n]), (2) an avidity assay based on the BioRad 1/2+O ELISA (BioRad-Avidity, reported as avidity index [AI]), and (3) the BED capture enzyme immunoassay (BED-CEIA, reported as OD-n). The performance of these three assays was evaluated using various assay cutoff values (LAg-Avidity: ≤1.5 OD-n; BioRad-Avidity: ≤40% AI; BED-CEIA: ≤0.8 OD-n).

Results: The percentage of samples misclassified by each assay as assay positive (below the assay cutoff) were: LAg-Avidity: 3.3% (17/510, 95% CI: 2.0-5.0), BioRad-Avidity: 12.9% (66/510, 95% CI: 10.0-16.0), BED-CEIA: 13.7% (70/510, 95% CI: 11.0-17.0). The misclassification frequencies of the assays for subtype A and D samples were: LAg-Avidity: 1.9% (4/212) for subtype A, 4.4% (13/298) for subtype D, p=0.13; BioRad-Avidity: 1.9% (4/212) for subtype A, 20.8% (62/298) for subtype D, p<0.01; BED-CEIA 11.8% (25/212) for subtype A, 15.1% (45/298) for subtype D, p=0.29. The mean LAg-Avidity result (OD-n) was higher for subtype A than D (4.54±0.95 vs. 3.86±1.26, p <0.01). The mean BioRad Avidity result (AI) was higher for subtype A than D (88.9%±12.5% vs. 75.1±30.5, p <0.01). The mean BED-CEIA result (OD-n) was similar for the two subtypes (2.2±1.2 and 2.2±1.3, p <0.9). Overall, 1.4% (7/510, 95% CI: 1.0-3.0) of the samples were misclassified by all three assays; 2.2% (11/510, 95% CI: 1.0-4.0) were misclassified by both LAg-Avidity and BED-CEIA; 2.6% (13/510, 95% CI: 1.0-4.0) were misclassified by LAg-Avidity and BioRad-Avidity, and 3.9% (20/510, 95% CI: 8.0-20.0) were misclassified by BED-CEIA and BioRad-Avidity.

Conclusions: The LAg-Avidity assay (used with a cutoff ≤1.5 OD-n) had the lowest frequency of misclassification in this Ugandan population. However, use of this assay is not recommended in areas where subtype D circulates because of differential misclassification by subtype.

1008 Incorrect Identification of Recent HIV Infection Using a LAg-Avidity Assay in Adults in the US

Andrew F. Longosz[1], Ron Brookmeyer[2], Shruti Mehta[3], Greg D. Kirk[3], Joseph B. Margolick[4], Joelle Brown[5], Thomas C. Quinn[1, 6], Susan H. Eshleman[7], Oliver Laeyendecker[1, 6]

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Background: The United States (US) Centers for Disease Control recently introduced the Limited Antigen-Avidity enzyme immunoassay (LAg-Avidity assay), a new, commercially-available, cross-sectional HIV incidence assay. We analyzed factors associated with misclassification by the LAg-Avidity assay among men who have sex with men and persons who inject drugs living in the US with long-term (2+ years) infection.

Methodology: Samples were obtained from the Multicenter AIDS Cohort Study (MACS), and AIDS Linked to the IntraVenous Experience (ALIVE) cohorts (1089 samples from 666 individuals: 612 samples collected 2-4 years after seroconversion and 477 samples collected 5-8 years after seroconversion). Paired samples from both time points were available for 423 (63.5%) of the 666 individuals. Samples were tested with the LAg-Avidity assay using an assay cutoff of ≤1.5 normalized optical density units (OD-n). Samples with results ≤1.5 OD-n were considered to be misclassified.

Results: Overall, 4.8% (52/1089) of the samples were misclassified by the LAg-Avidity assay. The percentages of samples that were misclassified for different sample subsets were as follows. Overall: 4.8% (52/1089); individuals who reported that they were not on antiretroviral treatment (ART): 3.3% (26/790); individuals with viral loads >400 copies/mL: 1.8% (16/884); individuals with viral loads >400 copies/mL who also had CD4 counts >200 cells/ul: 1.4% (10/705), 95% CI: 0.68-2.60). Age, race, gender and mode of HIV acquisition were not associated with misclassification. In an adjusted analysis, viral load <400 copies/mL (adjusted odds ratio [aOR]: 3.72, 95% CI: 1.61-8.57), CD4 <50 cells/ul (aOR: 5.41, 95% CI: 1.86-15.74) and have a low LAg-Avidity result (≤1.5 OD-n) from an earlier time point (aOR: 5.60, 95% CI: 1.55-20.25) were significantly associated with misclassification. Self-reported ART was not associated with misclassification in the adjusted analysis.

Conclusions: Individuals who are misclassified by the LAg-Avidity assay are likely to be misclassified for the duration of their infection. The current recommendations for the LAg-Avidity assay indicate that individuals on HAART and elite suppressors and AIDS (CD4 <200 cells/ul) should be excluded from analysis does not completely remove all sources of misclassification among long-term infected individuals.

Session P-W7 Poster Session
Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**
Disease Progression/Mortality

1009 Increasing Viral Suppression and Declining HIV/AIDS and Mortality in the Era of Expanded Treatment

Susan E. Buskin[1,2], Amy B. Bennett[1], Julia C. Dombrowski[1,3], Matthew R. Golden[1,3]
[1]Prevention Division, Public Health, Seattle & King County, Seattle, WA, United States, [2]Epidemiology Department, University of Washington, Seattle, WA, United States, [3]Department of Medicine, University of Washington, Seattle, WA, United States

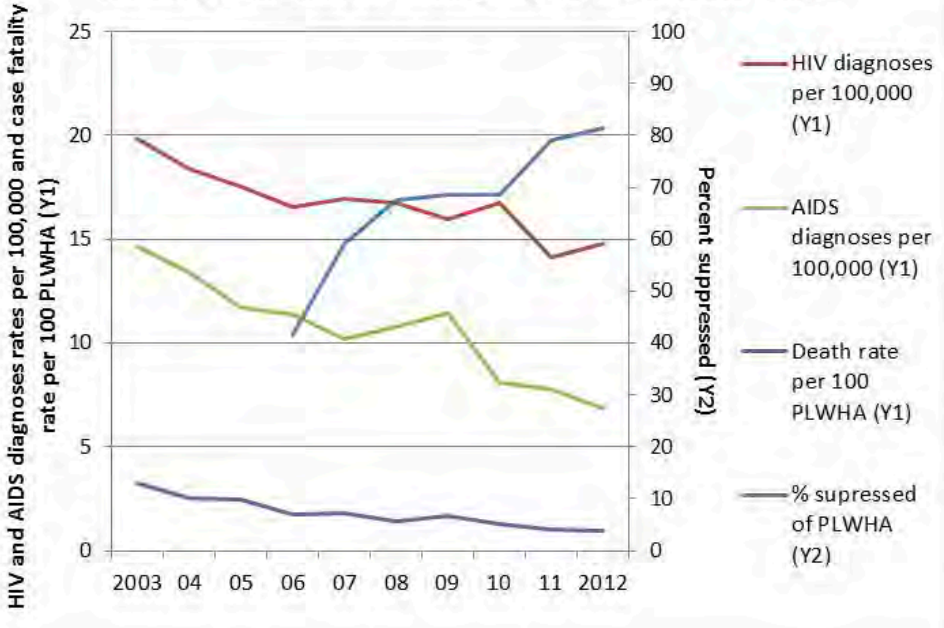
Background: U.S. national data suggest that the number of new HIV diagnoses is roughly stable. However, within that stability, there may be substantial heterogeneity, with divergent trends occurring in different parts of the U.S. and in sub-populations within geographical areas.

Methodology: We used data from the U.S. Census and the King County, WA HIV/AIDS Reporting System (eHARS) 2003-2012 to assess trends in the rate of new HIV diagnoses and AIDS diagnoses in the general population, and in age-adjusted mortality rates among people diagnosed with HIV infection (PLWHA). Trends in viral suppression, defined as any plasma viral load (VL) <200 in a year, were evaluated between 2006 and 2012, the period during which all VL results were reportable in WA State. We assessed trends using Chi-square testing.

Results: Between 2003 and 2012, the rate of new HIV diagnoses decreased from 19.8 to 14.8 per 100,000 residents (decline of 25%); death rates decreased from 3.2 to 0.9 per 100 PLWHA (decline of 72%); and AIDS diagnosis rates declined 53% from 14.7 to 6.9 per 100,000 ($p<0.0001$ for all three trends; see figure). Among 6,801 individuals with any laboratory results reported to HARS 2006 through 2013, viral suppression increased from 46% to 85% ($p<0.0001$). Rates of new HIV diagnoses significantly dropped in both MSM and IDU, and among Hispanics and U.S. born blacks. We did not observe any significant change in the rate of new HIV diagnosis among women, Asians, foreign-born individuals, or among MSM who injected drugs. HIV diagnosis rates significantly declined among individuals aged 35 to 44 years but not younger or older individuals. Death rates declined in both MSM and IDU ($p<0.001$ and $p=0.007$ respectively); the mortality rate among MSM was roughly half that for IDU. AIDS diagnosis rates declined in both MSM and IDU ($p<0.001$ for both) though the rate of decline was steeper among MSM relative to IDU.

Conclusions: The rates of new HIV diagnosis, AIDS diagnoses and mortality in persons living with HIV in King County, WA have significantly declined over the last decade. These changes have occurred concurrent with a dramatic increase in HIV viral suppression, and have affected diverse populations in our area, including racial and ethnic minorities.

Figure: HIV/AIDS diagnoses per 100,000, death rates per 100 people living with HIV/AIDS (PLWHA) and percent suppressed of PLWHA receiving plasma viral load testing; King County. WA 2003 - 2012



1010 BMI and CD4+ T-Cell Recovery at 12 Months Among Adults Initiating ART in the United States and Canada

John R. Koethe[1], Cathy Jenkins[2], Bryan Lau[3], Bryan E. Shepherd[2], Michael J. Silverberg[4], Aaron J. Blashill[5], Aranka Anema[6], Amanda Willig[7], Samuel E. Stinnette[8], Timothy R. Sterling[1], North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD)

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Background: Adipose tissue affects aspects of the cellular immune system, but prior studies have differed on whether a higher body mass index (BMI) promotes increased CD4+ T-cell recovery on antiretroviral therapy (ART). We used the multi-site NA-ACCORD dataset to analyze the relationship between pre-treatment BMI and 12 month CD4+ T-cell recovery among adults intiaiting ART and achieving virologic suppression in the United States and Canada.

Methodology: We included treatment naïve adults starting ART between 1998 and 2010 in NA-ACCORD who maintained HIV RNA levels <400 copies/ml for at least 6 months after ART initiation. The association between pre-treatment BMI and CD4+ T-cell change after 12 months of ART was assessed using multivariable regression models adjusted for age, race, baseline CD4+ count and HIV RNA level, year of ART initiation, protease inhibitor therapy, and clinical site. All continuous variables were fit using restricted cubic splines.

Results: 14,084 patients from 13 cohorts contributed data; 83% were male, 57% were non-white, median age was 40 years (IQR 33, 47), median baseline CD4+ T-cell count was 241 cells/μl (IQR 94, 377), and median baseline $\log_{10}$ viral load was 4.7 copies/ml (IQR 3.9, 5.3). 8,381 participants (70%) maintained virologic suppression for ≥6 months; of these, 4,422 (53%) had a BMI <25 kg/m^2, 2,713 (32%) were overweight (BMI 25.0-29.9 kg/m^2), and 1,246 (15%) were obese (BMI ≥30 kg/m^2). Pre-treatment BMI was associated with 12 month CD4+ T-cell change ($p<0.001$), but the relationship was non-linear ($p=0.006$). Compared with a reference of 25 kg/m^2, a BMI of 30 kg/m^2 was associated with a 26.0 cells/μl (95% CI: 9.7, 42.4) greater CD4+ T-cell count increase among women and a 11.9 cells/μl (95% CI: 5.0, 18.8) increase among men at 12 months. At a BMI over 30 kg/m^2 the observed benefit was attenuated among male patients to a greater degree than among female patients. Lower age and baseline viral load were also associated with a more robust 12 month gain ($p<0.001$ for both). Inferences were similar when the model was adjusted for prior AIDS-defining events, injection drug use, and hepatitis C co-infection among the subset with available data.

Conclusions: A BMI of approximately 30 kg/m^2 at ART initiation was an inflection point associated with greater CD4+ T-cell recovery at 12 months compared to higher or lower BMI values. This finding may indicate that relative adiposity affects peripheral CD4+ T cell recovery on ART, which should be explored further in translational studies to understand the mechanisms and potential therapeutic implications.

1011 Impact of Smoking On Life Expectancy Among HIV-Infected Individuals: The ART Cohort Collaboration

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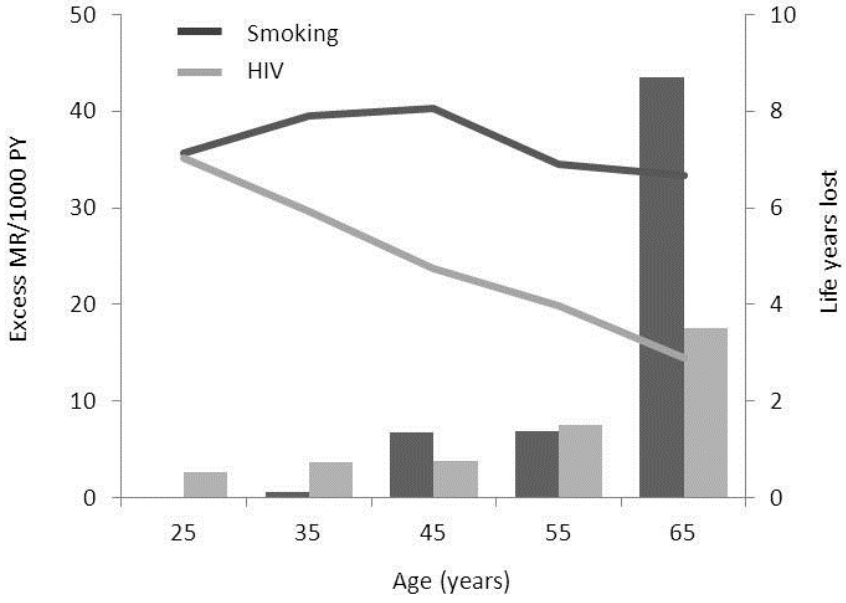
Background: Since the introduction ART non-AIDS related mortality rates (MR) in treated HIV positive people have exceeded AIDS-related MR, and the impact of smoking on life expectancy may have become substantial.

Methodology: We estimated associations of smoking with mortality among treated HIV-infected patients, whose presumed transmission was not via IDU, enrolled in 8 cohorts in Europe and North America (ART Cohort Collaboration). Start of follow up (baseline) was the later of date of ascertainment of smoking status and 1 year after ART initiation. Procedures for standardized coding of deaths were adapted from the CoDe protocol. We used abridged life tables to estimate life expectancy (average years remaining to be lived). Life years lost to HIV were estimated by comparing life expectancies of HIV-infected individuals with the French background population, adjusting for smoking frequency. Excess MRs were estimated by subtracting MRs of ever from never smokers and of HIV-infected individuals from the French background population, adjusting for smoking frequency. Numbers of life years lost were estimated by similar subtraction of life expectancies.

Figure 1: Impact of smoking and HIV on excess mortality rates (bars) and numbers of life years lost (lines) among HIV-infected men.



Results: Of 17,995 individuals followed for 79,760 person-years (PY) 10,767 (60%) were ever smokers MR ratios (MRR) were 1.80 (95%CI 1.47-2.21) comparing ever with never smokers and 1.67 (1.04-2.63) comparing

previous with current smokers. Rates of death from cardiovascular disease and non-AIDS related malignancies were substantially higher among ever compared with never smokers (MRR 6.28 (2.19-18.02) and 2.67 (1.60-4.46) respectively). The loss of life years associated with smoking and HIV among 35 year old HIV-infected men were 7.9 (95%CI 7.1-8.7) and 5.9 (4.9-6.9) years respectively. The life expectancy of 35-year old never smoking HIV-infected men with baseline viral load <400 copies/mL was 43.5 years (95%CI 41.7-45.3), compared with 44.4 years among 35-year old men in the background population. Excess MRs/1000 PY associated with smoking in HIV-infected individuals increased from 0.6 (95%CI -1.3-2.6) at age 35 to 43.6 (95% CI 37.4-49.3) at age ≥65 years (figure 1).

Conclusions: Among treated HIV-infected individuals more life years may be lost through smoking than through HIV. Excess mortality associated with smoking increases markedly with age, therefore increases in the impact of smoking on mortality can be expected as the population ages. Interventions for smoking cessation should be prioritized.

1012 Standardized Mortality Ratios Among Drug Users in Amsterdam Differ by HCV and HIV Infection Status

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Background: The start of a major heroin epidemic in the 1960s was followed by an hepatitis C (HCV) and HIV epidemic among drug users (DU). Therefore, harm reduction interventions (e.g. needle exchange programs) were introduced in Amsterdam during the 1980s. Over time effective HIV and HCV treatment also became available. We hypothesize that because of these health related interventions, DU have reached mortality rates more comparable to the general Dutch population in recent calendar periods. Hence, we investigated temporal trends in mortality rates among DU compared to the general population using Standardized Mortality Ratios (SMR). We also explored whether SMR differed by HIV/HCV infection status and cause of death.

Methodology: Using longitudinal data from the Amsterdam Cohort Studies among 1,263 DU (1985-2012), we estimated all-cause and cause-specific SMR. Four groups of causes of death were addressed: natural, non-natural, liver- and HIV-related deaths. SMR were standardized for calendar period, (<1990; 1990-1996; 1997-2000; 2001-2005 and >2005), age group (20-34, 35-49 and 50-64) and sex. We further obtained the SMR per serological group (HCV mono-, HIV mono-, HCV/HIV co-infected and un-infected for HCV and HIV). Univariable and multivariable Poisson models offsetting the natural logarithm of expected deaths were used to estimate SMR and p-values.

Results: During 18,672 person-years of follow-up, we observed 411 deaths. The all-cause $SMR_{1985\text{-}2012}$ was 14.0 (95%CI=12.7-15.4). There was a significant decline in the all-cause SMR after 1996, ranging from 25.6 during 1990-1996 to 10.8 during 2006-2012 ($p<0.001$). The highest SMR was observed among HCV/HIV co-infected individuals during 1990-1996 ($SMR_{1990\text{-}1996}$=62.9; 95%CI=51.5-76.9), which declined after this period. The SMR for HCV mono-infected and HCV/HIV un-infected DU declined after 1990-1996 and remained relatively stable afterwards. There was a significant decline in the SMR for non-natural deaths ($p<0.001$). The SMR for natural and liver-related deaths declined after 1990-1996 and remained stable afterwards. The SMR for HIV-related deaths was the highest during all calendar periods and increased after 1990-1996.

Conclusions: In line with our hypothesis, significant declines in mortality rates were observed among DU compared to the general Dutch population. However, DU are still at increased risk of dying compared to the general population. The decline in the SMR among DU is mainly attributable to the decline in mortality observed among those coinfected with HCV/HIV. However, HIV-related mortality still remains the main cause of death when compared to the general Dutch population. This study reinforces the importance of harm reduction and HCV/HIV treatment to reduce mortality among DU.

1013 Prognostic Value of the VACS Index for Mortality in British Columbia, Canada

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Background: The Veterans Aging Cohort Study (VACS) index, comprising routine measures of organ system injury alongside HIV indicators, more accurately predicts mortality compared to an index restricted to HIV markers alone. However, evaluation of the VACS index within the Canadian context is necessary to validate its generalizability to Canadian patients. We aim to evaluate the prognostic value of the VACS index after 1 year of combination antiretroviral therapy (ART) for mortality during follow-up compared to an HIV-restrictive index, overall and among subsets of patients reflecting this region's epidemic. We hypothesize the VACS index will remain more discriminative than the restrictive index, and that there may be differences in its predictive accuracy between subgroups of patients.

Methodology: Participants from the HOMER study, a cohort of HIV-positive individuals initiating ART naively after 1996 in British Columbia, were included. Eligibility criteria included having values for all VACS index data elements after 1 year of ART. Previously established weights and cut-offs were used to calculate VACS (age, CD4 count, HIV viral load, hemoglobin, FIB-4 [incorporates AST, ALT, platelets, age], eGFR, and HCV co-infection) and restricted (age, CD4 count, and viral load) index scores. Logistic regression models and C-statistics, along with net reclassification improvement (NRI) were used to test discrimination of the VACS vs. restricted index for all-cause mortality during follow-up.

Results: Of 1228 eligible participants, the median baseline age was 41 years (IQR 34-47), 12% (n=122) were women, and 24% (n=293) had hepatitis C co-infection. In the median follow-up time of 6 years (IQR 3-10), a total of 140 (11%) deaths were reported. After 1 year of ART, the median (IQR) VACS and restricted index scores were 36 (32-44) and 10 (10-23), respectively. Overall, compared to the restricted index, the VACS index showed greater

discrimination for mortality (C-statistic 0.81 vs. 0.74, NRI=19%, p<0.001). The VACS index also demonstrated greater discrimination of mortality among individuals with injection drug use history (n=376) (C-statistic 0.70 vs. 0.63, NRI=35%, p<0.001), and among persons of Aboriginal ancestry (n=105) (C-statistic 0.78 vs. 0.77), however NRI was truncated compared to the overall sample (NRI=8%, p=0.002).

Conclusions: The VACS index is a better predictor of mortality compared to HIV markers alone within this British Columbian cohort; however, its discrimination varies within certain socio-demographic groups.

1014 Impact of Low-Level Viremia On Clinical and Virological Outcomes in Treated HIV Infected Patients

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Background: The goal of antiretroviral therapy (ART) is to maintain undetectable viremia but the impact, particularly on clinical outcomes, of low-level viremia (LLV) between 50 and 500 cp/ml remains unknown.

Methodology: We analysed data from 19 cohorts in Europe and North America contributing to the ART Cohort Collaboration (ART-CC). Included patients started ART ("baseline") with 2 NRTI and either a NNRTI or a PI (atazanavir, darunavir or lopinavir) boosted with ritonavir, and continued ART for at least 6 months, achieving viral load (VL) <50 cp/ml 3-9 months after initiating ART ("virological suppression", VS). LLV50-199 was defined as at least 2 consecutive VL between 50 and 199 cp/ml and LLV200-499 as 2 consecutive VL between 50 and 499 cp/ml, with at least one between 200-499 cp/ml, after VS. All VL assays had 50 cp/ml lower limit of detection.

We used Cox models stratified by cohort to estimate crude and adjusted hazard ratios (HR) for associations of LLV (50-199 cp/ml and 200-499 cp/ml, compared to <50cp/ml) with death, first AIDS event and first virological failure (VF, defined as 2 consecutive VL >=500 cp/ml or 1 VL >=500 cp/ml followed by modification of ART regimen). Adjustments were for baseline age, gender, ART regimen, transmission group, CD4 count, VL and AIDS, and period of ART initiation. LLV categories were considered as time-updated variables.

Results: Among 17853 patients (mean age 40 years, male 76%, mean baseline CD4 238 cells/µL, NNRTI-based regimen 59%), 619 (3.5%) experienced at least one episode of LLV50-199 with no LLV200-499 (mean total duration: 6.8 months) and 481 (2.7%) at least one episode of LLV200-499 (mean total duration: 8.6 months). There were 478 deaths, 554 first post-ART AIDS events and 1022 VF in 68018 person-years follow-up.

LLV200-499 was strongly associated with higher risk of VF (adjusted HR (aHR) 4.15, 95% CI 3.19-5.39). LLV50-199 was weakly associated with VF (aHR 1.40, 0.96-2.02). There was little evidence that LLV50-199 or LLV200-499 were associated with AIDS (aHR 1.13, 0.79-1.61 and 0.91, 0.61-1.28, respectively) or death (aHR 1.20, 0.79-1.83 and 1.12, 0.73-1.71 respectively), compared with prolonged suppression. Neither type of ART regimen (NNRTI- versus PI/r-based) nor cumulative duration of LLV were associated with clinical or virological outcomes.

Conclusions: Among patients virologically suppressed 3-9 months after starting ART, LLV200-499 was strongly associated with virological failure, but not with AIDS events or death. LLV50-199 had little impact on virological failure or clinical outcomes.

1015 Increase in HIV Plasma Viral Load Set-Point Among UK MSM

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Background: The peak in HIV viral load (VL) during primary HIV infection (PHI) may disproportionately contribute to the propagation of the epidemic. Whether there has been a temporal increase in VL during PHI is debatable as findings are conflicting. We examined whether VL at initial presentation and viral load set-point (VLSP), a proxy for virulence, has changed over time.

Methodology: We used data from the UK Register of HIV Seroconverters and restricted analysis to men reporting HIV exposure through sex between men (MSM), diagnosed ≥01/01/1997 with a SC test interval (interval between negative and positive test dates) ≤12 months, and with ≥1 VL in the first 12 months. VLSP was defined as the mean of ART-naïve VL measurements 3-12 months after estimated SC. Using multiple regression models, we examined whether initial VL and VLSP had changed by year of SC (≤1999,2000-01, 2002-03, 2004-05, 2006-07, 2008-9, ≥2010), adjusting for age at SC, SC interval, and time to first VL measurement. Time was modeled using restricted cubic splines to allow for non-linear temporal trends.

Results: 1194 MSM seroconverting in median (IQR) 2006 (2003-2010) at median age 32.6 (26.8-40.1) years were included. They were predominantly white (91%), with SC interval 4.8 months (1.6-8.1), time to initial VL 2.9 months (1.1-4.5), and with VLSP based on 2 (2-3) VL measurements. Median (IQR) initial VL was 4.99 log10 copies/ml (4.34-5.62), increasing from 4.71 (4.05-5.21) ≤1999 to 5.05 (4.46-5.70) ≥2010. In univariate models, there was strong evidence of an increase in initial VL equivalent to 0.2 log copies/ml (95%CI 0.06-0.34) per SC year decade. After adjusting for other covariates, however, there was no evidence of such a linear trend (p=0.104), although initial VL ≥2012 was 0.31 log10 copies/ml (95% CI 0.09-0.54) higher compared to ≤1999. Median (IQR) VLSP was 4.64 log10 copies/ml (4.05-5.08) and increased from 4.51 (4.10-4.89) ≤1999 to 4.76 (4.15-5.16)

≥2010. In adjusted models this was equivalent to an increase of 0.23 log10 copies/ml (0.05-0.42) over the 15 year period, but there was only borderline statistically significant evidence of a linear increasing trend over time (p=0.074).

Conclusions: Our results suggest an increase in HIV virulence among UK MSM. This finding may translate to an increase in HIV incidence in the UK.

Session P-W8 Poster Session
Thursday March 6, 2014, 2:30 PM–4:00 PM Exhibit Hall D
Co-Morbidities

1016 HIV, Non-Communicable Chronic Diseases and Associated Factors in Tanzania and Uganda

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Background: HIV remains a major public health problem in sub-Saharan Africa (SSA), alongside a growing burden of non-communicable chronic diseases (NCDs). Expanded access to antiretroviral treatment has transformed HIV to become a manageable chronic condition, further increasing the burden of these diseases. We conducted a population survey in northwestern Tanzania and southern Uganda in May 2012-April 2013 to determine the prevalence of HIV, NCDs, and associated factors. The aim of this analysis was to assess factors associated with HIV and the distribution of NCDs by HIV status.

Methodology: We used a stratified, multistage sampling design, with 5 strata in each country. We sampled 9 clusters from each stratum with probability proportional to the number of households (HHs); within each cluster we took a random sample of 10 (urban) or 15 (rural) HHs. Adults (≥ 18 years) in the selected HHs were invited to participate. Consenting adults were interviewed and examined for signs of NCDs, and blood samples were collected for HIV and diabetes testing. We estimated the prevalence of HIV by country and location (urban and rural), and the prevalence of hypertension, diabetes, heart failure and chronic obstructive pulmonary disease (COPD) by HIV status. We investigated factors associated with HIV prevalence using logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI). All analyses were adjusted for the survey design.

Results: 1984 adults were enrolled. Age-adjusted HIV prevalence was slightly higher in Uganda (11.2%, CI=7.8-14.5%) than in Tanzania (10.0%, CI=5.5-14.5%). The prevalence of hypertension was 25.1% in Uganda and 16.5% in Tanzania; diabetes 3.2% in Uganda and 1.3% in Tanzania; and COPD 6.5% in Uganda and 5.0% in Tanzania. The prevalence of the NCDs did not vary by HIV status. Sociodemographic factors independently associated with HIV prevalence were increasing age, female gender, marital status (highest in those separated, divorced or widowed), and occupation group (highest in self-employed). Behavioural factors associated with HIV prevalence were current smoking and alcohol drinking (compared with non-drinking). However, there was some evidence that the effect of drinking varied by country: problem drinking was associated with an increased risk of HIV in Uganda, but not in Tanzania (p for interaction=0.09).

Conclusions: The high HIV prevalence indicates that the infection continues to be a major public health challenge in both countries. NCDs were common in both rural and urban areas, with hypertension having the highest prevalence. We found no differences in NCDs by HIV status, but may have been limited by low power. Control of emerging NCDs, alongside HIV prevention and treatment, has become a major priority in this population.

1017 Female Partner Bacterial Vaginosis and the Penis Microbiota: Rakai, Uganda

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Background: Bacterial vaginosis (BV) is a risk factor for HIV acquisition in women and is highly prevalent in African and African-American populations. BV is not currently considered a sexually transmitted infection; however, our previous work showed that male circumcision decreases female partner BV and reduces penile BV-associated bacteria in men. In the current study, we investigated the association between female partner BV status and the penile microbiota in uncircumcised men.

Methodology: We analyzed the coronal sulcus microbiota composition and density in uncircumcised men (n = 165) from Rakai, Uganda using 16S rRNA gene-based pyrosequencing and quantitative PCR, respectively. The association between host characteristics and microbiome composition was assessed using vector analysis and community state types (CSTs) were defined by hierarchal clustering. We then evaluated the association between partner BV status defined by Nugent score and coronal sulcus CSTs.

Results: Female partner BV was significantly associated with coronal sulcus microbiota composition (p = 0.04, r2 = 0.02). Although composition of the microbiota was variable, seven distinct community state types were identified (CST1-7). Based on the total amount of bacteria within the microbiota, i.e., bacterial density, the seven CSTs could be collapsed into low-density (CST1-3) and high-density (CST4-7) groups. In the high-density group, BV-associated organisms such as Prevotella, Porphyromonas, Mobiluncus, and Dialister were common and significantly more prevalent than in the low-density group. Men with high-density CSTs were more likely than men with low-density CSTs to have a female partner with BV (RR=1.55, 95% CI 1.07-2.24). In the low-density group, men whose partner had BV had decreased abundance of Lactobacillus and Staphylococcus and increased abundance of Prevotella and Mobiluncus.

Conclusions: We observed frequent carriage of BV-associated organisms in uncircumcised men and demonstrated an association between partner BV and male carriage of BV-associated bacteria. This suggests that men may serve as a reservoir of BV-associated bacteria, which could lead to BV recurrence and persistence.

1018 Low Viral Suppression and High HIV Diagnosis Rate Among MSM With Syphilis - Baltimore, Maryland

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Background: In 2011, Baltimore, MD, had the second highest rate of primary and secondary (P&S) syphilis and the sixth highest rate of diagnosed HIV infection among US metropolitan statistical areas. MSM are particularly affected by both infections and by coinfection; 65% of MSM with P&S syphilis in Baltimore in 2011 were infected with HIV. Viral suppression, though low nationally, can reduce HIV transmission. We determined HIV coinfection and viral suppression for MSM with single and repeat syphilis in the Baltimore area to guide prevention efforts among MSM.

Methodology: We analyzed STD and HIV surveillance data for MSM aged ≥15 years from Baltimore City or County who were diagnosed with early (primary, secondary, or early latent) syphilis infection during 2010-2011. MSM who received appropriate treatment for a previous syphilis diagnosis during 2007-2011 were defined as having repeat syphilis. We used HIV surveillance data to identify HIV coinfection and to obtain viral load results reported to the health department. For MSM diagnosed with HIV, we assessed viral suppression, defined as last viral load within the year prior to syphilis diagnosis ≤200 copies/mL. For MSM not diagnosed with HIV at or before their syphilis diagnosis, we used new HIV diagnoses divided by total person-years at risk (defined as days between syphilis diagnosis and the end of 2012, over 365.25) to estimate the annual HIV diagnosis rate; this analysis was limited to Baltimore City, where all new HIV diagnoses occurred.

Results: Of 460 MSM with early syphilis in 2010 or 2011, 92 (20%) had repeat infection; 26% of repeat infections occurred ≤12 months apart and only 47% were diagnosed as P&S syphilis. Fifty-five percent of Baltimore area MSM with single syphilis and 86% with repeat syphilis were HIV-infected at the time of their most recent syphilis diagnosis. Among MSM diagnosed with HIV, viral suppression was low (22% with single syphilis, 37% with repeat syphilis). For Baltimore City MSM who were not HIV-positive at the time of their syphilis diagnosis, the estimated annual HIV diagnosis rate was 4.8% (single) and 14.3% (repeat), compared with 3% for MSM overall in Baltimore City in 2011.

Conclusions: MSM with syphilis in Baltimore City have high HIV diagnosis rates. The majority of Baltimore area MSM with syphilis infection also have HIV, and consistent with national data, few appear to be virally suppressed (however, using data reported to surveillance has limitations and thus true levels of viral suppression may be underestimated). There may also be missed opportunities for early diagnosis of syphilis. Increasing the frequency of syphilis testing among MSM with a prior syphilis diagnosis and prioritizing MSM with syphilis in efforts to achieve viral suppression may improve outcomes for both infections.

1019 Trends in Comorbid Conditions Mentioned With HIV Disease On Death Certificates, US, 2000-2010

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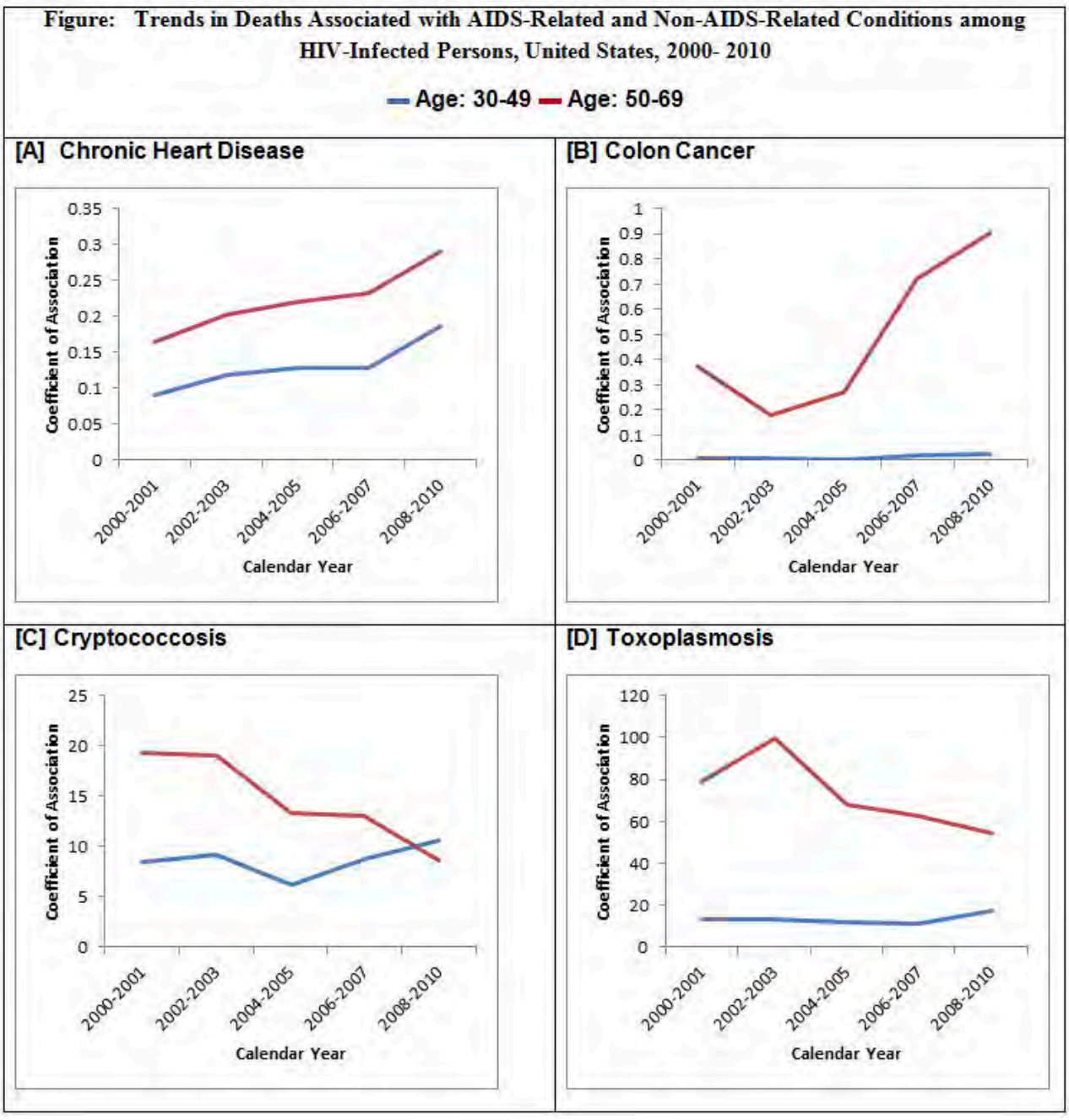
Background: HIV-infected patients are living longer due to advances in antiretroviral therapy (ART) but non-AIDS-related conditions (NARCs) in this aging population may limit survival. We explored temporal trends in AIDS-related conditions (ARCs) and NARCs recorded on death certificates along with HIV.

Methodology: Multiple causes of death data from the Centers for Disease Control and Prevention's (CDC) WONDER, an on-line database of public data compiled and managed by CDC programs, was used to identify deaths associated with HIV (HIV deaths) in the United States among individuals, 30-49 years and 50-69 of age, that occurred between 2000 and 2010. Coefficients of association (CoA) between HIV death and select representative NARCs and ARCs were determined to explore how associations between HIV and these conditions at death evolved over time.

Results: Of the 8,108,285 deaths among individuals aged 30-69 years in the United States that occurred between 2000 and 2010, HIV was mentioned as cause among 140,172; persons aged 30-49 years and 50-69 years accounted for 91,342 (65.2%) and 48,830 (34.8%) of these deaths, respectively. The overall percentage of HIV deaths was 1.7%: 4.6% for persons aged 30-49 years and <1% for persons aged 50-69 years. Between 2000 and 2010, the overall percentage of deaths declined from 2.1% to 1.2%; for persons aged 30-49 years it declined from 6.1% to 2.7% while for persons aged 50-69 years it remained stable and <1%. The percentage of HIV deaths with a non-HIV underlying cause increased from 8% in 2000-2001 to 12% in 2008-2010 among persons age 30-49 years, and from 18% in 2000-2001 to 26% in 2008-2010 among persons aged 50-69 years (all $p<0.01$). For example, among decedents aged 50-69 years, CoAs between HIV and both chronic heart disease and colon cancer increased while CoAs between HIV and both cryptococcosis and toxoplasmosis decreased during the 10-year period [Figure A-D]. Among decedents aged 30-49 years, the CoA between HIV and chronic heart disease increased but CoAs between HIV and other selected conditions did not change significantly [Figure A-D].

Conclusions: As the percentage of HIV deaths in the United States has declined, especially among young adults, both the percentage of deaths with a non-AIDS underlying cause and the associations between HIV and NARCs have increased. These trends highlight a growing need for chronic disease prevention in the aging U.S. HIV-infected population.



1020 The Association Between HPV and HIV Shedding in Vaginal and Anorectal Specimens

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Background: With growing observational evidence that HPV is associated with an increased risk of HIV acquisition, the potential of HPV vaccination as an HIV prevention strategy has been increasingly considered. However, the relationship between HPV and HIV transmission risk is unclear. In this analysis, the relationship between HPV and local HIV shedding was assessed in two diverse populations: Senegalese women and US men who have sex with men (MSM).

Methodology: Data from two longitudinal studies conducted in Senegal and Seattle with similar protocols was analyzed. The Senegal sample was comprised of 404 study visits from169 HIV-1 infected women from whom cervical cellular and cervicovaginal fluid (CVF) specimens were collected for cytologic screening, HPV DNA detection, and HIV RNA detection and quantification. The Seattle sample was comprised of 2346 visits from 333 HIV-1 infected MSM from whom anorectal swab specimens were collected and underwent similar laboratory assessment. Multivariable generalized estimating equation regressions, controlling for age, plasma viral load, and CD4 count, were used for all analyses.

Results: In the sample of treatment-naïve Senegalese women, cervical lesions, but not HPV infection, were significantly associated with increased detection of HIV RNA (aRRlesions=1.21, 95% CI= 1.09, 1.34) and quantity of HIV RNA in CVF (adjusted βlesions=0.60 log copies/ml, 95% CI=0.12, 1.09). In the sample of MSM, neither HPV infection nor anal lesions were associated with detection or quantity of HIV RNA in the anal canal. In MSM, subsequent analyses stratified by ART status yielded similar results.

Conclusions: The null results from two contrasting populations provide compelling evidence that HPV infection is unassociated with local HIV shedding; a finding that casts doubt on the potential of HPV vaccination to reduce the risk of HIV transmission at the population level. While it is theoretically possible that the prevention of cervical lesions through HPV vaccination could affect HIV shedding in the genital tract of HIV-positive women, the modest effect size observed in these data suggest that interventions through this causal pathway would yield minimal impact on HIV transmission at the population level. Nonetheless, the potential of HPV vaccination to prevent HIV acquisition remains unclear and might warrant further investigation.

Table 1: Relationship between HPV Infection and Detection of HIV RNA in Cervicovaginal Fluids Submitted by Senegalese Women and Anorectal Specimens Submitted by US MSM

	Detection of HIV RNA		Log Viral Load	
	Senegalese Women RR (95% CI)	American MSM RR (95% CI)	Senegalese Women β(95% CI)	American MSM β(95% CI)
HPV Infection				
None detected	1.00	1.00	--	--
Detectable HPV DNA	0.95 (0.83, 1.09)	1.03 (0.99, 1.06)	-0.13 (-0.58, 0.32)	0.8 (-0.01, 0.17)
Pap Smear Results				
Normal	1.00	1.00	--	--
ASCUS	1.09 (0.88, 1.36)	0.99 (0.94, 1.03)	0.17 (-0.52, 0.86)	-0.04 (-0.14, 0.05)
LSIL/HSIL	**1.21 (1.09, 1.34)**	1.00 (0.97, 1.04)	**0.60 (0.12, 1.09)**	0.02 (-0.06, 0.11)

Note: All estimates are adjusted for age, CD4 count, and log plasma viral load

1021 Incidence of Sexually Transmitted Diseases Among Persons With HIV, New York City, 2000-2010

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Background: Diagnoses of sexually transmitted diseases (STD) among persons with HIV (PWH) are objective markers of ongoing sexual risk behavior, and signal potential for secondary HIV transmission. Recent population-level estimates of STD incidence among PWH in New York City (NYC) are lacking.

Methodology: We conducted a retrospective cohort analysis of STD incidence among PWH using a match of the NYC HIV and STD surveillance registries. The matched dataset contained 232,295 HIV/AIDS cases reported through 3/31/2011, and 618,597 STD cases reported from 1/1/2000-6/30/2010. From the matched dataset, we constructed an analytic cohort of 42,120 PWH (≥13 years old) diagnosed with HIV during 6/1/2000-6/1/2009. Persons were followed until first incident STD (chlamydia (Ct), gonorrhea (GC), syphilis), death or end of follow-up (6/1/2010). Persons were considered at risk for incident STD only after ≥14 days from HIV diagnosis to allow opportunity for receiving their HIV test results, plus STD-specific intervals based on STD incubation periods. We calculated STD incidence overall and by demographic groups and identified predictors of incident STD in multivariable Cox regression models.

Results: Among the cohort of 42,120 PWH, 4,407 (10.5%) had an incident STD during follow-up. Among those, 33.2% were GC, 33.3% were Ct, and 33.5% were syphilis. A higher proportion of persons with incident STD were male, young, white and men who have sex with men (MSM) compared to persons without incident STD. Cohort participants contributed a total of 215,536 person-years (PY) of observation (median: 4.97). Overall STD incidence was 2.0/100 PY. Median time to incident STD was 1.9 years, and 12.9% of incident STD were diagnosed ≤6 months after HIV diagnosis. Incidence rates were higher among males (2.5/100 PY versus 1.1/100 PY in females); among young persons (6.9/100 PY in persons age 13-19 versus 2.0/100 PY in persons age 30-39); among whites (2.9/100 PY versus 1.9/100 PY each in blacks and Hispanics); and among MSM (4.1/100 PY versus 1.2/100 PY in heterosexuals). Young age, black race, Hispanic ethnicity and MSM status were predictors of STD incidence among men. Among women, young age, heterosexual HIV risk and history of injection drug use were predictors of incident STD.

Conclusions: We documented substantial risk of incident STD following HIV diagnosis in the population of PWH in NYC during an eleven-year period. Incidence was elevated among certain population subgroups, including young persons and MSM. Findings underscore the need for frequent STD screening and prevention counseling for all PWH, and especially for high-risk persons, at the time of HIV diagnosis.

1022 Increasing Rates of STI Are Linked To Reduced Condom Use in Patients With Primary HIV-1 Infection

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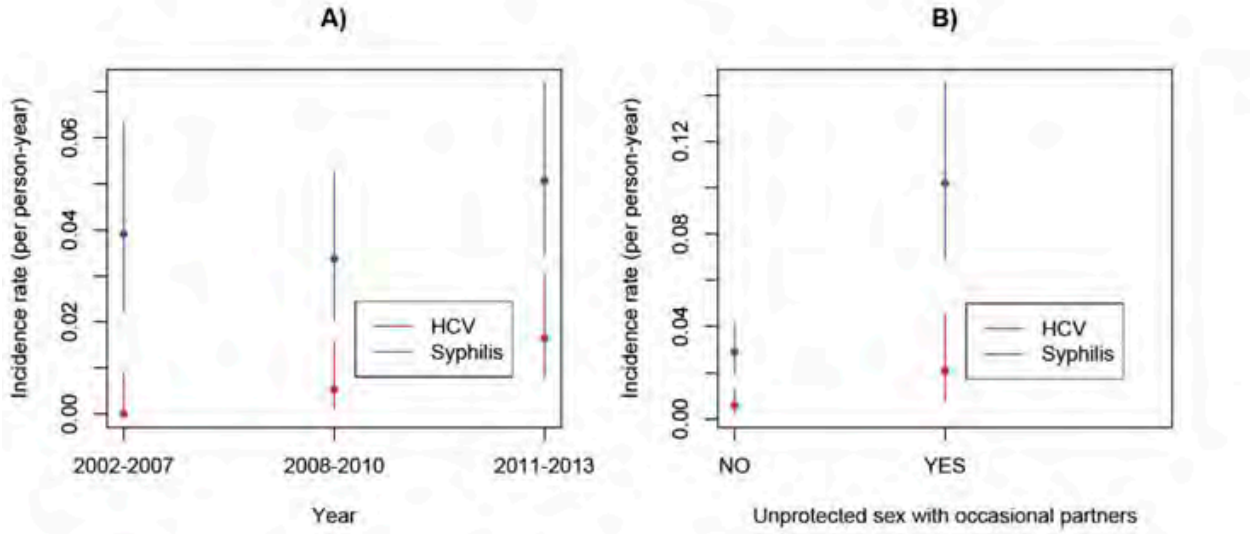
Background: In Switzerland, incidence of sexual transmitted infections (STI) is increasing in HIV positive individuals, particularly including an epidemic for sexually acquired acute HCV-infection in MSM. Patients with a primary HIV-infection (PHI) represent a sexual highly active population and may contribute to this epidemic, possibly due to changed sexual risk practices influenced by the "Swiss statement" in 2008, postulating that individuals on effective antiretroviral therapy are non-infectious.

Methodology: Between January 2002 and April 2013 we prospectively enrolled 293 individuals with a well defined PHI in the Zurich Primary HIV Infection Study and in the Swiss HIV cohort study (SHCS). At study-begin, individuals were actively screened for hepatitis C and B, syphilis, gonorrhea, chlamydia and herpes genitalis. During the study-period, STI-screening was performed based on clinical symptoms, reported sexual risk practices and by yearly serological syphilis and HCV testing. STI were determined by a detailed medical chart review including history, symptoms of STI and screening tests. Condom use is reported in the SHCS database 6 monthly. The impact of calendar year and condom use on HCV/syphilis incidence was assessed with Cox-proportional-hazard models.

Results: We analysed 293 individuals (271 males). Transmission mode included MSM (79%), heterosexual (20 %) and IVDA (1 %). Of all, 49 (17%) individuals had a concomitant STI at presentation. During follow-up period, syphilis was the most prevalent STI with 93 cases, followed by gonorrhoea: 40, chlamydia: 38; acute HCV-infection: 16; herpes genitalis: 8, acute hepatitis B: 2. Incidence rates of syphilis and acute HCV-infections were significantly increasing over the study-period, most pronounced in the latter (figure 1, panel A). For syphilis, there was a significant linkage between increasing incidence and imperfect condom use ($p<0.001$), whereas for acute HCV-infection such correlation was also found, but only as a trend ($p=0.18$) (figure 1, panel B).

Conclusions: Increasing incidence rates of STI's represent a surrogate for changed sexual risk behavior in patients with PHI, may be fostered by the "Swiss statement" that has been endorsed however only for patients in stable partnerships. The ongoing epidemic of acute HCV-infections affecting MSM can not solely be explained by unprotected sex and remains unclear. Risk-group targeted prevention programs, mainly propagation of condom use, are urgently needed.

Figure 1: Panel A shows the incidence rate of syphilis and HCV during the study-period, panel B the incidence rate influenced by the factor "unprotected sex".



1023 Does Substance Use Compromise Depression Treatment? A Randomized Trial of Homeless HIV+ Persons

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Background: Many clinicians will defer antidepressant treatment in the context of active substance use due to concern that active substance use will interfere with depression treatment response. Although there is evidence to the contrary, less is known about how active substance use affects depression treatment among persons with HIV. The public health impact of research in this area is particularly significant given the known adverse effects of depression on HIV-related health outcomes. We explored the effect of active substance use on depression treatment using data from a randomized clinical trial of depression treatment in HIV-infected, homeless and marginally housed persons in San Francisco.

Methodology: All participants were diagnosed with a depressive disorder and randomly assigned to either a referral to community mental health treatment (N=71) or directly observed therapy with fluoxetine (N=66). Assessments, conducted every three months over a nine-month period, included the Hamilton Rating Scale for Depression, the Beck Depression Inventory, and self-report of any alcohol, crack, cocaine, heroin, or methamphetamine use in the past 90 days. We fit multilevel mixed-effects linear regression models to estimate the effect of depression treatment on depressive symptom severity, stratified by any alcohol use or any drug use in the past 90 days.

Results: The effect of fluoxetine treatment on depression symptom severity was statistically significant irrespective of alcohol use status (see Table). When stratified by drug use status, the effect of fluoxetine treatment on depression symptom severity was statistically significant only among drug non-users. The observed treatment responses were generally smaller among alcohol and drug users than among nonusers, but the interaction terms were not statistically significant.

Conclusions: We found that antidepressant treatment reduces depression symptom severity among HIV-infected patients with depressive disorders irrespective of comorbid active substance use. Given prior work in this area, depression treatment among active substance users may also improve HIV-related health outcomes. An important limitation of this study was that our measures of substance use were self-reported and did not assess the extent to which substance use was associated with clinically significant impairment. Future studies should be powered to examine the effect of problematic substance use on antidepressant treatment response.

Table: Effect of fluoxetine treatment versus community referral on depressive symptoms

Stratification Group	Number in fluoxetine arm/ Number in control arm	Hamilton Rating Scale for Depression	Hamilton Rating Scale for Depression	Beck Depression Inventory	Beck Depression Inventory
		Effect of treatment* (95% CI)	p	Effect of treatment* (95% CI)	p
Alcohol users	31/38	-1.76 (-3.42 to -0.10)	.038	-3.95 (-7.36 to -0.54)	.023
Alcohol nonusers	35/33	-2.34 (-4.10 to -5.84)	.009	-6.45 (-10.1 to -2.78)	.001
[Alcohol use x fluoxetine treatment interaction]		-0.62 (-3.03 to 1.80)	.618	-2.49 (-7.49 to 2.52)	.330
Drug users	17/21	-1.51 (-3.47 to 0.46)	.133	-4.32 (-9.48 to 0.81)	.099
Drug nonusers	49/50	-2.22 (-3.72 to -0.73)	.004	-5.47 (-8.31 to -2.62)	<.001
[Drug use x fluoxetine treatment interaction]		-0.74 (-3.41 to 1.94)	.591	-1.15 (-6.72 to 4.41)	.685
		*Negative values represent greater reductions in depressive symptom scores in the group treated with fluoxetine		*Negative values represent greater reductions in depressive symptom scores in the group treated with fluoxetine	

Session P-W9 Poster Session
Thursday March 6, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

Transmission/Risk Factors

1024 National Estimates of Key Populations at High Risk of HIV Exposure in Kenya, 2012

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Background: In Kenya, 5.6% of the adult population were living with HIV in 2012. Embedded in this HIV epidemic are key populations (KP) that have higher risks for HIV exposure, including persons who inject drugs (PWID), men who have sex with men (MSM), and persons who engage in transactional sex, including male sex workers (MSW), female sex workers (FSW) and male clients of FSW. Lack of national estimates of population sizes and burden of HIV among KP impede HIV programmatic activities. We present data from the 2nd Kenya AIDS Indicator Survey (KAIS 2012), the first survey in Kenya to estimate the size of and HIV prevalence of KP on a national level.

Methodology: KAIS 2012 was a nationally representative survey of persons aged 15-64 years. Participants were interviewed and provided blood samples for centralized HIV testing. Data were weighted to account for the complex survey design and adjust for non-response. National population estimates were generated using un-normalized survey weights reflective of the 2012 projected population from the 2009 national census.

Results: Out of 5,766 men and 7,954 women, 0.1% (95% confidence interval [CI] 0.03-0.2) reported ever injecting drugs. Among men, 0.6% (CI 0.3-0.9) ever had anal sex with another man, and 0.1% (CI 0-0.2) had done so in the past 12 months. The percentage of men who engaged in MSW behavior was 3.0% (CI 2.4-3.7) and in the past 12 months was 0.8% (CI 0.5-1.1). Among women, the percentage that had ever engaged in FSW behavior was 4.5% (CI 3.8-5.2) and in the past 12 months was 1.3% (CI 1.0-1.7). Among men, 17.6% (CI 15.6-19.5) had ever been a male client of FSW, and 5.7% (CI 4.7-6.7) had reported engaging in this behavior in the past 12 months. Among male clients of FSW, 11.6% had ever engaged in MSW behavior. HIV prevalence was 0% MSM, 6.3% (CI 0.0-33.5) PWID, 6.9% (CI 4.7 - 9.1) male client of FSW, 7.3% (CI 1.7- 12.8) MSW, and 10.9% (CI 6.4 - 15.3) FSW.

The estimated population sizes were PWID: 20,600 (CI 6,500-34,800); MSM: 51,800 (CI 27,300-76,400); MSW: 271,700 (CI 212,200-331,300); FSW: 421,000 (CI 356,000-485,900); and male client of FSW: 1,547,500 (CI 1,355,700-1,739,200).

Conclusions: National population sizes of KP were consistent with the 2012 national consensus estimates for KP based on regional-level data. However, HIV prevalence for MSM, MSW, and FSW were lower than those reported in other studies. These data should be considered minimum estimates as KP are less likely to be included in a household survey sampling frame and reporting bias due to stigmatization of high-risk behavior is likely. Special studies targeting KP are needed to fully understand their contribution to the HIV epidemic.

1025 HIV Incidence in Rural Western Kenya Using Longitudinal Analysis From Home-Based HIV Testing

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Background: Quantifying HIV incidence rates in affected communities is vital to epidemic characterization and response. We analyzed HIV acquisitions among repeated participants in a community-wide home-based testing and counseling (HBTC) program in rural western Kenya in which rapid scale-up of combination HIV prevention services is ongoing.

Methodology: Two rounds of community HBTC were carried out in the KEMRI/CDC Health and Demographic Surveillance Area spanning January 2010 to August 2011 [R1] and January 2012 to October 2012 [R2]. Persons ≥13 years of age found at home were asked to consent, answer questions about past testing, and undergo point-of-care rapid HIV testing using a Kenyan national algorithm. An aggregate HIV status variable was defined for each round, prioritizing HIV test results whenever available but also including self-reports. HIV+ persons previously HIV- were identified, and person-time denominators defined by time between participation in the two rounds of HBTC. Analysis was performed for participants 15-64 years of age because incidence was negligible for those <15 and ≥64 years of age.

Results: Among 33,651 participants in R1, overall HIV prevalence was 15.0% (95% Confidence Interval, CI: 14.6%, 15.5%); gender-specific prevalence was 11.6% among males (95% CI: 11.0%, 12.1%), and 17.5% among females (95% CI: 16.9%, 18.1%). Out of 8,706 individuals who participated in both rounds of testing, 124 became HIV+, resulting in an annual estimated HIV incidence rate of 1.17% (95% CI: 0.98%, 1.39%). No differences were noted between genders; however, incidence peaked among females at 25-34 years of age (1.6% ; 95% CI: 1.07%, 2.43%), and among males at age 35-44 years (2.4%; 95% CI: 1.4%, 4.2%).

Conclusions: HIV transmission continues despite programmatic scale-up of HIV prevention, care, and treatment services in this highly characterized community with traditionally low male circumcision (MC) coverage. Longitudinal incidence estimates and home-based testing campaigns have limitations, including differential nonparticipation by those most likely to be HIV infected. Cross-sectional incidence estimation, and analyses of socio-behavioral correlates of incident HIV infections for the same population should be undertaken to guide implementation of optimized HIV prevention efforts.

1026 Temporal Trends in HIV-1 Incidence and Risk Behaviors Among MSM, Bangkok, Thailand, 2006-2013

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Background: We assessed temporal trends in HIV-1 incidence and behavioral risk factors from two data sources among men who have sex with men (MSM) attending the Silom Community Clinic (SCC) in Bangkok from 2006-2013.

Methodology: Incidence was calculated from: 1) a cohort of clients attending voluntary counseling and testing (VCT) services who were HIV-negative at baseline and returned for at least one additional test; and 2) MSM and transgender women aged ≥18 years participating in the Bangkok MSM Cohort Study (BMCS) who were HIV-negative at enrollment and returned for 4-month follow-up visits to a maximum of 60 months . BMCS participants provided socio-demographic and sexual risk behavior data by audio-computer-assisted self-interview. VCT HIV testing followed a three-step algorithm using rapid HIV tests on blood. BMCS HIV testing was performed on oral fluid; with serologic confirmation of all reactive specimens, and all negative specimens obtained after February 2010. Assuming uniform distribution of seroconversion between last negative and first positive test, we evaluated trends in HIV incidence per 100 Person Years (PY) by quarter using a restricted cubic spline for time in a Poisson regression, and trends in behavioral risk factors were assessed using Generalized Estimating Equations logistic regression with 95% Confidence Intervals (CI).

Results: From 2006-2013, 7263 MSM clients came to the SCC for VCT; 1779 (24%) participants were initially seronegative and voluntarily returned for another test (median testing interval 203 days). Among these individuals, we detected 192 seroconversions for an overall HIV incidence density of 5.5 PY (95% CI: 4.7-6.3). Modeling of the time trend showed a significant positive linear effect ($p = 0.03$). Among 1744 BMCS participants followed from 2006-2013, 1372 tested HIV-negative at baseline, and 1259 (72%) seronegative MSM at baseline repeated testing. We detected 232 seroconversions, for an overall HIV-incidence density of 5.3 PY (95% CI: 4.7-6.1). Over time HIV incidence rose, then declined (inverted U-shaped curve). Modeling of the time trend showed significant non-linear and quadratic effects ($p < 0.001$). Overall drug use ($p = 0.045$), drug use to enhance sex, use of erectile dysfunction drugs, and 100% condom use increased (all three at $p < 0.001$), while the proportion of MSM reporting unprotected receptive anal intercourse decreased ($p = 0.04$) over time.

Conclusions: Between 2006 and 2013, the incidence of HIV infection increased among MSM seen for VCT. In contrast, HIV infection among MSM in the BMCS increased from 2006 to 2008 but had an overall downward trend thereafter, possibly due to changing behavior after study enrolment. Regular testing, counseling, and education may have had a positive impact.

1027 The Potential Impact of Targeting Prevention Strategies To HIV-Discordant Households

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Background: While HIV prevention trials have identified promising interventions, it remains unclear how to maximize population-level impact and efficiency. Swaziland HIV Measurement Survey (SHIMS) data allow exploration of the potential public health gains achieved through targeting prevention to HIV-negative individuals living in HIV-discordant households.

Methodology: SHIMS estimated HIV incidence in Swaziland using prospectively observed seroconversions in a population-based longitudinal cohort. From a representative sample of 14,891 households, 18,172 adults (age 18-49) provided baseline clinical and demographic information and underwent HIV counseling and testing; 11,227 HIV-uninfected participants (6,225 women, 5,002 men) were re-tested 6 months later. Using logistic regression models, we examined whether HIV-negative individuals living in households with HIV-positive members, i.e., in HIV-discordant households, were at heightened risk of seroconversion. We compared the number needed to treat (NNT) to prevent one seroconversion per year under a hypothetical roll-out of pre-exposure prophylaxis (PrEP), applying the highest observed PrEP efficacy of 73%.

Results: Baseline HIV prevalence in 2011 was 32% (women: 38%, men: 22%). Of 6,948 households with at least one HIV-negative member followed for seroconversion, a total of 1,938 households (28%) were HIV-discordant per baseline testing.

There were 148 seroconversions (101 women, 47 men), corresponding to an annualized incidence of 2.4% (women: 3.0%, men: 1.7%), and 40% of seroconversions occurred in HIV-discordant households. Having an HIV-positive household member of either sex predicted seroconversion for women (OR: 1.6, 95% CI: 1.1-2.4) and men (OR: 1.9, 95% CI: 1.1-3.5). For women, having an HIV-positive man in the household was associated with seroconversion (OR: 3.4, 95% CI: 2.1-5.5); however, for men, having an HIV-positive woman in the household was not (OR: 1.6, 95% CI: 0.9-3.0). The NNT with PrEP in order to prevent one seroconversion per year would be 37 among individuals of either sex living in HIV-discordant households, 15 among women living in households with HIV-positive men, and 51 among men living in households with HIV-positive women.

Conclusions: In Swaziland, a large fraction of seroconversions occur in HIV-discordant households. Identification of women in HIV-discordant households may allow more efficient targeting of prevention for women, while targeting prevention for men may require other approaches. Further work is needed to distinguish whether the observed association between household HIV-discordancy and seroconversion is due to within-household transmission or shared household risk factors.

1028 The Effect of Sexually Transmitted Infections On HIV Incidence Among MSM in Atlanta, GA

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Background: Sexually transmitted infections (STI) have long been associated with HIV acquisition. However, controlling for behaviors that confound the examination of a causal relationship is difficult. Also, data examining the relationship between STI and HIV acquisition among men who have sex with men (MSM) in the southeastern US are lacking.

Methodology: The InvolveMENt study is an ongoing, longitudinal cohort of black and white HIV-negative, sexually active MSM aged 18-39 in Atlanta. MSM were recruited from community venues and the internet, screened routinely at 3-6 month intervals for urethral and rectal N. gonorrhoeae (GC) and C. trachomatis (CT) by NAAT, syphilis by RPR/Treponemal IgG, HIV with rapid antibody tests, and completed questionnaires. MSM were linked to care for treatment of new STI and HIV. To address the dual and potentially conflicting needs for confounding control and statistical efficiency in estimating effects of STI on HIV incidence, we used propensity-score weighted cox proportional hazards models. Weights represented the inverse probability of incident STI diagnosis from logistic regression models of STI diagnosis as a function of age, race, time, time-dependent number of unprotected anal intercourse partners, report of receptive anal intercourse, poverty, and drug use.

Results: We included 512 HIV-negative MSM with 743 person-years of follow-up in this analysis. Over the study course, 20 syphilis, 27 urethral CT, 8 urethral GC, 45 rectal CT, 38 rectal GC, and 23 HIV incident cases were diagnosed. Overall, ≥90% of STI were treated. No MSM with urethral STI or syphilis acquired HIV during study follow-up. Only having a rectal STI (GC and/or CT) was significantly associated with subsequent HIV incidence in unadjusted analyses (HR 5.2; 95% CI 1.8,15.2). Adjustment with modeled weights refined the rectal STI association (aHR 4.0; 95% CI 1.9, 8.5), using weights from a rectal STI propensity model that substantially controlled confounding (c-statistic = 0.79). Analyses limited to rectal CT alone or rectal GC alone gave similar estimates.

Conclusions: Among MSM in Atlanta undergoing routine STI screening and referral for treatment, only incident rectal STI was associated with HIV acquisition after controlling for known confounders. This suggests a causal effect of rectal STI on HIV acquisition among MSM even in the setting of aggressive case finding and treatment. This effect may be related to rectal mucosal changes after STI. Our data underline the importance of routine screening for STI, including rectal STI, among sexually active MSM and support targeting of intensive HIV prevention interventions for MSM diagnosed with rectal STI. Further studies of the effect of STI on the rectal mucosa are needed to better understand HIV transmission in MSM.

1029 Factors Associated With HIV Discordance Among Couples in Kenya: Results From a Population Survey

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Background: The majority of HIV-1 infections in Africa occur among individuals in stable partnerships. Improving our understanding on the correlates of discordance will provide information on the dynamics and risk factors of couple transmission that can assist in the development of interventions to reduce transmission within couple relationships.

Methodology: The Kenya AIDS Indicator Survey (KAIS) 2012 was a population-based survey among persons aged 18 months to 64 years that collected interview data on demographics and behaviour; and a blood sample from participants for HIV testing. We analyzed data from married/cohabitating couples where HIV test results were available for both partners. We used logistic regression to identify factors associated with HIV discordance. Variables that were statistically significant at 0.10 p-value level in bivariate analyses were selected for the final multivariable model. Analyses were weighted to account for the sampling design and adjusted for non-response. Population estimates of HIV discordant couples were computed using un-normalized survey weights.

Results: There were 4,226 married or cohabiting couples of whom, 2,032 (48.1%) completed interviews and had HIV test results. Of all couples tested, 92.0% (95% CI 90.3-93.7; n=1,870) were HIV- concordant, 3.2% (95% CI 2.2-4.1; n=65) were HIV+ concordant and 4.8% (95% CI 3.6-6.1; n=97) were HIV discordant; translating to 260,000 discordant couples. Testing rates among discordant couples were high; 97.4% (95% CI 94.7-100.0) of women and 80.0% (95% CI 70.4-89.6) of men whose partners were HIV+ reported ever having been tested. Among all discordant couples 24.2% (95% CI 13.4-35.0) of the HIV+ partners were on antiretroviral therapy (ART). Of the individuals within a discordant couple who knew they were HIV+, 64.1% (95% CI 19.9-51.8; N=36) were on ART. In the final model, factors associated with HIV-discordance were an increasing number of lifetime sexual partners in women (adjusted odds ratio [AOR] 1.3, 95% CI 1.1-1.5; p=0.0001); and for men, lack of male circumcision (AOR 4.4, 95% CI 2.4-7.9; p<0.001) and reporting sexual partners outside of the relationship in the past 12 months (AOR 2.1, 95% CI 1.2-3.7; p=0.0063).

Conclusions: These findings underscore the importance of couple-based prevention strategies that focus on reducing sexual transmission of HIV among couples including voluntary medical male circumcision, reduction of number of sexual partners, routine couples HIV counselling and testing and knowledge and disclosure of partner status. Furthermore, given the effect of antiretroviral therapy on viral load suppression, interventions that increase access and adherence to treatment can contribute to reduction in HIV transmission among discordant couples.

1030 Partners of Individuals With Acute HIV Infection Have a High Frequency of Known HIV Infection

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Background: We evaluated if partners named by people with acute HIV infection (AHI) were more likely to be HIV-infected than those named by people with established HIV infection.

Methodology: The STOP study is an on-going prospective study evaluating AHI diagnosis linked to partner services at 12 HIV testing sites in New York City (NYC), North Carolina (NC), and San Francisco. Individuals newly diagnosed with either acute or established HIV infection were offered partner notification services. Contact information was elicited for sex partners from the previous three months for participants with AHI and the previous 12 months for participants with established HIV infection.

Results: From September 2011 to May 2013, partner services were offered to 110 individuals with AHI and 579 individuals with established HIV infection. Partner notification was accepted (i.e., provided contact information for at least one sex partner) by 82% (96/117) of individuals with newly diagnosed HIV infection in NC, 62% (192/312) in NYC (p<0.0001 vs. NC), and 30% (78/260) in San Francisco (p<0.0001 vs. other two sites). Among the 366 participants who accepted partner notification, the majority were young (59% were 17 - 29 years of age) men (94%) who have sex with men (90%). Forty-six percent reported meeting sex partners online and 38% reported having five or more sex partners. Overall, the 366 participants named 803 sex partners, of whom 32% (n=259) had been previously diagnosed with HIV infection; 38% (n=304) accepted an HIV test and 41 partners (13.5% of tested, 5.1% of all partners) were newly diagnosed with HIV infection. A comparison of partner services investigation outcomes (n=366) for participants with AHI and with established HIV infection did not demonstrate significant differences in the proportion with at least one partner: (i) with known HIV infection (59% for AHI vs. 58% for established HIV infection), (ii) with newly diagnosed HIV (12% vs. 11%), and (iii) who tested HIV negative (47% vs. 45%) [Table]. Among investigations with more than one partner, 39% (73/188) had both HIV-infected and HIV-negative partners.

Conclusions: In addition to diagnosing new HIV infections, notification services identified partners with known HIV infection in a similar high proportion (58%) of participants with newly diagnosed acute or established HIV infection. Ensuring that these HIV-infected partners are linked to care and treatment may be an important intervention to interrupt further HIV transmission.

Table. A Comparison of Partners Services Investigation Outcomes Among Participants with Acute and Established HIV Infection in a Prospective Study in Three Regions of the United States (N = 366).

Partner services investigation outcomes	Participant with Acute HIV infection (49)		Participant with Established HIV infection (317)		P-value
	N	Percent	n	Percent	
Number of named partners per investigation					
1	20	40.8	158	50.2	0.37
2	12	24.5	53	16.8	
3	7	14.3	37	11.7	
4	1	2.0	21	6.7	
≥5	9	18.4	46	14.6	
Number of partners with known HIV infection per investigation					
0	18	41.4	131	42.1	0.48
≥1	31	58.6	180	57.9	
Number of partners with newly diagnosed HIV per investigation					
0	43	87.8	275	88.7	0.85
1	6	12.2	35	11.3	
Number of partners who test HIV negative per investigation					
0	26	53.1	170	54.8	0.17
≥1	23	46.9	140	45.2	

1031 Baseline Predictors of HIV-1 Acquisition Among Women Participating in MTN-003 (VOICE)

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Background: In the Microbicide Trials Network (MTN) Study 003 (VOICE), the overall HIV-1 incidence was higher than anticipated, with incidence as high as 10% at some sites, despite the provision of comprehensive HIV-1 risk reduction services and condoms. Improving our understanding of predictors of HIV-1 acquisition in women is urgently needed to identify populations at greatest risk and to inform the scale-up of targeted HIV-1 prevention activities.

Methodology: MTN-003 was a randomized, double-blinded, placebo-controlled trial conducted in South Africa, Uganda and Zimbabwe between 2009-2012 that assessed the safety and effectiveness of daily oral tenofovir, oral tenofovir-emtricitabine, and 1% vaginal tenofovir gel for HIV-1 prevention. Baseline demographic, behavioral and laboratory data were analyzed from enrolled participants. Univariate and multivariable stepwise Cox proportional hazards models stratified by study site were used to assess baseline predictors of HIV-1 seroconversion.

Results: Among 5,029 women enrolled in MTN-003, 22 were determined to be HIV-1-seropositive at enrollment, 38 failed to return for follow-up, and 135 were missing baseline data, leaving 4,834 women for inclusion in the analysis; of these, 305 acquired HIV-1. The overall HIV-1 incidence was 5.68% (305/5,370 person-years). Over 20 predictors were evaluated and HIV-1 incidence (per 100 person-years), hazard ratios (HR) and 95% confidence intervals (CI) for significant predictors of HIV-1 acquisition are presented in the table.

Conclusions: Among women enrolled in MTN-003, young age and being unmarried/not living with a partner were the strongest risk factors for HIV-1 acquisition. Several other factors including not knowing if partner has other partners, having a curable STI at baseline (a biologic marker for unprotected sex), HSV-2 positive status, and alcohol use were also risk factors for HIV-1 infection. Programs and interventions that target women with these characteristics may optimize HIV-1 prevention efforts.

Predictors of HIV-1 acquisition in MTN-003					
Baseline characteristic	Category	HIV Incidence	HR	(95% CI)	p-value
Age (years)	Less than 25 25 or older	8.11 3.38	1.78 Ref	(1.36, 2.32) --	<0.001 --
Married or living with husband/primary partner	No Yes	7.85 1.85	1.91 Ref	(1.29, 2.84) --	0.001 --
Partner provides financial or material support	No Yes	8.73 5.10	1.34 Ref	(1.03, 1.75) --	0.03--
Primary partner has other partners	Yes Don't know No	5.54 6.55 3.70	1.67 1.68 Ref	(1.10, 2.53) (1.23, 2.30) --	0.02 0.001 --
Curable STI (Chlamydia, gonorrhea, trichomonas, or syphilis)	Yes No	10.12 4.64	1.57 Ref	(1.23, 2.00) --	<0.001 --
HSV-2 seropositive	Yes No	7.05 4.54	1.71 Ref	(1.35, 2.16) --	<0.001 --
Alcohol use per week in the past 3 months	2 or more times 1 time or fewer None	6.46 7.16 5.22	1.72 1.30 Ref	(0.99, 2.99) (0.99, 1.71) --	0.05 0.06 --

1032 Measuring Purposefully Adopted Seroadaptive Behaviors vs Reported Sexual Behaviors Among MSM

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Background: Seroadaptive behaviors are common among men who have sex with men (MSM) and may protect against HIV. Most studies define seroadaptive behaviors based on men's self-reported sexual behavior history, regardless of whether those behaviors reflect purposefully adopted risk mitigation strategies. This may not accurately define the population engaging in seroadaptive behaviors and could affect the ability to detect their potential protective effect.

Methodology: Among MSM attending an STD clinic in Seattle, WA from February-August 2013, we used two methods to estimate the prevalence of seroadaptive behaviors: (1) a 12-month sexual behavior history reported in a clinical computer-assisted self-interview (CASI); and (2) a research CASI which asked if subjects purposefully adopted risk reduction behaviors in the past 12 months based on partners' perceived HIV status. We examined 3 behaviors (defined as follows for sexual behavior history vs. purposeful adoption): serosorting (only partners with concordant HIV status vs. choice of partners was based on partner's status); condom serosorting (condom use with discordant/unknown but not with concordant status partners vs. choice to use/ not use condoms was based on partner's status); and strategic positioning (insertive partner is HIV-negative and receptive partner is HIV-positive/ unknown vs. choice to adopt an insertive or receptive role was based on partner's status). For each behavior we compared the prevalence (McNemar's chi-square for paired data) and agreement (kappa) between the two methods of estimation, stratified by HIV status.

Results: Of 1902 eligible MSM, 964 (51%) completed both CASI's. The mean age of participants was 34 (SD=11) and 835 (87%) were HIV-negative. The prevalence of behaviors was similar for the two methods of estimation, but the agreement was low (Table). Among 388 MSM classified as serosorters per their sexual behavior history, only 175 (50.4%) of 347 HIV-negative and 29 (70.7%) of 41 HIV-positive men reported purposefully choosing not to have sex with HIV discordant/unknown status partners.

Conclusions: Serosorting is overwhelmingly the most common seroadaptive behavior in our clinic. The prevalence of seroadaptive behaviors varies only slightly depending on the method of estimation, but using men's sexual behavior history likely includes men who did not purposefully adopt these behaviors. This misclassification may alter the estimated effect of seroadaptive behaviors on HIV risk.

Comparison of Two Measures of Seroadaptive Behaviors				
	Method of Estimation			
	Sexual behavior history	Purposeful adoption of behavior		
Seroadaptive Behavior	N (%)	N (%)	P-Value	Kappa
HIV-negative MSM				
Serosorting (N=827)	347 (42.0)	323 (39.1)	0.17	0.40
Condom serosorting (N=828)	54 (6.5)	43 (5.2)	0.22	0.31
Strategic positioning (N=835)	59 (7.1)	54 (6.5)	0.52	0.18

HIV-Positive MSM				
Serosorting (N=125)	41 (32.8)	33 (26.4)	0.14	0.41
Condom serosorting (N=127)	14 (11.0)	7 (5.5)	0.11	0.22
Strategic positioning (N=129)	13 (10.1)	14 (10.9)	0.83	0.05

1033 Prevalence and Predictors of HIV Disclosure Among Adults Receiving Care in the United States

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Background: Disclosing one's HIV-positive status to sex partners is important for preventing HIV transmission as it allows partners to make informed decisions about how to reduce their risk. However, there are no nationally representative estimates of disclosure in the United States (U.S.). We present estimates of the number and proportion of HIV-infected adults in care who disclosed their status to all sex partners in the past 12 months, along with factors associated with disclosure.

Methodology: We used interview and medical record data from the Medical Monitoring Project, which collects information from a probability sample of HIV-infected adults receiving medical care in the U.S. Participants were considered to have disclosed if they reported discussing their HIV-positive status with all sex partners in the past 12 months the first time they had sex with each partner. This analysis was limited to persons diagnosed with HIV for ≥1 year. We evaluated factors associated with disclosure using logistic regression analyses to calculate crude and adjusted prevalence ratios. All analyses accounted for clustering, unequal selection probabilities, and non-response.

Results: Among an estimated 222,648 sexually-active HIV-infected adults in care in the U.S., 178,603 or 72% (95% Confidence Interval (CI) 70%-74%) disclosed their HIV status to all partners. In adjusted analyses, men who had sex with men, Blacks/African Americans, Latinos, people who experienced homelessness, alcohol and drug users, and people who reported any unprotected vaginal or anal sex were less likely to disclose their status to all sex partners in the past 12 months (Table 1). Current use of antiretroviral therapy and viral suppression were not associated with disclosure.

Conclusions: Although the majority of sexually-active HIV-infected adults in care in the U.S. disclosed their status to all sexual partners in the past year, over 1 out of 4 (an estimated 69,380) did not. Disclosure was less likely among those who engaged in behaviors that increase the risk of HIV transmission (i.e., substance use and unprotected sex), highlighting the need for increased prevention efforts to encourage disclosure and receipt of risk reduction counseling among these populations.

Characteristics of Sexually-active HIV-infected Adults in Care in the U.S. in 2009 by disclosure status.

	Disclosed to all partners			Did not disclose to all partners				
Characteristic	Sample n	Weighted %	95% CI	Sample n	Weighted %	95% CI	Crude PR (95% CI)	aPR (95% CI)
Men who have sex with men	872	49	43-55	437	63	57-69	ref	ref
Men who have sex with women	451	24	21-27	129	19	16-23	1.14 (1.07-1.21)	1.17 (1.08-1.27)
Women who have sex with men	464	27	23-31	129	18	14-22	1.19 (1.12-1.26)	1.22 (1.14-1.31)
White	212	32	26-38	667	39	32-46	ref	ref
Black or African American	278	40	33-47	693	38	29-47	0.93 (0.88-0.99)	0.86 (0.80-0.92)
Latino	188	25	20-30	370	18	13-24	0.86 (0.79-0.94)	0.83 (0.77-0.90)
Homeless	155	8	7-9	73	11	9-14	0.89 (0.81-0.98)	0.90 (0.83-0.99)
Binge Drinking	318	17	15-19	187	26	22-29	0.85 (0.80-0.91)	0.89 (0.83-0.96)
Non-injection drug use	545	30	28-33	281	40	36-43	0.89 (0.84-0.94)	0.94 (0.88-1.00)
Unprotected vaginal/anal sex	697	42	37-47	303	50	44-54	0.92 (0.87-0.97)	0.92 (0.87-0.98)

1034 Trends in HIV Diagnoses Among Persons Who Inject Drugs – United States, 2008-2011

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Background: Injection and sexual behavior among persons who inject drugs (PWIDs) contribute importantly to the HIV burden in the United States (U.S). In 1983, the U.S. Centers for Disease Control issued HIV prevention guidelines for PWID and others at high risk of becoming infected and transmitting infection to others. We aimed to inform how to focus prevention strategies by showing burden, trends, and geographic variations in HIV infection among PWIDs.

Methodology: In addition to the number of HIV diagnoses among PWIDs, we calculated diagnosis and prevalence rates for 2008 through 2011 using HIV case surveillance data and estimates of the number of U.S. residents with a history, as given in meta-analysis of national survey data, of ever having injected drugs illegally. Trends are described with estimated annual percentage change in the number of diagnoses, and stratified by sex and race/ethnicity. Further, we describe the geographic variations in HIV burden as given by counts of diagnoses among PWIDs and persons whose infections were attributable to sex with PWIDs.

Results: Nationally, the number of HIV diagnoses among PWIDs decreased from 5,075 in 2008 to 3,648 in 2011, yielding a statistically significant annual percentage change of -11.2% (95% CI, -14.1, -8.1) per year, and by -10.5% (CI -14.3, -6.6) among males and by -12.2% (CI, -16.9, -7.2) among females. In 2010, 118,699 PWIDs and 28,158 sex partners of PWIDs with HIV infection were living in the U.S. The largest numbers of PWIDs with HIV infection were living in DHHS Region II (New York City, 38,648), III (D.C., 20,663), and IV (Atlanta, 17,516), and the largest numbers of sex partners of PWIDs with HIV infection were living in DHHS Region IV (7,038), II (6, 617), and III (3,463). In 2011, the estimated national HIV diagnosis rate was 48.9 per 100,000 males who inject drugs and 67.4 per 100,000 females who inject drugs. In 2011 among males who inject drugs, the black to white diagnosis rate ratio was 13.9 to 1, and among females was 9.0 to 1. In 2010, national prevalence rates were about 2,000 and 2,500 per 100,000 males and females who inject drugs, respectively.

Conclusions: Pronounced racial inequities in HIV burden were observed during the period 2008-2011, and gender inequity was observed, with higher rates among females who inject drugs. Prevention efforts may have greatest impact along the Atlantic Coast and the southern U.S. where the HIV burden among PWIDs appears to be most heavily concentrated. Current prevention efforts, such as increasing availability and uptake of sterile injection equipment, can sustain successes in thwarting HIV transmission within the drug-injecting subpopulation. Novel prevention efforts, such as post-exposure prophylaxis for PWIDs and their sex partners can be considered for implementation.

1035 An Emerging HIV Epidemic Among Injection Drug User Networks During Austerity in Athens, Greece

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Background: There is growing consensus on the role that social risk environments play in perpetuating HIV risk and transmission. Network analysis provides one method of examining the social risk environment. Networks may function as vectors of disease transmission (risk networks) or as mediums for social influence (social networks). Previous studies have described the importance of risk and social networks to HIV transmission and prevalence, but few analyses examine both network functions within the same context and population. Further, we explore these network functions within a unique context of an emerging HIV epidemic in Athens, Greece.

Methodology: We used the network generated by a respondent driven sampling referral-recruitment structure within a large HIV screening and linkage to care program among injecting drug users in Athens, Greece in 2012. For each of the 1,404 respondents, we created first, second and third degree networks. Network proportions, the proportion of a respondent's network with a given characteristic, were calculated. Several logistic regression models were developed to assess the relationship between these network proportions and individual HIV seroprevalance, injection frequency and unprotected sex.

Results: A total of 1030 first-degree networks were generated with a network size ranging from 2 to 5. Respondent HIV seroprevalence was associated with greater proportions of network members that were HIV infected (AOR=3.11, 95% CI: 2.10 to 4.62), were formerly incarcerated (AOR=2.82, 95% CI: 1.48-5.37), divided drugs (AOR=1.60, 95% CI: 1.10 to 2.3), were high frequency injectors (AOR = 1.50, 95% CI: 1.02 to 2.21) or shared injection equipment (AOR=2.44, 95% CI: 1.10 to 5.38). High frequency injecting was associated with having more network members that were HIV infected (AOR = 1.61, 95% CI: 1.14 to 2.28), high frequency injectors (AOR = 1.66, 95% CI: 1.23 to 2.26), and homeless (AOR=1.41, 95% CI: 1.03 to 1.93). Unprotected sex was associated with having more network members that were drug partners (AOR = 1.81, 95% CI: 1.03 to 3.17), and engaged in unprotected sex (AOR = 1.66, 95% CI: 1.03 to 2.67). Associations diminished when these models were run for more distal second and third degree networks.

Conclusions: Our analyses show that networks are an independently important contributor to the HIV outbreak in Athens Greece. These effects were strongest for the immediate network, but residual effects were seen moving out to second and third degree network members. Our results suggest that future public policies and programs should consider network-level interventions in addition to those that work at the individual level.

1036 High HIV Prevalence Among Injection Drug Users in India: Women Bear a Disproportionate Burden

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Background: While several low- and middle-income countries (including most in sub-Saharan Africa) have demonstrated >25% declines in HIV prevalence over the past decade, the burden of HIV often remains high in vulnerable subgroups, including injection drug users (IDUs). In India there has been a 50% overall decline in HIV prevalence between 2001 and 2009, however, limited data available suggest that HIV prevalence remains high in IDUs. Additionally, rates of IDU have increased sharply in some regions in North and Central India, and less is known about HIV among IDUs in these areas than in regions where IDU is endemic.

Methodology: We used respondent driven sampling (RDS) to recruit IDUs across 15 cities in India (target=1000 per site). Participants had to be ≥18 years and report history of injection drug use in the prior 2 years. All participants underwent a survey and provided a blood sample. HIV infection was diagnosed using double ELISA and HIV prevalence was estimated incorporating RDS weights. Multi-level logistic regression was used to identify correlates of prevalent HIV infection. HIV incidence was estimated using a multi-assay algorithm incorporating HIV BED, avidity, CD4+ count and HIV RNA.

Results: 11,897 IDUs with a median age of 29 years were recruited from 01/2013 to 09/2013 across 15 cities in India. 93% were male and 39% were married. Median age at first injection was 20 years and 89% reported injecting in the prior 6 months. The median HIV prevalence across sites was 16.7% and median HIV incidence was 0.76% per year (Table). Older age, lower education, being divorced/separated, injecting drugs in combination, higher frequency and longer duration of injection, sharing needles and larger peer-networks were positively associated with prevalent HIV. Further, women had nearly 5-fold higher odds (odds ratio: 4.60; 95% confidence interval: 3.78, 5.60) of being HIV-infected (HIV prevalence in women vs. men = 46.8 vs. 20%; p<0.0001). Women were also less likely than men to report ever accessing needle exchange (37% vs. 47%; p<0.0001) or opiate substitution (14 vs. 26%; p<0.0001).

Table. HIV Prevalence and Incidence among IDUs in India (n=11,897)

Region	Site	Sample Size	HIV Incidence % per year (95% CI)	HIV Incidence % per year (95% CI)
Central India	Bhubaneswar	313	NC	NC
	Bilaspur	414	NC	NC
	Kanpur	440	NC	NC
	Mumbai	613	NC	NC
North India	Amritsar	1001	2.78 (1.17, 4.38)	2.78 (1.17, 4.38)
	Chandigarh	998	0.41 (0, 0.98)	0.41 (0, 0.98)
	Delhi	1001	2.79 (1.24, 4.34)	2.79 (1.24, 4.34)
	Ludhiana	1002	0.93 (0.01, 1.84)	0.93 (0.01, 1.84)
Northeast India	Aizawl	1002	0.51 (0, 1.23)	0.51 (0, 1.23)
	Churchandpur	646	NC	NC
	Dimapur	1002	1.12 (0.13, 2.10)	1.12 (0.13, 2.10)
	Gangtok	1003	0	0
	Imphal	1002	0.53 (0, 1.25)	0.53 (0, 1.25)
	Lunglei	1001	0.60 (0, 1.28)	0.60 (0, 1.28)
	Moreh	459	3.44 (0.38, 6.50)	3.44 (0.38, 6.50)

CI = confidence interval; NC = not calculated as site is still recruiting

Conclusions: IDUs continue to face a high burden of HIV infection in India despite overall general population-level declines in HIV prevalence. Future prevention and treatment efforts need to target IDUs especially in regions with emerging drug use epidemics such as North and Central India to curb the spread of HIV. Further, HIV prevention efforts need to employ novel strategies in order to reach female IDUs.

1037 HIV Prevalence Among Women Who Inject Drugs and Exchange Sex for Money or Drugs: 20 US Cities, 2009

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Background: In some countries, exchange sex - sex in exchange for money or drugs - plays a key role in HIV transmission due to the high prevalence of HIV among women who exchange sex and the high percentage of men who pay for sex. There is limited information in the United States about exchange sex and the association with HIV prevalence among injection drug users. We used 2009 data on female injection drug users (IDUs) from the National HIV Behavioral Surveillance System (NHBS) to estimate the percentage who exchanged sex in the past 12 months, compare HIV testing and HIV risk behaviors among women who exchanged sex and those who did not, and investigate factors associated with being HIV-positive but unaware of one's infection.

Methodology: We analyzed data from female IDUs, aged ≥18 years, recruited using respondent-driven sampling, interviewed and tested for HIV. Women testing positive who did not report a prior positive HIV test were considered to be unaware of their infection. Using chi-square tests, we assessed differences in HIV risk behaviors, HIV testing, HIV prevalence and the percentage HIV-positive but unaware of their infection among women who did and did not exchange sex in the past 12 months. To evaluate the association between engaging in exchange sex and being HIV-positive but unaware, we used generalized estimating equations, clustered on recruitment chain, controlling for race/ethnicity, employment, total number of partners and unprotected sex in the past 12 months.

Results: Among 2784 women, 903 (32%) reported any exchange sex in the past 12 months. Unprotected sex was more common among women who exchanged sex than among those who did not (88% compared to 65%, p<0.001), as was sharing of injection equipment (56% compared to 30%, p<0.001). There was no difference in HIV testing in the past 12 months between women who exchanged sex and those who did not (55% compared to 51%, p=0.13) and no difference in HIV prevalence (10.0% compared to 8.7%, p=0.26). The percentage HIV-positive but unaware was 5.2% among those who exchanged sex and 3.4% among those who did not (p=0.02). In multivariable analysis, exchange sex was associated with being HIV-positive but unaware (adjusted prevalence ratio 1.76, 95% confidence interval 1.21-2.55).

Conclusions: Exchange sex was common among female IDUs in NHBS. Women who exchanged sex were more likely to be HIV-positive but unaware of their infection after adjusting for important covariates. HIV prevention efforts may benefit from strengthening interventions among female IDUs who exchange sex. These efforts could include reducing unprotected sex, increasing safe injection practices, and HIV testing with prompt linkage to care and treatment for those testing positive.

1038 Erectile Dysfunction Medication Use Associated With Unprotected Intercourse in HIV-Infected MSM

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Background: Although prior research has found an association between erectile dysfunction medication (EDM) and increased sexual risk behavior, little is known about how frequently EDM is prescribed to HIV-infected men who have sex with men (MSM) or about its association with increased sexual risk behavior nationally.

Methodology: Using 2009 data from the Medical Monitoring Project, a nationally representative sample of HIV-infected adults receiving medical care in the United States, we assessed the characteristics of sexually active MSM, including men who have sex with men only and men who have sex with men and

women, who were prescribed EDM and the independent association between EDM prescription and unprotected intercourse (UI) using multivariate logistic regression. EDM prescription was defined as documentation of sildenafil, vardenafil, or tadalafil in the medical record in the 12 months prior to interview. UI was defined as at least one episode of anal or vaginal sex without a condom during the 12 months prior to interview. All analyses accounted for clustering, unequal selection probabilities and non-response.

Results: Among an estimated 136,320 sexually active HIV-infected MSM in care in the United States, 13% (95% Confidence Interval (CI) 10%-15%) received an EDM prescription and 56% (95% CI 50%-61%) had unprotected intercourse. MSM prescribed EDM were more likely to be aged 40 years or older, white or Hispanic, with college or higher education, above poverty level, insured, diagnosed with HIV for at least 5 years, having more than 5 sex partners, and those who used illicit drugs before or during sex. MSM prescribed EDM were significantly more likely (Prevalence Ratio 1.2; 95% CI 1.1-1.4) to have unprotected intercourse, while controlling for identified risk factors including race and ethnicity, total number of partners, depression, and illicit drug use before or during sex. Only 40% of MSM prescribed EDM had received counseling from their healthcare provider in the past 12 months on ways to protect themselves or partners from HIV or other STDs.

Conclusions: HIV-infected sexually active MSM prescribed EDM were significantly more likely to have unprotected intercourse after adjusting for other independent predictors. Despite having been prescribed EDM by their HIV provider, only 40% of MSM received risk reduction counseling. HIV providers should be aware of the potential for increased HIV transmission risk associated with prescribed EDM use.

1039 A Novel Analytical Approach Confirms Stabilization of HIV Epidemic in Pregnant Women in Namibia

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Background: In most African countries with generalized epidemics, HIV prevalence trends are monitored primarily through antenatal care (ANC) based HIV sentinel surveillance (HSS). Reliable national and sub-national estimates of trends in HIV prevalence are needed; however, standard methods of analysis do not properly address potential biases from differences among sites and addition of sites over time. We report a novel, statistically principled estimate of trend in HIV prevalence among pregnant women from HSS from 2002 to 2012 in Namibia using Bayesian hierarchical logistic models.

Methodology: HSS data from 35 sites representing all Namibian health districts from 2002-2012 were analyzed. Two Bayesian models, hierarchical linear logistic and state space autoregressive, were used to quantify site specific and national trends in HIV prevalence among women within 15-49, 15-19, 20-24, 25-29, 30-34, and 35-49 year age groups. Within age groups, the two Bayesian models were compared by deviance information criterion (DIC). The model which produced smaller DIC value was selected for its superior predictive ability within the age group. National trends were quantified by the linear logistic slope (b) or autoregressive (ar) parameters from the respective models, and by the probability of decreasing prevalence, Pr(↓), as measured by Pr(b<0) or Pr(ar<1), respectively. 1-Pr(↓) was used to quantify the probability of increasing prevalence. Unchanging prevalence is indicated by b=0 or ar=1 for the linear-logistic and autoregressive models, respectively. Pr(↓) ≥0.80 and Pr (↓) ≥0.99 were chosen thresholds for highly probable or nearly certain decrease/increase, respectively.

Results: From 2002-2012, HIV prevalence remained stable among women aged 15-49 (ar =0.96, Pr(↓)=0.78). A decline in prevalence was nearly certain among women aged 15-19 (b= -0.07, Pr(↓)>0.99) and 20-24 (b= -0.09, Pr(↓)>0.99), and highly probable among women aged 25-29 (ar =0.92, Pr(↓) = 0.93). An increase in prevalence was nearly certain among women aged 30-34 (b = 0.02, 1-Pr (↓) =0.99) and 35-49 (b = 0.05, 1-Pr(↓) >0.99).

Conclusions: Overall, the trend analysis does not show strong evidence of a change in HIV prevalence, indicating epidemic stabilization since 2002. Among women aged 15-19 and 20-24, prevalence appears to have decreased, by approximately 7.0% and 9.0%, respectively, which likely indicates decreasing incidence among younger women. Among women aged 30-34 and 35-49, prevalence appears to have increased, which may indicate decreasing mortality and improved health outcomes due to ART and PMTCT scale-up, and continued occurrence of new infections among older women. The novel analytic method presented here can be adapted by other countries to produce reliable HIV prevalence trends estimates.

1040 Viral Load Strategy: Impact On Risk Behavior and Serocommunication of MSM in Specialized Care

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Background: Incidence and prevalence of HIV continue to be high among German men, who have sex with men (MSM). Different transmission risk minimizing strategies have been observed. The viral load strategy (VLS) rates patients unlikely to be sexually infectious if their viral load under effective therapy is stably suppressed during six months and no other sexually transmitted infections (STI) are present ("Swiss statement"). Until now, no data on a German sample of HIV+ MSM in specialized outpatient care are available. Supported by the German Competence Network for HIV/AIDS, we aim to objectify the current popularity of VLS, the adherence to its basic conditions and its impact on risk behavior and serocommunication.

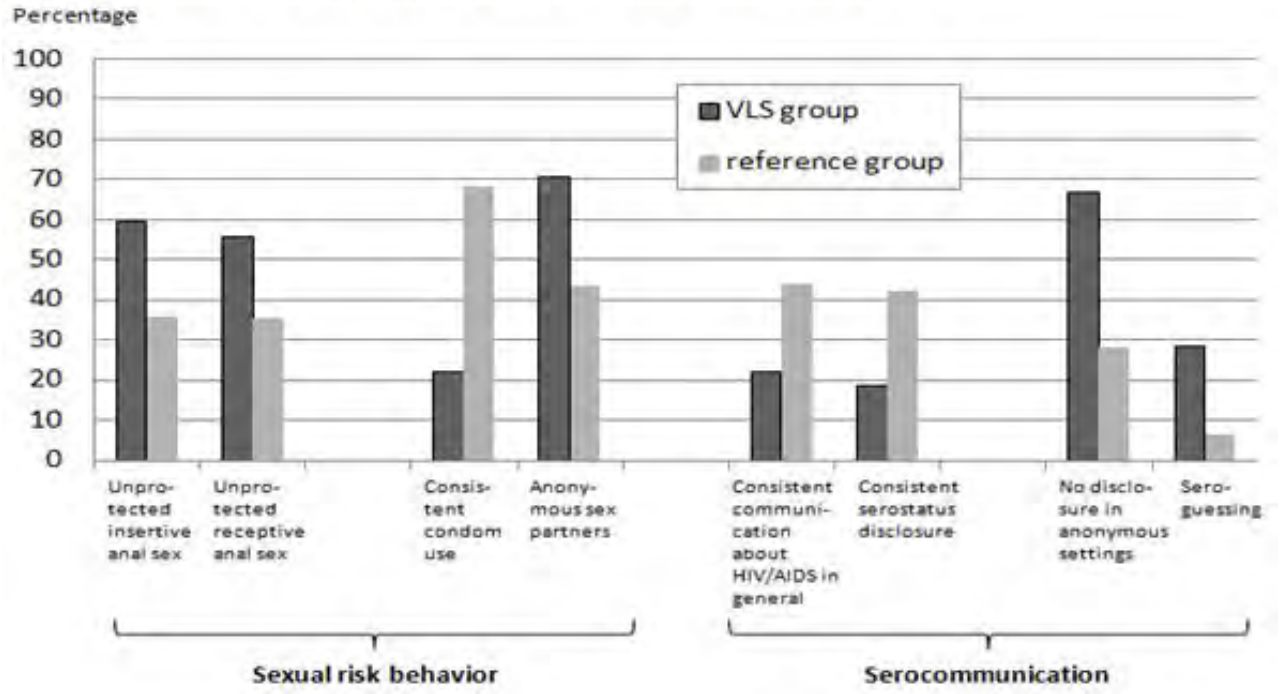
Methodology: 269 structured interviews and self-report questionnaires were conducted with German HIV+ MSM in specialized outpatient care. Group comparison between the user and the non-user group of VLS was carried out by using standardized tests (χ^2 test, Fisher´s exact test, Mann-Whitney U-test; significance level: $\alpha = 0{,}05$).

Results: Among the sexually active respondents, 10% stated using the VLS. As shown in Tab. 1, this subgroup reported more unprotected insertive (59.3% vs. 36.0%) and receptive (55.6% vs. 35.5%) anal intercourse and more anonymous sex partners (70.4% vs. 43.6%). Consistent safer sex was less common (22.2% vs. 68.3%), monogamous relationships were reported by 11.1%. Analyzing serocommunication, less addressing HIV/AIDS in

general (p=.043) and less frequent disclosing to sex partners (p=.023) were found, especially in anonymous settings. Differentiating serocommunication characteristics, a focus on seroguessing was depicted.

Conclusions: The user group of VLS is small, but it diverges greatly from the targeted group of VLS, which requires an informed and monogamous relationship. A less frequent, more reactive and assumptive serocommunication leads to an imprecise information exchange, paired with a higher frequency of risky behavior, especially in anonymous settings. Without an open serocommunication in these settings, other - potentially asymptomatic - STI may be passed on. Thus, a subversion of a basic condition of the VLS seems possible and the HIV transmission risk may be much higher than assumed.

Table 1. Overview of results on sexual risk behavior and serocommunication



1041 Transmission Rates and Not Sexual Contact Patterns Drive HIV Epidemic Intensity in Africa

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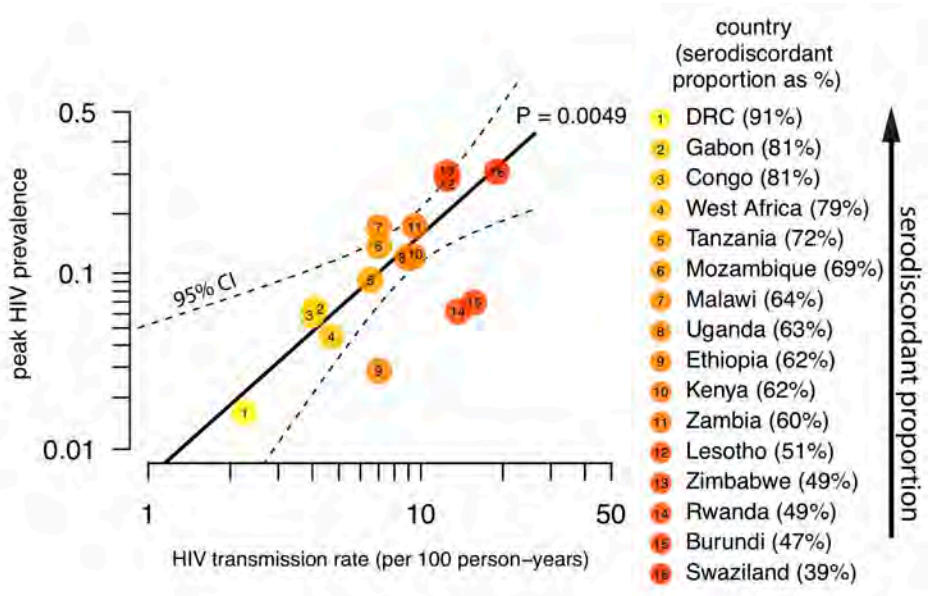
Background: HIV prevalence has peaked at less than 1% in some African countries while surpassing 30% in others. After decades of research it remains widely debated whether this variation is driven by variation in biological factors influencing the HIV transmission rate (e.g. male circumcision, coinfections, and viral or host genetics) or by variation in sexual contact patterns (concurrency, promiscuity, and age-mixing). The serodiscordant proportion (SDP; proportion of couples with any seropositive partners that are serodiscordant) also varies geographically, ranging from 38-92% across Africa, and exhibits a negative correlation with prevalence. We identify which processes shape the observed variation in both prevalence and SDP and the relationship between the two.



Methodology: First, we fit an HIV transmission model to Demographic and Health Survey data from 45,041 cohabiting

couples in 25 African countries to estimate country-specific transmission rates and sexual contact patterns. Second, we quantify the sensitivity of SDP to the HIV transmission rate, sexual contact patterns, and AIDS mortality. Third, to identify drivers of country-to-country variation in SDP, we inserted country-specific HIV prevalence, transmission rates, or sexual contact patterns estimated from a "donor" country into a model fit to a "recipient" country, and measured the extent to which the substitution shifted the SDP from that of the recipient toward that of the donor. Finally, we used generalized linear models to estimate the contribution of these factors to country-to-country variation in HIV prevalence.

Results: The SDP is primarily determined by the HIV transmission rate. Thus, greater HIV transmission rates explain both why certain countries have greater HIV prevalence (49% of variance explained; Figure) as well as smaller SDPs (89% explained). In contrast, sexual contact patterns explained less than 3% of variation in SDP and were not statistically significant predictors of prevalence ($P > .01$).

Conclusions: By exploring variation in HIV prevalence through the lens of serodiscordance patterns, we provide a novel and testable empirical framework to compare the two leading hypothesized drivers of variation HIV epidemic intensity. We find that, while risky sexual contact patterns cause a large proportion of HIV incidence in all countries examined, greater intinsic transmission rates--and not riskier sexual contact patterns--explain why certain countries have suffered worse epidemic

Session P-X1 Poster Session

Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

HIV Testing in Low Income Settings

1043 HTC Campaign in Households Reached the Majority of Women But Only 50% of Men in Botswana Community

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Background: The identification of populations at high risk of HIV infection, or unaware of their HIV status, is a critical component of clinical trials and public health interventions. Better understanding of who the people are who are not covered by provider-initiated HIV-1 counseling and testing (HTC), or household (HH)-based HTC campaigns, could improve strategies aimed to link these individuals to care and reduce rates of onward HIV transmission in communities.

Methodology: A baseline and two follow-up enhanced HTC campaigns targeted 16-64-year-old (y.o.) residents in the northeastern sector of Mochudi, a southern African community with 3,650 households. Following community mobilization and engagement, individuals were approached during HH visits and were offered consenting, HIV testing, counseling, data collection and blood sampling. HIV testing was performed in HHs using the Botswana National HIV Testing guidelines. The data collected during HH campaigns were compared with the United Nations (UN) estimates for the Botswana population stratified by age and gender, and in the context of HIV status.

Results: A total of 6,187 age-eligible residents in the northeastern sector of Mochudi were tested for HIV-1 status in HH, and 1,234 of them were found to be HIV positive. Among those tested in HH, 3,933 were females and 2,254 were males. HIV prevalence rates increased from 3% in males and 5% in females in the age group 16-19 y.o. to 32% in males 40-44 y.o. and 44% in females 35-39 y.o. Comparison with the UN estimates revealed that 88.4% (95% CI 87.5% to 89.4%) of females and 49.5% (95% CI 48.0% to 51.0%) of males aged 16-64 were reached by the HH-based HTC in Mochudi. The proportion of missing men reached 58.8% (95% CI 55.3% to 62.2%) in the age group 25-29 y.o., 63.4% (95% CI 59.6% to 67.1%) in the age group 30-34 y.o., and 61.2% (95% CI 56.6% to 65.6%) in the age group 35-39 y.o. The proportion of missing women was 19.8% (95% CI 16.9% to 23.1%) in the age group 16-19 y.o. and 23.4% (95% CI 20.0% to 27.0%) among women 30-34 y.o. The social and behavior risks of missing populations remain unknown.

Conclusions: The HTC campaign in Mochudi, Botswana, reached 49.5% of men and 88.4% of women in HHs. However the HH-based HTC campaign in Mochudi missed about half of men, and about 12% of women. The proportion of missing men aged 25-39 y.o. was at the level of 60%. To bring the identified age-specific categories of men and women to care and reduce HIV incidence, the identified groups should be targeted by alternative non-standard strategies of HIV testing and counseling in communities.

1044 Implementation of Routine, Opt-Out HIV Testing Does Not Increase Loss To Follow-up

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Background: In 2010, South Africa launched an ambitious national HIV counseling and testing (HCT) campaign. Routine opt-out HCT may impact retention in care, as it is expected to result in a higher proportion of asymptomatic patients with lower levels of immunodeficiency who may not be motivated to seek HIV care. We examined retention in care before and after implementation of routine opt-out HCT at a primary care clinic.

Methodology: In January 2011, Witkoppen Health and Welfare Centre in Johannesburg, South Africa, implemented routine opt-out HCT for all adult (≥18 years) clinic clients with unknown HIV status and those testing negative >3 months ago, regardless of reason for clinic visit. Prior to 2011, clinic clients were tested upon request (voluntary CT), if they accessed antenatal care services, TB services, or if the health care provider requested HCT due to symptoms compatible with HIV infection. We compared patient characteristics and retention in care among clinic clients newly diagnosed with HIV from January-June 2010 (pre-intervention) and February-July 2012 (post-intervention).

Results: In total, 1092 individuals were newly diagnosed during the pre-intervention period and 967 post-intervention. During both periods, median age was 32 years and almost half had immigrated to South Africa from neighboring countries. Most new HIV diagnoses were women (67.2% in 2010 and 65.9% in 2012), but the proportion of pregnant women decreased from 26.6% in the pre-intervention to 16.2% in the post-intervention period (p<0.001). Surprisingly, the median CD4 count at time of HIV diagnosis was similar during both periods: 253 (IQR 128-398 cells/µl) in 2010 and 268 (IQR 139.5-408 cells/µl) in 2012 (p=0.15). The proportion of individuals eligible for ART was 66.7% in the pre-intervention period and 64.1% in the post-intervention period (p=0.21). Within the first 12 months following HIV diagnosis more than half of all individuals newly diagnosed with HIV were lost to follow up: 58.4% during the pre-intervention and 54.6% during the post-intervention. Adjusting for age, CD4 count, gender, pregnancy and nationality, the hazard of LTFU was not impacted by the change in policy (HR 0.97, 95% CI: 0.86-1.09).

Conclusions: Implementation of routine opt-out HCT at the primary care facility level did not increase baseline CD4 count or proportion of people eligible for ART, and did not impact the risk of loss to follow up among those newly diagnosed with HIV. Retention in care after HIV diagnosis, however, was extremely low, with more than half of those newly diagnosed lost to care by one year. To be successful, expansion of HIV testing should be coupled with effective strategies to increase retention in care among those newly diagnosed.

1045 Assessment of the Potential Cost-Effectiveness of HIV Self-Testing in Resource Limited Settings

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Background: Implementation studies demonstrated that HIV self-testing (ST) is highly acceptable in resource limited settings and could allow savings given its potentially lower implementation cost compared to provider-delivered HIV testing and counselling (HTC). We aimed to evaluate the cost-effectiveness of introduction of ST from 2015 over 20 years in a country such as Zimbabwe.

Methodology: The 'HIV Synthesis' model was used to simulate an HIV epidemic similar to the one in Zimbabwe. Simulated age and gender specific rates of HTC for the first time, and repeat HTC fitted approximately to those observed; rates incorporated a 3-fold reduction in rate of testing for people who never had condom-less sex and increased rates of HTC for women attending antenatal clinics and for subjects experiencing symptoms. Sensitivity was assumed to be 92% and 98% and specificity 99% and 100%, for ST and HTC respectively. The cost was assumed to be $3 for ST, $9 for HTC if negative and $25 if positive, or following a positive ST. HTC was required for a person to be diagnosed and it was assumed only 80% of those who had a positive ST would be diagnosed within 1 year as a direct result of the ST. Once diagnosed, linkage to care at 1 year was assumed to be 60% and the same reduction in condom-less sex (13% with long-term partner and 17% with short-term partners declining to 9% after 6 months) was assumed for people testing positive by HTC or ST. Two main scenarios were considered from 2015. In the reference scenario (RS), ST is not available and the rate of HTC for first time and repeat HTC increases linearly by 0.005 per year. In the intervention scenario (STS), the following effects are assumed: halving of the population not willing to receive a HTC (from 5 to 2.5%), replacing 30% of repeat HTC with ST, replacing 10% of first HTC with ST, and increasing in the rate of repeat testing and of testing for the 1st time by 20%, due to the availability of ST.These assumptions are believed to be conservative in estimating the potential benefits of ST.

Table 1. Cost effective scenario (STS or RS) under base case assumptions and alternative assumptions, and according to cost effectiveness threshold

		Cost effectiveness threshold (CET)		Total incremental discounted costs in US$ millions, compared to RS (95% CI)	Discounted incremental DALYs averted in thousands, compared to RS (95% CI)
		0$	1,000$		
Base case (B)		STS	STS	-51 (-49;-53)	35 (30;39)
Cost of ST (B: US$3) = cost of negative HTC (US$9)		RS	RS	118 (116;121)	35 (30;39)
Sensitivity of ST = 0.5 (B: 0.92)		STS	STS	-60 (-53;-67)	-5 (-21;10)
Probability of diagnosis (HTC) following a positive ST = 0.25 (B: 0.8)		STS	STS	-46 (-38;-54)	-8 (-24;8)
Linkage to care following diagnosis for those who had a ST 24% by 1 year (B: 60%)		STS	STS	-66 (-54;-79)	15 (-12;41)
ART initiation at <500 (B: <350)		STS	STS	-30 (-22;-38)	52 (35;69)
No reduction in risk behaviour following a positive ST		STS	STS	-63 (-55;-70)	9 (-8;25)
Increase in rate of 1st test due to ST (B: 20%)	2.5%	STS	STS	-84 (-75;-93)	-43 (-63;24)
	7.5%	STS	STS	-74 (-66;-82)	-17 (-34;0.5)
Increase in rate of repeat test due to ST (B: 20%)	2.5%	STS	STS	-93 (-83;-103)	-15 (-37;7)
	7.5%	STS	STS	-81 (-76;-87)	-2 (-15;10)
Replacement (B: 30% of repeat test, 10% 1st test)	5% of repeat, 2% 1st test	RS	RS	9 (0.7;17)	5 (-10;20)
	15% of repeat, 5% 1st test	STS	STS	-20 (-12;-28)	-6 (-23;11)
	25% of repeat, 8% 1st test	STS	STS	-45 (-39;-52)	18 (4;32)

Note: the total cost of the R scenario over 20 years from 2015 is US$ 2,945 millions

Results: We predict the introduction of ST could lead to savings in health care costs of $51 million, while averting around 35,000 DALYS over 20 years in Zimbabwe. Table 1 indicates the most cost-effective scenario under different circumstances.

Conclusions: These results suggest the introduction of ST is cost-effective under most of these assumptions and should be made available. Further work is needed to gather more data to inform modelling assumptions and allow updated evaluations.

Session P-X2 Poster Session
Tuesday March 4, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**
HIV Treatment and Care

1046 Treatment Outcomes Before and After the Decentralization of ART in an Urban Setting in Mozambique

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Background: There are few data on the effect of decentralization, task shifting and scale-up on the treatment outcomes of antiretroviral treatment (ART) in Mozambique. We hypothesized that decentralization, task shifting, and scale-up of ART to primary health care centers did not affect the quality of care provided.

Methodology: We compared treatment outcomes and evolution of CD4 cell counts of HIV-infected adults initiated on ART before (2003 to July 2006) with those initiated on ART after (2009-2011) the decentralization ART to primary health care centers in the Chamanculo Health District of Maputo, using routine data. To avoid bias due to changes in referral criteria we included outcomes from an ambulatory referral site in the district, which was created during the decentralization process. We used Kaplan-Meier plots and calculated incidence rates to compare treatment outcomes between groups. We used Poisson regression for adjusted analysis including as possible confounders age, sex, as well as CD4 cell count and WHO stage at treatment initiation.

Results: The study included 3,963 adults initiated on ART before the decentralization and 13,505 adults initiated on ART after the decentralization process had been completed. The overall attrition rate was slightly higher in the decentralized than the centralized cohort (19.0 events per 100 person years [py], 95% confidence interval [CI]: 17.9 to 20.1 versus 20.4 events per 100 py, 95% CI: 19.8 to 21.0). The reported mortality rate was higher in the centralized than the decentralized cohort (3.6 deaths per 100 py, 95% CI 3.1 to 4.1 versus 1.3, 95% CI: 1.1 to 1.4), as was the rate of transferals (4.1 transferals per 100 py, 95% CI: 3.6 to 4.6 versus 3.3, 95% CI: 3.1 to 3.6), while the rate of loss to follow-up (LTF) was lower in the centralized than the decentralized cohort (11.3 events per 100 py, 95% 10.5 to 12.2 versus 15.8, 95% CI: 15.3 to 16.4). The slightly higher rate of adverse events (death and LTF combined) in the decentralized cohort is explained by the loss of patients directly after the initiation of ART (adjusted incidence rate ratio [IRR] for the first three months: 1.2, 95% CI: 1.1 to 1.3). There was no difference in the rates of adverse events after three months (adjusted IRR: 1.1, 95% 1.0 to 1.2) between both groups. Among patients with available CD4 cell counts, CD4 cell recovery was slightly slower in the centralized as compared to the decentralized cohort, but reached similar values at 2.5 years after treatment start (median 364 cells per µl, interquartile range [IQR] 253 to 494 versus 360 cells per µl, IQR: 254 to 495).

Conclusions: Decentralization, task shifting and scale-up of ART to primary health care centers in the Chamanculo District of Maputo, Mozambique, did not strongly impact the quality of care provided.

1047 CD4 Count at ART Initiation and Economic Restoration in Rural Uganda

Atheendar Venkataramani[1], Harsha Thirumurthy[2], Jessica Haberer[1], Yap Boum[3], Mark Siedner[4], Annet Kembabazi[5], Peter Hunt[6], Jeffrey Martin[6], David Bangsberg[5,7], Alexander Tsai[8]
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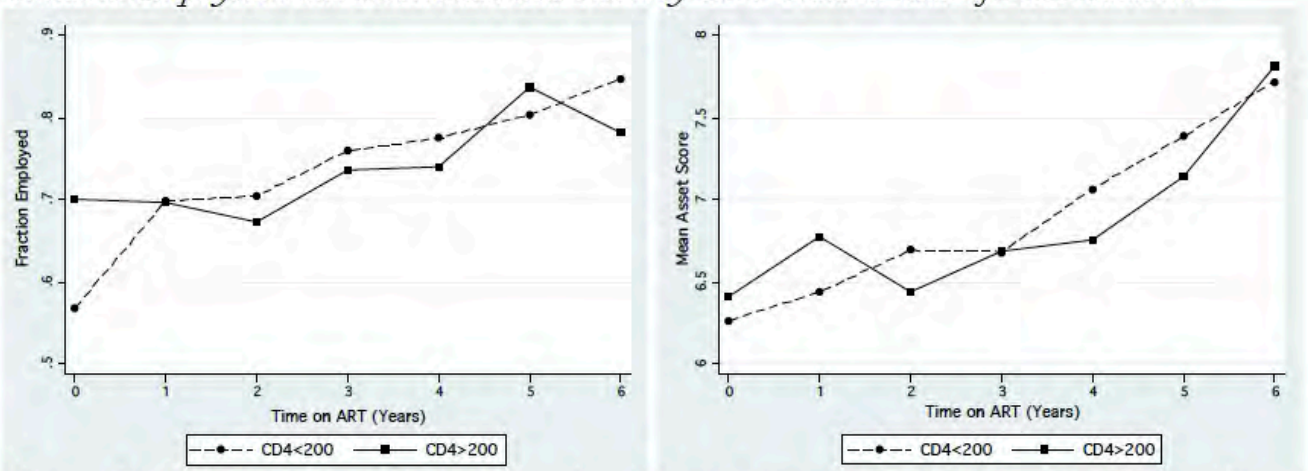
Background: Earlier initiation of ART may prevent morbidity driven pre-treatment declines in socioeconomic status and may also influence subsequent economic recovery. We examined associations between CD4 count at time of ART initiation and economic measures both at the start of therapy and during six years of follow-up.

Methodology: Starting in 2005, participants initiating ART at a regional referral clinic in Uganda were enrolled in the Uganda AIDS Rural Treatment Outcomes study (UARTO) and followed prospectively. We collected data on employment and asset ownership annually. Using multivariable regression, we assessed whether economic outcomes at baseline and in the 6 years following ART initiation varied by our primary exposure of interest, baseline CD4 count ≥ or < 200 cells/uL, adjusting for age, gender, education level, and marital status.

Results: We followed 505 individuals for a median of 5 years (IQR 1-7). Participants initiating ART at CD4≥200 (n=179) were more likely to be employed at baseline than those initiating below this threshold (n=327) (0.71 vs. 0.57, p<0.01 for absolute difference, 95% CI 0.06-0.21). Those in the CD4<200 group achieved a similar level of employment within 1 year of initiating ART, and employment rates remained similar throughout the 6 years of follow-up. Both groups had similar asset ownership scores at baseline and demonstrated similar increases in asset scores during follow up.

Conclusions: Those initiating ART at CD4≥200 had higher employment levels at baseline, though those initiating with advanced disease erases the difference within 1 year, of therapy. Individuals at all pre-therapy CD4 counts showed significant increases in asset ownership through at least 6 years of therapy. The results suggest that earlier initiation of therapy may help prevent initial declines in employment, though the similarities in baseline asset ownership across CD4 count groups suggests aspects of HIV infection beyond morbidity, such as a reduced propensity to invest in durable assets due to perceived reductions in life expectancy after diagnosis, may impact economic status, as well.

Trends in Employment and Household Asset Scores by CD4 Count at Time of ART Initiation



Notes – Employed = 1 if the individual is employed, hence the mean is the fraction employed. Asset Score ranges from 0-16. Time on ART = 0 refers to pre-ART baseline. CD4 refers to CD4 count at the time of initiation. Only the differences in baseline employment status were statistically significant (0.7 versus 0.57, p<0.01). Standard error bars omitted so as to reduce clutter.

1048 48-Week Outcomes in Adults Starting ART at CD4>350 Using Streamlined Care in Rural Uganda

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Background: As WHO guidelines promote earlier ART initiation, there is concern that asymptomatic individuals in Sub-Saharan Africa with high CD4+ counts may not successfully adhere to therapy and achieve virologic suppression. We previously reported high uptake of ART among persons with high CD4+ counts in the EARLI Study (Early Antiretroviral Therapy in Resource Limited Settings in Persons with High CD4+ Counts; NCT:01479634). We report here the 48 week virologic and safety outcomes of EARLI patients with CD4+ >350 receiving ART using a streamlined ART delivery model in a prototypic rural Ugandan Health Center.

Methodology: In this open-label study, ART-naïve, HIV-infected Ugandan adults (≥18 years) with CD4+ >350 were offered ART (tenofovir/emtricitabine plus efavirenz). Participants were seen by a medical officer at baseline and 4 weeks, and had subsequent nurse visits at 8, 12, 24, 36, and 48 weeks. Safety laboratory evaluations were done at 8, 12 and 48 weeks. HIV RNA levels (viral load) were measured (Abbott) at baseline, 24, and 48 weeks. Undetectable VL was defined as ≤400 copies/mL. Patient self-reported adherence was measured by 3-day recall. Participants did not receive incentives for clinic attendance or adherence, nor appointment reminders.

Results: 200 adults were enrolled; 3 were excluded after baseline HIV status was determined to be negative. Median age was 35 years, 65% of participants were female, median CD4+ count was 564 cells/uL (IQR 448-712), and median HIV RNA level was 22,400 copies/mL. Retention at 48 weeks was 98%. Participants reported high adherence (no missed ART was reported in 1093/1116 [98%] of visits from weeks 4-48). Overall, ART was well tolerated: a total of 22 grade III/IV laboratory abnormalities (DAIDS scale) occurred in a total of 18 participants. The most common abnormality was neutropenia (n=11). Two participants died, one from inoperable gastric carcinoma, and the other from complications following a cholecystectomy. Grade III/IV creatinine elevations occurred in 2/197 participants. In both individuals, tenofovir/emtricitabine was discontinued temporarily and restarted successfully with no subsequent creatinine elevation. The proportion of adults with virologic suppression at 24 weeks was 188/197 (95.4%), and at 48 weeks was 186/192 (96.9%).

Conclusions: 48-week HIV RNA suppression rates exceeded 95% in an open label study of ART in 197 adults with CD4>350 receiving streamlined care in a rural Ugandan clinic. This high CD4+ count population showed robust retention in care, strong ART adherence, and little medication toxicity in a streamlined ART delivery system. These data challenge current views that asymptomatic HIV-infected adults will not be interested or able to comply with ART when initiated at high CD4+ cell counts.

1049 Second-Line Failure and Protease Inhibitor Resistance in a Clinic in Johannesburg, South Africa

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Background: In resource limited settings, where few options exist for patients failing second line antiretroviral therapy (ART), programmatic approaches to treatment failure must be developed. We report on an approach to standardizing care for patients failing second line in South Africa.

Methodology: We conducted a retrospective study of 314 patients on second line protease inhibitor (PI) ART with a HIV-1 RNA >400 copies/ml at Themba Lethu Clinic in Johannesburg, South Africa between March 2012 and September 2013. Patients underwent adherence counselling and repeat viral load testing. Those with a repeat viral load after re-adherence of >1000 copies/ml underwent testing for HIV-1 drug resistance. If adherence remained a significant problem HIV resistance testing was not done. Sequences were graded as intermediate or resistant using the Stanford University HIV Drug Resistance Database.

Results: Of the 314 patients who underwent adherence counselling, 61% were female. The median age was 40.5 years (IQR 35-47), median CD4 count was 346 cells/mm3 (IQR 205-422) and viral load was 6458 copies/ml (IQR 2044-40006). The average length of time since ART initiation was 5.3 years (IQR 3.2-7.1) and 2.4 years (IQR 1.0- 4.5) on second line therapy. Compared to other patients on second line, patients with treatment failure had lower rates of viral suppression at 6 months (53% vs. 15%) and 12 months (46% vs. 14%) after starting second line.

Of the 314, 282 (90%) had ≥1 repeat viral load, 26 (8%) had none, and 6 patients (2%) died or were lost to follow-up. 166 (59%) achieved viral re-suppression (<400 copies/ml) over a median (IQR) of 63 days (87-146). 67 of the 282 (24%) had HIV-1 drug resistance tests done of which 21% (14/67) did not amplify. Of the 53 successful tests 45% (24/53) had no clinically significant resistance, 19% (10/53) had NRTI resistance without PI resistance, 17% (9/53) had low level PI resistance and 19% (10/53) had significant PI resistance (Table 1).

In total 19 (6%) patients initiated third line (raltegravir, etravirine or darunavir). Half of these patients have had repeat viral loads and all are suppressed.

Conclusions: Although most second line failures remain related to adherence and can be overcome with careful counselling, we found that 38% of patients who underwent HIV drug resistance testing had significant NRTI or protease inhibitor resistance requiring third-line treatment. Strategies for preventing second line failure are critical in areas where limited treatment options exist.

Resistance mutations in second line failure patients who underwent HIV genotype testing		
	N = 53	%
No clinically significant resistance	24	45%
Fully sensitive	7	13%
M184V and/or first line NNRTI (efavirenz, nevirapine) resistance only	17	32%
NRTI resistance without PI resistance	10	19%
Low level PI resistance	9	17%
Single PI (typically nelfinavir)	5	10%
Multiple PI including Atazanavir	4	7%
Significant PI resistance	10	19%
Intermediate lopinavir	6	11%
High level lopinavir	2	4%
Intermediate darunavir	2	4%

1050 A 5-Year Comparison of Viral Load and CD4 Cell Count Monitoring for ART Patients in Rural Uganda

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Background: The Home-Based AIDS Care (HBAC) project was a clinical trial which found no difference in clinical outcomes between participants who were randomized to viral load (VL) monitoring and CD4 cell count monitoring in comparison to CD4 cell count monitoring alone after 3 years of follow-up. We further report on clinical outcomes from this study with an additional 2 years of follow-up.

Methodology: Beginning in May 2004, HIV-infected members of The AIDS Support Organisation (TASO) - Tororo with a CD4 count of <250 cells/mm3 or WHO Stage 3 or 4 disease were offered ART and randomized to one of three monitoring groups: Arm A) Clinical monitoring and quarterly CD4 cell counts and VL; Arm B) Clinical monitoring and quarterly CD4 cell counts; or Arm C) Clinical monitoring alone. Field workers delivered ART to participants' homes

and collected data to monitor potential toxicity, morbidity and mortality. In April 2007, following analysis of the first phase of the study which demonstrated that Arm C participants were at increased risk for death and/or new opportunistic infections (OIs); these individuals were re-randomized to Arms A or B and all participants were followed until March 31, 2009. Clinical events prior to re-randomization in Arm C patients were not included in this analysis. We conducted bivariate analyses of clinical and demographic characteristics of study participants in the remaining two arms and used Cox Proportional Hazard models to determine if study arm was independently associated with the development of OIs or death.

Results: A total of 1012 participants (73.7% female) were randomized to one of the 3 original study arms and of these, 316 survivors from Arm C were re-randomized to Arms A and B. The median age was 38 years and the median CD4 cell count at enrollment was 134 cells/ mm3. 509 individuals were followed in Arm A/C and the 503 in Arm B/Cfor a median of 4.4 years of follow-up. There were no significant differences in clinical or sociodemographic characteristics between two groups at randomization or re-randomization. Over the entire length of the study, 38 deaths and 20 new OIs occurred in Arm A patients and 36 deaths and 21 new OIs occurred in Arm B patients. Randomization to Arm B was not associated with the risk for new OIs or death (adjusted hazard ratio [AHR] = 1.03; 95% CI 0.75 - 1.43). We also found no effect on randomization when we excluded the original Arm C patients (AHR = 0.97; 95% CI 0.68 - 1.39).

Conclusions: We found no differences in clinical outcomes associated with the addition of quarterly VL monitoring to quarterly CD4 cell count monitoring. These data continue to support expanding access to ART in resource-limited settings, irrespective of the availability of VL testing.

1051 Success of Transfer of HIV Care From a PEPFAR Site To Community-Based Clinics in South Africa

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Background: PEPFAR funding changes have resulted in HIV clinic closures, necessitating the transfer of large cohorts of patients to government-funded, community-based clinics. We evaluated linkage to care following a rapid, large-scale transfer of patients from a hospital-based HIV clinic in South Africa.

Methodology: All adult (≥18y) patients on ART who visited the hospital-based HIV clinic in Durban from March to June 2012 were transferred to >170 clinics. Hospital counselors identified patients' target transfer clinic based on their home location and care needs. Study staff surveyed subjects 5-10 months after transfer to assess self-reported linkage to the target clinic. To examine the validity of self-report, we randomly selected 8 clinics from the 80 clinics closest to the hospital for record reviews. We estimated the overall success of transfer as a weighted average of linkage to care for subjects reached and not reached for the survey, adjusted for results of the validation visits.

Results: Of the 4,690 patients who visited the HIV clinic in the year prior to its closure, 3,927 (84%) were transferred and phoned at least once. Mean age was 40 years (sd 9.3), 59% were female, and most recent CD4 prior to transfer was 375/µl (IQR 251-530). Of transferred patients, 3,384 (86%) were reached and completed the survey; 3,376 (99.8%) reported attending a transfer clinic. Of those reached, 866 (26%) reported visiting a different clinic than that assigned. The most common reasons for attending alternative clinics were: told by the receiving clinic to go elsewhere (23%), stigma concerns (16%), and inconvenient location (14%).

Among the 756 patients assigned to the 8 validation clinics, 659 (87%) were reached for the survey. 531 (81%) of those surveyed reported going to their assigned clinic. Among those who self-reported attending their assigned clinic, 446 (84%) had a visit validated in the clinic record. Of the 46 people who self-reported attending a validation clinic to which they were not originally assigned, 39 (85%) had a validated visit. Of the 97 patients who could not be reached for the survey, 59 (61%) had a validated visit at their assigned clinic. Based on the validation rates for reached, self-reported, and unreached patients, the estimated success of transfer for the cohort overall was 81%.

Conclusions: A large majority of patients reported successful transfer from a hospital- to a community-based clinic in South Africa, though a quarter of patients attended a different clinic than assigned. Validation of self-reported attendance at a clinic highlights that nearly 20% of patients may not have linked to care. Efforts to optimize transfers to community sites require accurate contact details and collaboration with receiving clinics to ensure successful linkage to care.

1052 The Feasibility and Economic Impact of Time Designated Appointment System in a Busy HIV Care Clinic

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Background: As efforts are made to put the remaining 40% of people in Kenya on HIV treatment, the problem of congestion at HIV care clinics is likely to worsen. Averting the likely negative impact of this problem require instituting new measures to improve overall patient flow. We evaluated the feasibility and the economic benefits of a time designated appointment system as a solution to decongest a large HIV care and treatment clinic in Kisumu, Kenya.

Methodology: This was a two arm open label randomized controlled trial recruiting 354 patients at Lumumba Health Centre in Kisumu, Kenya_a large urban HIV care and treatment clinic supported by Family AIDS Care and Education Services (FACES). Consenting participants were enrolled during their normal clinic days and followed up at subsequent clinic appointments for up to 12 months. Intervention arm participants were given specific dates and

times to come to the clinic for their next appointment. In comparison, control arm participants were given the date to come for the next appointment and had full discretion to decide on the time to arrive as is the standard practice in Kenya. All participants reported at the study office for arrival and departure time clocking and to respond to a brief follow up questionnaire. The study was designed to fit into FACES clinic schedules and procedures with minimum interruption. All clinicians at the site took care of study participants as part of their normal workflow. To get valuation of the work participants were involved in on their clinic day, we asked them the nature of the work they did before and after their clinic appointment and how much they would pay if they were to hire someone to do the work for them.

Results: Nearly two thirds (60.7%) of the participants were women with a mean age of 37 (standard deviation [SD] 9). About 87% of participants were on antiretroviral treatment. The most recent mean CD4 count was 548 (SD 233). In all the visits in the intervention arm combined, 72.1% of the participants arrived on time, 13.3% arrived ahead of time and 14.6% arrived past scheduled time. Participants in the intervention arm spent less time at the clinic [1.8 hours (SD 1.1)] compared to control [3.2 hours (SD, 1.2) ($p<0.001$)]. Furthermore, participants enrolled in the intervention arm were more productively engaged on their clinic days valuing their work at USD 3.3 (SD 3.1) compared to control participants who valued their work at USD 2.6 (SD 2.1) ($p=0.017$).

Conclusions: Time designated appointment system in HIV care clinics is feasible and provides substantial time savings, and was associated with greater economic productivity for HIV patients at a busy HIV care and treatment clinic. Further research is required to determine if a time designated appointment system is scalable, and functions well in other settings.

1053 Long-Term Virologic Response in a Cohort of HIV-Infected Patients in South Africa

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Background: While much is known about virologic response to antiretroviral therapy (ART) in resource-rich settings, much less is known about long-term rates of virologic suppression in resource-limited settings. We aimed to describe virologic response on ART over 8 years among a cohort of patients initiating ART the first year of the public sector roll out in South Africa.

Methodology: We included all ART-naïve patients, ≥18 years, who initiated first-line ART from April 2004-March 2005 at 4 public sector HIV treatment clinics in Gauteng and Mpumalanga Provinces. Patients were followed from ART initiation until death, transfer, loss to follow-up (LTF) or dataset close (May 2013). LTF was defined as being ≥3 months late for a scheduled visit with no subsequent visit. Virologic suppression was defined as a viral load (VL) 1000 copies/ml. A transient elevated viral load (TEV) was defined as a failing VL followed by a suppressed VL.

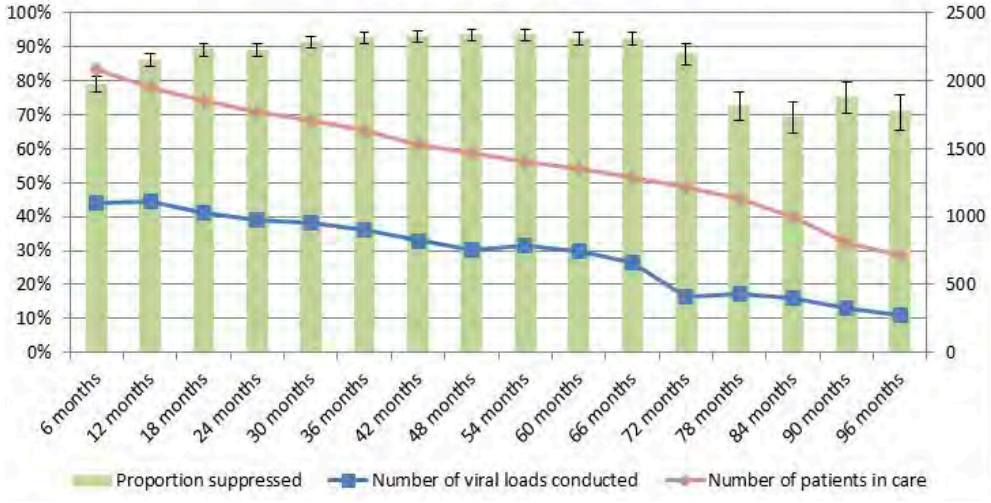
Results: 2357 patients were included. 68.8% were female with a median (IQR) age of 35.4 (30.5-42.0) years and a median (IQR) baseline CD4 count of 80 (34-141) cells/mm3. Patients were followed for a median (IQR) of 6.2 (2.1-8.3) years. At the end of follow-up, 18.0% of patients had died, 24.4% of patients were LTF, and 30.1% of patients had transferred.

1912 (81.1%) patients had ≥1 VL recorded with a median (IQR) of 11 (6-14) VLs over the duration of follow-up. Of those, 96.0% (n=1835) achieved virologic suppression and 68.4% (n=1255) of those patients suppressed on their first VL. Among those 1255 patients, 53.2% remained suppressed at every subsequent VL (median: 11; 1QR: 6-13). For the 535 patients who did not remain suppressed, patients experienced a median (IQR) of 2 (1-3) detectable VLs and the first detectable VL occurred in a median (IQR) of 2.7 (1.1-6.1) years after the first suppressed VL (Figure).

704 (36.8%) patients experienced ≥1 TEV and were less likely to die (7.7%) or become LTF (15.6%) compared to patients who never experienced a TEV (death: 13.1%; LTF: 23.0%), potentially due to increased monitoring of patients experiencing adverse virologic response.

Conclusions: Long-term suppression is common in this cohort of HIV-infected individuals. However, over 70% of patients left the cohort (died, transferred, or left care) by the end of follow-up. Further research is needed to determine successful interventions for retaining patients in care in order to ensure continued success of the ART program in South Africa.

Figure 1. Proportion of patients who initiated ART between April 2004 and March 2005 with a suppressed viral load in 6 monthly intervals at Themba Lethu Clinic in Johannesburg, South Africa



1054 CD4 Cell Decline and Time To Reaching ART Eligibility in HIV Patients From Rwanda

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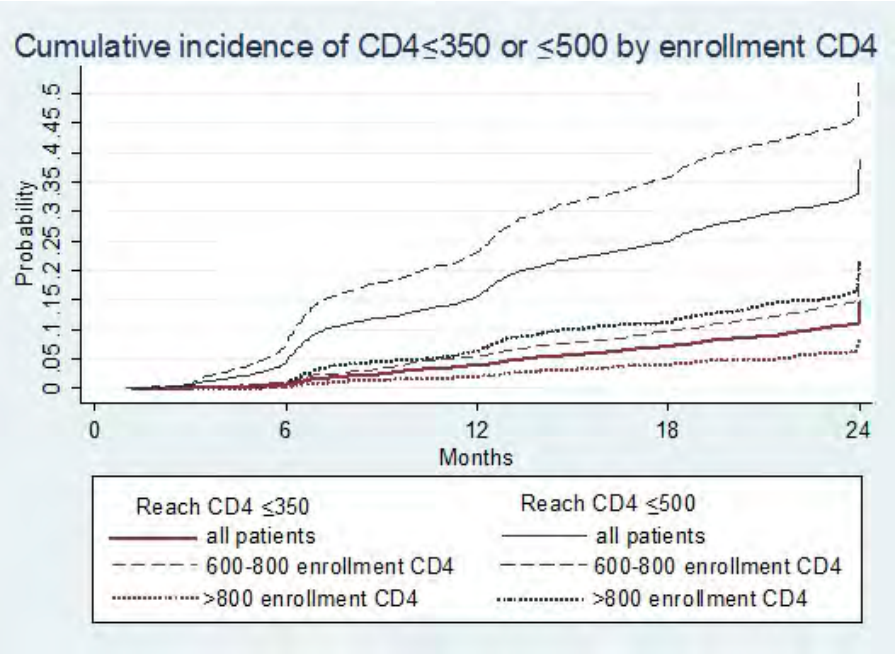
Background: CD4 cell count thresholds are a key parameter used for assessing antiretroviral therapy (ART) eligibility. Determining the rate of CD4 decline is important in estimating the impact of different CD4 thresholds for ART initiation and for establishing monitoring frequency for patients not eligible for ART. Few data are available on CD4 decline in HIV-infected patients in resource limited settings. We analyzed the rate of CD4 decline in ART-naïve adults in Rwanda and assessed time to reaching ART eligibility as per 2010 and 2013 WHO guidelines.

Methodology: We examined CD4 decline in HIV-infected patients >15 years with CD4>600 cells and at least one follow-up CD4 prior to ART initiation enrolled from 2005-2010 at 41 Rwandan health facilities supported by ICAP-Columbia University. CD4 decline in the first 24 months was estimated using mixed linear regression modeling. Competing risk estimators were used to assess time to reaching ART eligibility at CD4<350 or CD4<500, accounting for loss to follow-up, death and ART initiation as competing risks.

Results: We analyzed data for 4,643 patients with a median age of 32.1 years [Interquartile range (IQR): 25.9-40.1], 73% female, 65% with WHO stage 1 at enrollment and median pre-ART follow-up time of 21.4 months. Median and mean CD4 at enrollment were 773.0 [IQR: 676-923] and 830.1 [IQR: 676-923], respectively. Mean CD4 counts were significantly lower among men (-38.6, 95%CI 25.1-52.1, p<.0001) and patients >40 years of age (-20.9, 95%CI 7.1-34.7, p<.01). The average CD4 decline over 24 months of follow-up was 5.3 cells/month (95%CI 5.0-5.6) and 63.6 cells by 12 months (95%CI 60.2-67.0). No significant difference was observed in the rate of CD4 decline for men compared to women, however patients >40 years of age had a CD4 decline of 10.8 more cells per year (95%CI 3.0-18.6, p<.01). By 24 months, 11.1% (95%CI 10.1-12.1%) of patients reached CD4<350 and 33.0% (95%CI 31.4-34.5%) reached CD4<500. Among patients with CD4 600-800 cells at enrollment, less than half (45.9%, 95%CI 43.7-48.1) reached CD4<500 and 15.0% (95%CI 13.3-16.4) reached CD4<350 in 24 months of follow-up.



Conclusions: In this large cohort of ART-naïve HIV patients from Rwanda with CD4>600 cells, average CD4 decline was estimated to be 63.6 cells/year, a very similar rate to that found in resource-rich settings. One third of patients reached ART eligibility within 24 months using current WHO guidelines of CD4<500 and only 11% reached CD4<350 cells as per 2010 WHO guidelines.

1055 Predictors of Late Engagement To HIV Care in Western Kenya: A Cross-Sectional Study

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Background: Late patient presentation contributes significantly to the high mortality reported in HIV-care and treatment programs in sub-Saharan Africa.

Methodology: To assess the factors associated with late engagement we conducted a cross-sectional study using data extracted from the electronic medical records system of the Academic Model Providing Access to Healthcare (AMPATH). AMPATH provides HIV treatment across 80 clinics in western Kenya. Data from all the 80 clinics were included in this analysis. Patients were eligible for analysis if they were > 14 years and enrolled between 1st December 2010 and 31st December 2012. Late engagement was defined as an enrollment CD4 count ≤100/µl. Analysis was conducted using a Chi-Square test of associations between categorical /dichotomous variables, a T-test comparison of group means and a multivariable logistic regression model to assess risk factors associated with late engagement.

Results: Of the 10,533 participants included in the analysis, 67% were female; mean age 36.7 years (sd 11.0) and median baseline CD4 cell count was 258 cells/µl (IQR 111,437). Overall, 2,421 (23%) of the participants presented with baseline CD4 cell count ≤ 100/µl. Median time to ART initiation was 28 days (IQR 14 to 44).Factors associated with late engagement included male gender (AOR: 1.57, 95% CI: 1.38-1.78); older age (AOR: 1.02, 95% CI:

1.01-1.03); longer travel time to clinic (AOR: 1.23, 95%CI: 1.09-1.39); being employed (AOR: 1.21, 95%CI: 1.06-1.39) and having tuberculosis (AOR: 3.10, 95% CI: 2.71- 3.54)

Conclusions: Nearly one-quarter of HIV infected patients in our setting present with advanced immune-suppression at initial encounter. Being male, older in age, employed, living further away from clinic and having tuberculosis are associated with late engagement to care. There is an urgent need to identify innovative ways to engage males in testing, test in the work place and ensure that TB clinics are testing for HIV at presentation into care.

1056 Cost Savings of Viral-Load Testing Before ART Second-Line Switch in a Resource-Limited Setting

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Background: WHO guidelines for patients on antiretroviral therapy (ART) recommend immunologic monitoring when viral load (VL) testing is not available. In sub-Saharan Africa immunologic monitoring is neither sensitive nor specific and leads to switching to second-line regimens that are more costly than first-line ART. We sought to determine if VL testing in patients suspected of immunologic failure was cost-saving.

Methodology: We reviewed the records of patients who had VL testing prior to ART switching as recommended by the existing program in 7 government-run urban clinics in Kampala, between October 2008 and October 2011. VL testing was performed in an unsubsidized central lab facility where the cost of a VL test is $62. The cost of first-line ART averaged $14.68 per person per month and second-line ART, $35.99 per person per month.

Results: 312 patients were tested at 7 clinics in Kampala City. 185 (59%) had detectable VL (>400 copies/mL) and 127(41%) had undetectable VL (< 400 copies). Of the 185 with detectable VL, 24 had 5000 (51.6%) were switched to second-line while 151 patients with VL < 5000 (48.4%) remained on first-line therapy. The cost of targeted VL testing in patients with immunologic failure was recouped in 6.0 months when compared to the increased cost of treating patients who had immunologic failure but suppressed VL with the second line regimen as indicated in table 1

Conclusions: Testing with VL prevents the unnecessary switching to second-line ART in 50% of patients and recouping of the cost of VL testing in those who immunologically fail at 6.0 months.

Table 1: Initial costs of each model/month

Model of care	Viral load testing carried out	No viral load testing
Costs (USD)	(312×$62) + (161×$35.99)+ (151x$14.68)	(312x$35.99)
($62x312 patients)+ (161x35.99) X + (151x14.68) X = (312x35.99) X ; where X=number of months to break even.		

1057 Peer Support and Engagement, HIV Care and Sexual Behaviors Among PLHIV Not On ART: A Randomized Trial

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Background: People living with HIV (PLHIV) not on antiretroviral therapy (ART) benefit from engagement in care, preventive care interventions, and decreasing risky sexual behaviors. Peer support may be an economical intervention to facilitate these issues in an integrated approach. We conducted a randomized trial on the impact of peer support on HIV care and prevention outcomes among PLHIV not on ART in Rakai, Uganda (The PeerCARE or Peer Community-based Assistant in Retention and Engagement Study).

Methodology: Participants recently identified as HIV-infected by the Rakai Health Sciences Program (RHSP) but not on ART were randomized to peer support or standard of care. Peer support consisted of monthly home visits to reinforce engagement in care, preventive care interventions (cotrimoxazole prophylaxis, bednet, and safe water vessel use), and safer sexual behaviors (using condoms and decreasing partners) based upon an Information, Motivation, and Behavioral Skills conceptual framework of behavior change. Standard of care was referral to local RHSP clinics. Patients were administered an end of study survey assessing key outcomes after one year of follow-up. Log binomial regression with robust standard errors were used to calculate prevalence risk ratios (PRR) with 95% CIs.

Results: 447 participants were enrolled and followed June 2011-July 2013 (225 intervention; 222 control). Baseline characteristics were balanced: median age was 30 (IQR 27-37); 64% were female; 62% had previously visited an RHSP clinic; 45% had already initiated cotrimoxazole prophylaxis. After a median follow-up of 363 days (IQR 352-378), 87% of intervention and 90% of control participants completed the end of study survey (p=0.33). As shown in the Table, intervention participants were more likely to be in care, have initiated cotrimoxazole prophylaxis, and be adherent to safe water vessel use. No effects were observed on ART initiation or sexual behaviors. Most of the attributable effect was among participants with no history of prior linkage to RHSP clinics (see Table, n=151).

Conclusions: Patients randomized to a peer support were more likely to remain in care, initiate cotrimoxazole prophylaxis, and be adherent to safe water vessel use at one year of follow-up. This effect was mostly seen in patients not previously linked to RHSP care. No effects were observed on ART initiation or sexual behaviors. Peer support may be an effective intervention to address care and prevention needs of PLHIV not on ART.

Table: Study Outcomes, All Participants and Participants Not in Care at Baseline								
Outcome	All Participants				Participants Not in Care at Baseline			
	Intervention n/N (%)	Control n/N (%)	PRR (95% CI)	p value	Intervention n/N (%)	Control n/N (%)	PRR (95% CI)	p value
In Care	179/195 (92%)	167/199 (84%)	1.09 (1.02-1.18)	0.017	67/80 (84%)	43/71 (61%)	1.38 (1.11-1.71)	0.003
Initiated ART	71/195 (36%)	71/199 (36%)	1.02 (0.78-1.32)	0.88	24/80 (30%)	15/71 (21%)	1.42 (0.81-2.49)	0.22
Initiated Cotrimoxazole	174/195 (89%)	161/199 (81%)	1.10 (1.01-1.20)	0.021	64/80 (80%)	43/71 (61%)	1.32 (1.06-1.64)	0.012
Bednet Adherent	91/195 (47%)	95/199 (48%)	0.98 (0.79-1.20)	0.83	42/80 (53%)	30/71 (42%)	1.24 (0.88-1.75)	0.22
Water Vessel Adherent	45/195 (23%)	28/199 (14%)	1.64 (1.07-2.52)	0.024	17/80 (21%)	3/71 (4%)	5.03 (1.53-16.5)	0.008
Any Condom Use[1]	108/171 (63%)	101/174 (58%)	1.09 (0.92-1.29)	0.33	46/72 (63%)	35/66 (53%)	1.18 (0.88-1.58)	0.27
Multiple (>1) Sexual Partners	62/195 (32%)	50/199 (25%)	1.27 (0.92-1.74)	0.15	23/80 (29%)	22/71 (31%)	0.93 (0.57-1.52)	0.77
[1] Among sexually active participants only.								

1058 Community-Based ART Programs in Resource-Limited Settings

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Background: Patients in ART programs in rural African settings are challenged by the high costs of transportation which can lead to high rates of loss-to-follow-up (LTFU) and death. We examined program retention among long-term patients of an ART program in rural Uganda which has used a community-based distribution of ART and satellite clinics since its inception in 2004

Methodology: We conducted a retrospective cohort analysis of all patients >18 years who initiated ART at TASO-Jinja between January 2004- July 2009. We identified all clients in community and facility-based ART delivery arms using an electronic clinical monitoring database. The catchment area included participants in villages up to 75kms away from Jinja town. Enrollees were expected to attend regular clinic or outreach visits every one- to- three months. CD4 cell count testing was offered every six months. We calculated the proportion of participants who had at least one recorded clinic or outreach visit in the six months before June 2013 and examined associations with the combined outcome of LTFU or death using Cox proportional hazards model

Results: A total of 3345 participants began ART during 2004 - 2009 and the median time on ART in June 2013 was 5.69 (IQR=4.10 - 7.23years). Of these, 2380 (71%) were females the median age was 40 years (IQR= 34- 46) and the median CD4 count at initiation was 184 cells/ µL (IQR= 95 - 298). A total of 1335 (40%) were residents of Jinja district and 2005 (60%) resided in outlying districts. Of these, 2322 (69%) were retained in care, 577 (17%) died, 161 (5%) transferred out, 285 (9%) were LTFU. Factors associated with mortality or LTFU included male gender (adjusted hazard ratio [AHR]=1.56 95% CI 1.28-1.9), CD4 cell count<50 (AHR=4.09; 95% CI. 3.13 -5.36) or 50 - 199 cells/ µL (AHR = 1.86 ; 95% CI 1.46 - 2.37) ART initiation , WHO stage 3 (AHR= 1.35 ; 95% CI 1.1 - 1.66) or 4 (AHR=1.74 ; 95% CI 1.23-2.45) illness; initiating ART on D4T,3TC and NVP (AHR=1.37 ;95% CI 1.08 -1.75) and year of ART initiation (AHR = 1.32; 95% CI 1.20 - 1.46).Notably, residence outside of Jinja district was not associated with mortality/ LTFU(AHR = 0.87; 0.71, 1.05)

Conclusions: Among participants enrolled in an ART program for a median of over 5 years, rates of mortality and LTFU were very low and did not differ based on the geographic residence of program participants. This suggests that community-based distribution systems can effectively mitigate the time and cost constraints associated with transportation to ART clinic sites

Session P-X3 Poster Session
Wednesday March 5, 2014, 2:30 PM–4:00 PM **Exhibit Hall D**

The Treatment Cascade and Loss To Follow-Up

1059 Gender Differences in Loss To Follow-up and Mortality in Older Adults On ART in Sub-Saharan Africa

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Background: People living with HIV (PLWH) ≥50 years of age are a growing but understudied population in Sub-Saharan Africa. Gender differences in outcomes after ART initiation have been well documented for PLWH aged 15-49 years but less is known about older PLWH. We explored the effect of gender on loss to follow up (LTF) and recorded mortality after ART initiation among PLWH aged ≥50 years.

Methodology: We used routinely collected patient-level data from PLWH ≥50 years initiating ART at 199 HIV health facilities supported by ICAP-Columbia University in Rwanda, Tanzania, Mozambique and Kenya. Age was categorized in 5 year increments. PLWH were considered LTF if they had no record of death or transfer and did not have a recorded clinic visit for 6 months. Cox Proportional Hazard Models examined gender differences in LTF and mortality 12 months after ART initiation in three ways: (1) across all age groups; (2) stratified by age; and (3) stratified by gender. All models controlled for disease status (CD4+ <100cells/mL or WHO stage 4 vs. CD4+ ≥100 cells/mL or WHO stage 1-3) at ART initiation, point of entry into HIV care (i.e. in-patient ward vs. all other entry points), and country.

Results: From 2005-2011, 21,634 PLWH aged ≥50 years (median (IQR): 55 years (52-59)) initiated ART; 50% were 50-54 years, 26% 55-59 years, 14% 60-64 years, 6% 65-69 years, and 4% ≥70 years of age. Across all ages, men had significantly higher rates of LTF (HR: 1.23, 95% CI: 1.13-1.34) and death (HR: 1.38, 95% CI: 1.24-1.53) compared to women at 12 months after ART initiation. When stratified by age, this gender difference remained significant only among PLWH aged 50-59 years (see table). Stratification by gender showed LTF increased for men aged 60-69 years compared to those aged 50-54 years. For women, LTF was similar across all ages except for the oldest (≥70 years), where the rate was higher than women aged 50-54 years. Mortality rates increased with age among both men and women.

Hazard ratios and 95% CIs for outcomes 12 months after ART initiation, adjusted for advanced HIV disease, point of entry, and country.

Stratified by age (men compared to women)		
Age Group	LTF	Death
50-54 years	1.35 [1.18-1.53]	1.50 [1.29-1.76]
55-59 years	1.23 [1.08-1.39]	1.38 [1.07-1.78]
60-64 years	0.94 [0.78-1.13]	1.20 [0.90-1.59]
65-69 years	1.03 [0.75-1.42]	1.21 [0.80-1.84]
70 years and above	1.22 [0.85-1.74]	0.96 [0.62-1.49]
Stratified by gender (all age groups compared to ages 50-54)		
Age Group	LTF	Death
Among men:		
55-59 years	1.08 [0.95-1.23]	1.05 [0.83-1.31]
60-64 years	1.33 [1.14-1.54]	1.40 [1.09-1.81]
65-69 years	1.31 [1.02-1.67]	1.81 [1.26-2.60]
70 years and above	1.34 [0.97-1.85]	2.49 [1.70-3.65]
Among women:		
55-59 years	0.97 [0.88-1.08]	0.98 [0.80-1.20]
60-64 years	0.94 [0.83-1.07]	1.12 [0.85-1.46]
65-69 years	1.02 [0.84-1.24]	1.47 [1.07-2.02]
70 years and above	1.23 [1.03-1.48]	1.52 [1.08-2.12]

Conclusions: Our study extends prior research that men aged 15-49 years on ART have worse outcomes than women by showing that this gender differential holds among patients aged 50-59 years. Interestingly, this gender difference is lost among PLWH aged 60 years and older in our study. These results imply that future research and interventions addressing poor outcomes among men on ART should include older patients, at least through age 59.

1060 Comparative Effectiveness of HIV Care and Treatment Programs in East Africa

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Background: Survival after initiation of antiretroviral treatment (ART) among HIV-infected patients in Africa is a critical measure of the effectiveness of the public health response. Regional differences in mortality, after adjustment for biological factors (e.g., pre-therapy CD4 value), would suggest that the behavior of health care systems and patient populations play an important role in effectiveness. In routine program settings, however, high loss to follow-up (i.e., unknown outcomes) is common and many deaths are not ascertained.

Methodology: We evaluated HIV-infected adults on ART in five HIV care programs in Kenya, Uganda and Tanzania. Socio-demographic and clinical data were recorded during routine care on standardized forms issued by respective Ministries of Health. To manage the effects of loss to follow-up, we intensively traced a random sample of patients without unknown outcomes (defined as at least 90 days late for last visit) in the community. Outcomes in this sample of traced patients were incorporated into survival analysis using probability weights to revise estimates of mortality.

Results: Over two years, we followed 33,947 adults on ART: 15,613 from Kenya program 1; 4,844 from Kenya 2; 2,615 from Uganda 1; 7,532 from Uganda 2 and 3,343 from Tanzania 1. The median age was 35 years (IQR: 29-42), 66% were women, median pre-therapy CD4 count was 155/µl (IQR: 70-237). Overall 5,801 (25%) were lost to follow-up and of these, 980 (17%) were randomly selected for tracing and vital status was ascertained in 89% of the 980. Using only deaths known to programs before tracing, the two-year cumulative incidence of mortality was 2.4% (95% CI: 2.3%-2.6%). Incorporating outcomes among the lost led to a revised estimate of 7.5% (95% CI: 6.9%-8.1%). After adjustment for age, sex, pregnancy, whether patient was new to clinic at observation start, pre-therapy CD4 value, and tuberculosis at ART initiation, the clinical care program of the patient remained associated with mortality. Using Kenya program 1 as reference group, the adjusted hazard ratio for death in Kenya 2 was 1.04 (95% CI: 0.78-1.38), in Uganda 1 was 1.36 (95% CI: 1.0-1.84), in Uganda 2 was 0.56 (0.38-0.79) and in Tanzania 1 was 1.91 (95% CI: 1.46-2.52).

Conclusions: After accounting for biological drivers of mortality, program-to-program differences in survival on ART remain substantial. Even within the standardized and simplified public health approach to HIV treatment effectiveness may vary. Understanding regional variability in health delivery (e.g., quality, patient-centeredness) and patient behavior (e.g., engagement, adherence) is needed to optimize HIV treatment in Africa.

1061 Loss To Follow-Up: Determining Outcomes for Adults Enrolled in HIV Services in Kenya

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Background: Loss to follow-up (LTF) from HIV programs can present a barrier to effective evaluation of patient outcomes, such as death, and may be misinterpreted as an indicator of engagement in care. We used data from defaulter tracing for a random sample of patients LTF in one PEPFAR-supported HIV clinic to correct death estimates and estimate true disengagement from care for the larger population from which the sample was derived.

Methodology: Patients of the HIV clinic at Gatundu District Hospital in Kenya with at least 1 clinic visit between 2008-12 were assessed for LTF status using electronic data, with LTF defined as no visit in the past 3 (ART) or 6 (pre-ART) months and not dead or transferred-out. Of these, a random sample, stratified by pre-ART and ART status, was selected for study tracing. Tracers tracked patients and completed a questionnaire for patients or contacts found, collecting information including patient vital status (alive/dead) and engagement in care (in care/disengaged). Rates and percent dead and in care were presented using the initial clinic data and data updated with outcomes from defaulter tracing, weighted to represent all patients LTF. Patients reported by a contact as alive were classified as in care (optimistic scenario) or disengaged (pessimistic scenario) in separate analyses.

Results: 413 (21%) of the 1,974 clinic patients were LTF, of which 66 (16%, 40 pre-ART, 26 ART) were sampled. Questionnaires were completed for 65 (98%) patients (46 patients, 19 contacts). Seven (18%) pre-ART and 6 (23%) ART patients reported being disengaged from HIV care. Nine (23%) pre-ART and 5 (19%) ART patients were reported to have died. Updating the initial data with sample outcomes increased overall retention in care for pre-ART patients from 61% to 69% (pessimistic) or 75% (optimistic) and for ART patients from 84% to 88%; deaths increased from 10% to 18% for pre-ART patients and from 8% to 10% for ART patients. Incidence rates for death were lower and for LTF/disengagement substantially higher in the initial data than in the updated data, for both pre-ART and ART patients (see table).

Incidence rates per 100 PY			
		LTF (initial) / Disengagement (updated)	Death
Pre-ART	Initial	12.8	3.5
	Updated	2.3* or 4.6**	6.4
ART	Initial	5.5	3.6
	Updated	1.2* or 1.3**	4.7
*Optimistic scenario; **Pessimistic scenario			

Conclusions: This suggests that only a minority of patients classified as LTF by one large HIV clinic in Kenya are actually disengaged from HIV care. Also, death rates were underestimated. While our data are from a single facility, these findings suggest that high levels of LTF observed in routinely-collected data may be a poor proxy for disengagement from care and obscure higher death rates.

1062 Community ART Delivery for High Patient Retention - TASO Uganda Operational Research

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Background: The AIDS Support Organization (TASO) implements a mixture of ART service delivery models (facility, home and community models since 2005. An increasing numbers of ART lost to up, 1433 (6.4%) and 1498(6.7%) deaths from a cohort of 22315 was noted between 2000 to 2009. Community drug distribution points (CDDPs) were started to improve ART retention and adherence among clients on the programme. Little has been known about structural interventions that can sustainable very good ART adherence and retention of patients into the ART. A study to assess and compare adherence and retention out comes from the community and facility ART delivery models was conducted.

Methodology: Analytical retrospective study by design. Data collection was electronic data review for all registered TASO Jinja clients who have been on ART for the period above two months by July 2010. Uni-variates and bi-variates analysis was done. A comparison of outcomes was done using the chi-square test. Retention was based number of patients reported not lost to follow up and dead while on ART. Good adherence was defined as taking ART doses at 95% and above of the prescribed treatment. P- Value < 0.05 was considered to statistically significant for the study.

Results: A total of 3457 clients were studied with 1055(30.5%) males and 2402(69.5%) females.1302 (37.65%) were facility based and 2155(62.35%) CDDPs based. Loss to follow-up was four times higher in the facility arm with 215(16.5%) of 1302 patients compared to103 (4.28%) of 2155 CDDP clients, p0.074 for facility clients. Fewer deaths were reported in the CDDP arm 84(3.9%) compared to facility with 77(5.7%), p=0.008.

Conclusions: Community drug distribution points (CDDPS) model has better patient retention outcomes evidenced by four times reduction in lost to follow up. CDDPs is a good retention approach especially for health facilities with high volume ART clinics supplementing the traditional facility based model.

1063 HIV Care Cascade Among Hard To Reach Populations in India: Need To Expand HIV Counseling and Testing

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Background: Early identification of HIV infection, prompt linkage to care, retention, initiation of ART and suppression of viral load (VL) are critical steps along the HIV care cascade. Hard-to-reach groups such as injection drug users (IDUs) and men who have sex with men (MSM) lag behind at each step, particularly in low-and-middle-income settings where access challenges are complicated by stigma and discrimination. We characterize the spectrum of engagement in HIV care for IDUs and MSM in India.

Methodology: We recruited 12,022 MSM and 11,897 IDUs across 27 cities in India (target=1000 per site) using respondent-driven sampling from 10/2012 - 9/2013. Participants had to be ≥18 years old, self-identify as male and report sex with a man in the prior year (MSM) or report injection drug use in the prior 2 years (IDU). All participants underwent a survey and blood draw. HIV was diagnosed using double ELISA. We report the median of site-level proportions of each outcome along with 10th and 90th percentiles.

Results: 1150 MSM were HIV-infected with prevalence across sites ranging from 2 - 15%. Among those infected, a median 44% were diagnosed, 40% linked to care, 34% retained (saw provider in prior 6 months), 30% initiated on ART and 24% had suppressed VL. However, there was tremendous variability by site (percent diagnosed range: 0 - 92%; suppressed VL range: 0 - 59%). 2534 IDUs were HIV infected with prevalence across sites ranging from 5 - 47%. Among those infected, a median 36% were diagnosed, 32% linked to care, 25% retained, 20% were on ART and 15% had suppressed VL. Similar variability across site was observed (percent diagnosed range: 3 - 92%; suppressed VL range: 0 - 46%). Factors significantly associated with diagnosis in both groups included older age, larger network size, more education, and a history of tuberculosis. Among MSM, diagnosis was also significantly associated with being married, being a receptive partner and history of a sexually transmitted infection. Among IDUs, diagnosis was also significantly associated with a history of opiate substitution.

Conclusions: In this large sample of MSM and IDUs across India, the major barrier to successful engagement in HIV care was diagnosis, with fewer than 50% having been diagnosed. Overall, engagement was better in sites with higher HIV prevalence where there have been more government-led targeted interventions. Efforts should focus on improving access to HIV testing for these groups in all settings by linking HIV testing to other essential services.

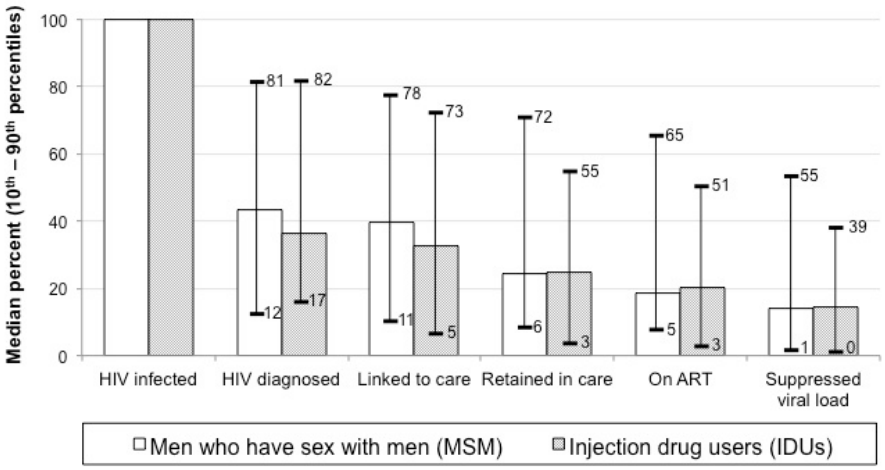

Figure. HIV care cascade among 1,150 MSM and 2,534 IDUS across 27 cities in India [Median and 10th and 90th percentiles of site-level proportions are presented]. **MSM Sites:** Bangalore, Belgaum, Bhopal, Chennai, Coimbature, Delhi, Hyderabad, Lucknow, Madurai, Mangalore, Vijayawada, Vizag; **IDU Sites:** Aizawl, Amritsar, Bhubaneswar, Bilaspur, Chandigarh, Churchandpur, Delhi, Dimapur, Gangtok, Imphal, Kanpur, Ludhiana, Lunglei, Moreh, Mumbai

1064 Unplanned Interruptions in HIV Care in Nigeria: Rates and Implications

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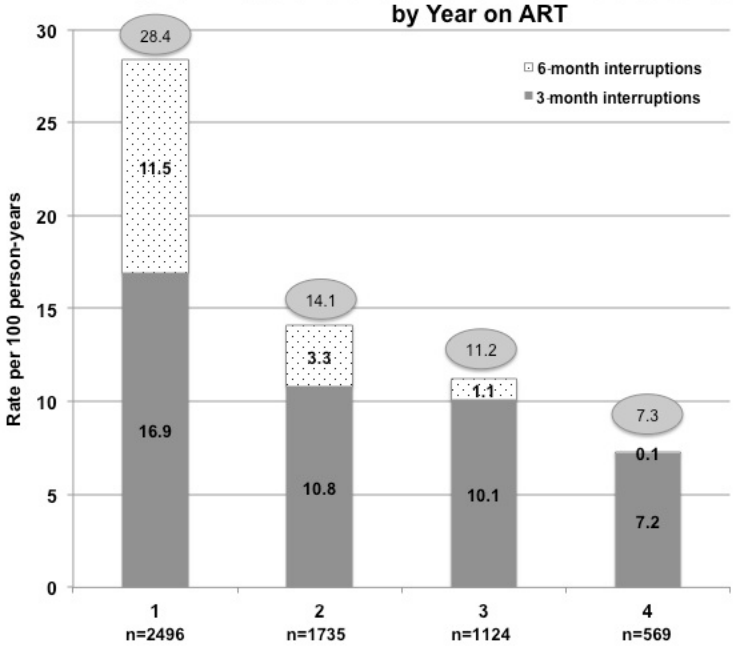
Background: Unplanned care interruptions pose a challenge to effective HIV treatment. However, little is understood about rates of interruptions and how to minimize interruptions in care in resource-limited settings. Our objective was to determine the frequency, risk factors, and impact of unplanned care interruption on virologic outcomes among HIV-infected patients in Nigeria.

Methodology: We conducted a retrospective cohort study at a university-affiliated HIV clinic in Nigeria. The cohort included adults (≥14yrs) who enrolled in care and initiated ART between January 2009 and December 2011. Follow-up was through December 2012. We defined unplanned care interruption as a period in which patients had no contact with the HIV clinic for clinical, laboratory, or ART pick-up visits. We studied interruptions of >3 months, > 6 months, or any interruption (>3 or > 6 months). We used multivariate logistic regression models adjusted for observation time to measure associations between baseline clinical and demographic factors with having at least one care interruption. We assessed HIV RNA levels at return to care in those with unplanned interruptions.

Results: Among the 2,496 patients in the cohort, 69% were female, median age was 32 years and 8% were students. In the 1st year on ART, median days between clinic visits was 30. Over 90% of all visits involved drug-pick-up. Thirty-seven percent of patients had ≥ 1 care interruption lasting at least 3 or 6 months. Sixteen percent of patients had one 3-month interruption, 10% had one 6-month interruption, and 11% had combinations of both. Rates of interruption were highest in the 1st year on ART (28.4/100PY), and declined with each year on ART [Figure 1]. In multivariate analysis, students (OR1.6, p=0.025), those with baseline CD4 >350/uL (OR2.7, p<0.0001), and those with any hospitalization during follow-up (OR1.6, p = 0.020) were at increased risk for any interruption of 3- or 6-month duration. On return to care, 49% of those with 3-month and 61% with 6-month interruptions had HIV RNA >1,000 copies/ml.

Figure 1: Rates of 3- and 6-month Unplanned Care Interruptions by Year on ART



Conclusions: Nearly 40% of all patients starting ART in a large treatment program in Nigeria had interruptions in care of 3 or 6 months. Interruptions occurred most commonly in the 1st year on ART, and were associated with loss of virologic suppression. Students, those with high baseline CD4 count and those hospitalized during the follow-up period were at highest risk. Focused interventions in the 1st year on ART are essential to ensure continuity of HIV care.

1065 Using the Side Door: Non-Linear Patterns Within the HIV Treatment Cascade in Zambia

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Background: Although the HIV care and treatment cascade has typically been portrayed as a linear process starting from HIV testing and counseling to treatment and retention, patients may actually be dropping out of care and re-entering at a later time. We sought to characterize this "side door" phenomenon in a large public health program in Zambia among adults who initiated antiretroviral therapy (ART).

Methodology: Our analysis cohort comprised treatment-naïve, HIV-infected adults (≥15 years) initiating ART in 18 Lusaka sites Jan. 2002 - Feb. 2008, including follow-up for their first 3 years on ART. Individuals were divided into 3 groups based on outcomes at 3 years post-ART initiation: 1) remaining on treatment, 2) >60 days late for a scheduled visit but not returning, and 3) >60 days late for a scheduled visit but "re-presenting" into care. Baseline characteristics for the 3 groups were compared and frequency of re-presentation was enumerated. A multivariable logistic model was constructed among those lost to follow-up (LTFU), with a dependent variable of re-presentation/ continued loss and covariates including baseline characteristics.

Results: 48,126 patients were included, median age 34 years (IQR 29,41), 61% women, and median initiation CD4: 132 (IQR 66,205). Among those >60 days late for a scheduled visit (n=28,417), 65.4% never returned, 27.8% had 1 re-presentation episode, 5.3% had 2 re-presentation episodes, and 1.3% had 3 representation episodes. Average period of loss before first re-presentation was 105 days (SD 161), and median 35 days (IQR 10,124). Re-presenting patients were less likely to have CD4<200 cells/mm3, WHO stage 3/4, and anemia (Hemoglobin (Hb) <8 g/dL) at baseline ART initiation (Table). Among those meeting the days-late threshold for LTFU, predictors for

	Lost and re-presenting	Remaining on ART	p-value†	Lost and not returning	p-value†
n	9,846	19,709		18,571	
Age (median, IQR)	34 (29,40)	35 (30,41)	<0.01	34 (29,41)	0.19
Female (%)	59.00	64.21	<0.01	57.98	0.10
BMI<16 (%)	7.25	6.39	0.01	12.27	<0.01
Hemoglobin <8g/dL (%)	8.72	7.15	<0.01	12.29	<0.01
CD4 cell count <200/mm^3 (%)	70.11	74.11	<0.01	74.01	<0.01
WHO Stage (% Stage 3 or 4)	67.5	66.0	0.01	72.5	<0.01
Active tuberculosis (%)	13.3	13.5	0.58	13.6	0.41
Pregnant (%)	4.9	6.8	0.10	5.1	0.82

*P-values for continuous variables calculated using the Wilcoxon-Mann-Whitney test; p-values for categorical variables calculated using the chi-square test.

re-presentation in a multivariable logistic regression model included lower baseline WHO stage (OR 0.82; 95% CI 0.77-0.88 for WHO Stage 3/4), and higher CD4 cell count (OR 0.92; 95% CI 0.85-0.99 for CD4 <200 cells/mm3), higher BMI (OR 0.61; 95% CI 0.55-0.68 for <16), and higher Hb (OR 0.77; 95% CI 0.70-0.85 for Hb <8g/dL).

Conclusions: Re-presentation after initial loss to follow-up is common in an urban HIV treatment cohort in Zambia and is more likely in healthier individuals. This is one of the first empiric characterizations of this important phenomenon in ongoing HIV care and treatment efforts, and one that should be considered in the design of future interventions for program retention and monitoring.

1066 Effectiveness of Potential Improvements in the Cascade of HIV Treatment and Care in South Africa

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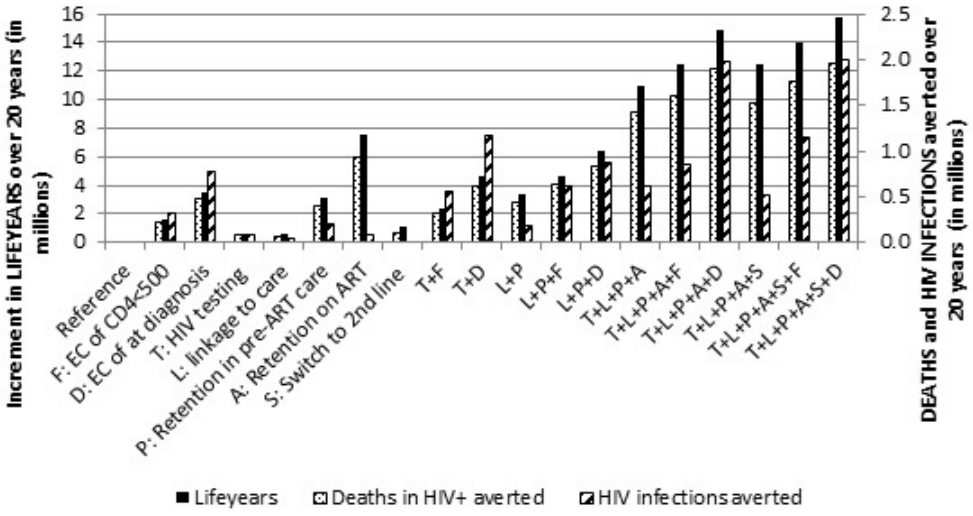
Background: Implementation studies demonstrated that it is possible to substantially reduce the leakages at different steps of the cascade of care. Our aim is to evaluate the effectiveness of potential improvements in each step and of changing the eligibility criteria to initiate ART (EC) in South Africa.

Methodology: The 'HIV Synthesis' model calibrated to South Africa was used. By the end of 2013 it is assumed 62% of the population ever tested for HIV, 29% in the last year, 71% are linked to care (LK) by 1 year since diagnosis, 42% of those not eligible at staging are retained in pre-ART care (RPC) at 1 year, EC is CD4<350 cells/μ, 84% are retained on ART (RA) at 1 year since initiation and the median time to switch to 2nd line after virological failure is 12 months. The maintenance of this status is referred to as R. The following improvements, implemented over 2014 and 2015, are considered: EC of CD4<500 cells/μ (F), EC at diagnosis (D), increase in HIV testing so that 85% ever tested for HIV (T), reduction in loss at diagnosis so that 85% are LK (L), improvements in pre-ART retention, so that 72% are RPC (P), improvements in retention on ART, so that 92% are RA (A), reduction in the time to switching to 2nd line to 5 months (S). In addition the following combination of the above are considered: improvement in T with change in EC to CD4 <500 cells/μ (TF) and at diagnosis (TD); improvement in LK and RPC with EC respectively CD4<350 cells/μ (LP), <500 cells/μ (LPF) and at diagnosis (LPD); as LP with improvement in HIV testing and on ART (TLPA); as TLPA with EC at CD4<500 cells/μ (TLPAF) and at diagnosis(TLPAD); improvements at all steps with EC at CD4<350 cells/μ (TLPAS), <500 cells/μ (TLPASF) and at diagnosis (TLPASD).

Results: The single improvement which leads to the highest increment in life-years over 20 years is the improvement in retention on ART (7.6 million), which leads to the greatest reduction in deaths among HIV+ (930,000). Modifying the EC to initiate ART at diagnosis saves the highest number of HIV infections (760,000), but results in an increment in lifeyears of 3.5 million. Improvements at all steps of the cascade allow gaining over 15 million life-years over 20 years.



Conclusions: Our modelling helps to understand which interventions will have the biggest impact on maximising life years, and shows that improving retention on ART has the greatest impact. Cost-effectiveness analysis could help to identify which interventions would represent value for money from limited health sector resources.

Session P-X4 Poster Session

Wednesday March 5, 2014, 2:30 PM–4:00 PM Exhibit Hall D

Mental Health in HIV Care

1067 Trends in Depression Among Patients Presenting for ART in Rural Uganda

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Background: Among people living with HIV (PLHIV), depression has been associated with poorer HIV-related outcomes, including increased transmission risk, poorer ART adherence, and more rapid CD4 decline or progression to AIDS and death. Little is known about trends in depression at ART initiation among PLHIV in low- and middle-income countries (LMICs) during the early years of expansions in access to ART. We used data from the Uganda AIDS Rural Treatment Outcomes (UARTO) study, an ongoing cohort of treatment-naïve PLHIV begun in 2005, to estimate secular trends in depression among PLHIV at ART initiation and to understand the factors explaining these trends.

Methodology: A linear regression model was fitted to the baseline data with depression symptom severity, measured using a locally adapted version of the Hopkins Symptom Checklist (HSCL-D), as the outcome variable and year of cohort entry (2005-2012) as the explanatory variable. We adjusted our estimate using baseline socio-demographic characteristics (age, gender, educational attainment, marital status, household asset wealth, and employment status). Next, we assessed physical health score and CD4 count as potential mediators of the secular trend in depression symptom severity by adding the variables of interest to the model and re-assessing the statistical significance of the regression coefficient for year of entry.

Results: 498 persons with complete data, including 355 women (71.3%), were included in the models. 140 (28.1%) respondents had HSCL-D scores consistent with probable depression (women, 34.7% vs. men, 11.9%; p<.001). A linear regression model revealed a statistically significant negative association between year of entry into cohort and HSCL-D (b = -.04; 95% CI, -.06 to -.02) at entry, suggesting a 2.5% relative decline in the mean depression symptom severity score at ART initiation in each year of study recruitment after the first year. After inclusion of baseline socio-demographic characteristics, the adjusted regression coefficient for year of entry remained statistically significant. The addition to the model of physical health score, but not CD4 count, caused a reduction in magnitude and loss of statistical significance for the regression coefficient for year of entry (b=-.014; 95% CI, -.034 to .007).

Conclusions: Mean depression severity scores at ART initiation declined over time among PLHIV in a rural Ugandan cohort. This secular trend appeared to be explained by better physical health at ART initiation. Secular improvements in depression at ART initiation may be related to ART being initiated among patients with better physical health, which warrants further study and may provide an important further rationale for earlier ART initiation in LMICs.

1068 Mental Health and Mortality in an HIV Treatment Cohort in Rural Uganda

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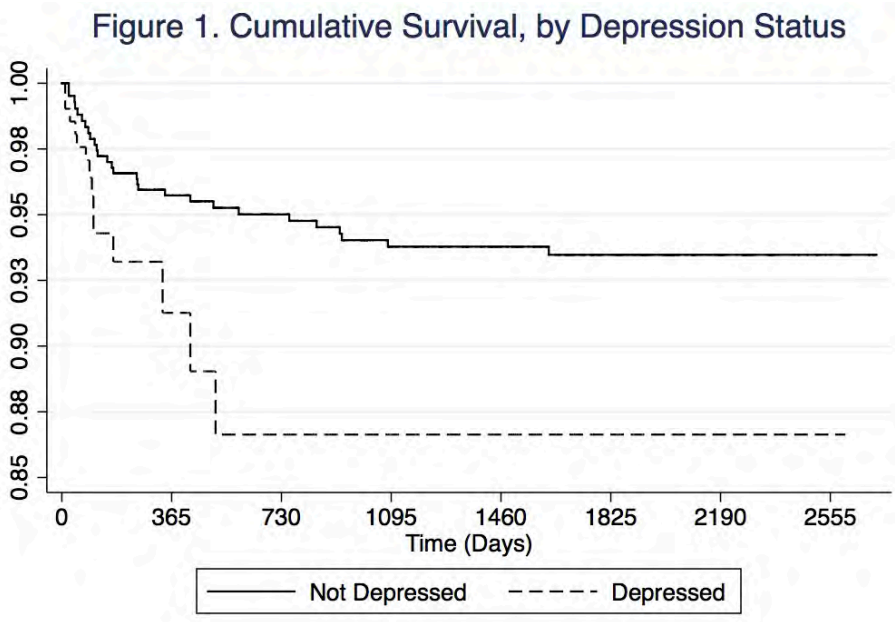
Background: Depression has been associated with systemic immune activation and increased mortality in HIV+ persons. The only study in sub-Saharan Africa to examine the depression-mortality relationship was conducted among HIV+ women who lacked access to HIV antiretroviral therapy (ART). To address this gap in the literature, we used data from an ongoing HIV cohort in rural Uganda to determine the extent to which the depression-mortality relationship holds among HIV+ persons initiating ART.

Methodology: Beginning in 2005, treatment-naïve HIV+ men and women were enrolled into the Uganda AIDS Rural Treatment Outcomes cohort at the time of treatment initiation. Participants completed bloodwork and structured questionnaires at pre-treatment baseline and quarterly thereafter. Baseline depression symptom severity and mental health-related quality of life were measured using locally adapted versions of the Hopkins Symptom Checklist (with a score >1.75 indicative of probable depression) and MOS-HIV mental health summary. Vital status was ascertained through participant tracing in the event of missed study visits. We fit Cox proportional hazards regression models, adjusting our estimates for baseline age, sex, marital status, educational attainment, household asset wealth, CD4+ T-lymphocyte cell count, body mass index, and MOS-HIV physical health summary.

Results: Of 694 participants, 480 were women (69%), and pre-treatment median baseline values were: age, 34 years (IQR, 28-40); CD4 count, 162 (IQR, 91-249); depression score, 1.4 (IQR, 1.2-2.0); and MOS-HIV mental health summary score, 53 (IQR, 47-59). 216 participants (31%) met screening criteria for probable depression. Over 4.3 median years of follow-up, only 48 participants (7%) were lost to follow-up and there were 44 deaths. After multivariable adjustment, probable depression was associated with increased mortality (AHR=2.24; 95% CI, 1.08-4.62), while mental health-related quality of life was not (AHR=0.98; 95% CI, 0.94-1.03).

Conclusions: Depressed mood is associated with increased mortality among HIV+ persons initiating ART. Screening for depression may be a relatively low-cost method of identifying HIV+ persons at high risk for mortality. Whether pre-ART depression reflects underlying immune activation or poor overall health status should be addressed in future studies.



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Speaker Name	Name of Commercial Interest	Nature of Relevant Relationship
Till Barnighausen	Merck and Sanofi-Pasteur; Gilead	Grants/grants pending; Payment directly from commercial firms for lecture(s), including service on speakers' bureaus
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