Highlights of the 2014 Conference on Retroviruses and Opportunistic Infections

CROI 2014: Basic Science Review  574
Mario Stevenson, PhD
Host Antiviral Restriction Factors • Viral Reservoirs and Cure Research • Immunopathogenesis

CROI 2014: New Tools to Track the Epidemic and Prevent HIV Infections  579
Susan P. Buchbinder, MD, and Albert Y. Liu, MD, MPH
Tracking the Epidemic • Risk Factors for HIV Transmission and Acquisition • Prevention Strategies

CROI 2014: Neurologic Complications of HIV Infection  594
Serena S. Spudich, MD
Mechanisms of Persistent CNS Injury on Antiretroviral Therapy • CSF HIV Escape or CSF/Plasma HIV Discordance in Patients on Antiretroviral Therapy • Persistent CNS Immune Activation During Antiretroviral Therapy • Vascular Pathology, Aging, and CNS Injury in HIV Infection • CNS Consequences of Antiretroviral Therapy Exposure and Toxicity • Potential Significance of Early HIV Infection and Treatment to CNS Injury • Novel Alternative Mechanisms of HIV Neuropathogenesis

CROI 2014: Complications of HIV Disease, Viral Hepatitis, and Antiretroviral Therapy  602
Anne F. Luetkemeyer, MD, Diane V. Havlir, MD, and Judith S. Currier, MD
Overview of Hepatitis C Virus Direct-Acting Antiviral Drugs: Present and Future • Complications of HCV Infection • Hepatitis B Virus and Hepatitis Delta Virus • Hepatitis E Virus • Complications of HIV Infection • CVD • Pulmonary Disease • Renal Disease • Bone • Frailty and Aging • Kaposi Sarcoma • Tuberculosis

CROI 2014: Advances in Antiretroviral Therapy  616
Barbara S. Taylor, MD, MS, Noga Shalev, MD, and Timothy J. Wilkin, MD, MPH
Clinical Studies Investigating HIV-1 Cure • Investigational Antiretroviral Therapy Agents • Clinical Trials of Initial Antiretroviral Therapy • Maintenance and Switch Strategies • Clinical Trials in Treatment-Experienced Patients • Clinical Trials to Reduce Immune Activation • Pharmacokinetic Considerations • Examining the HIV Care Cascade in Resource-Limited and Other Settings • Antiretroviral Therapy Scale-Up in Resource-Limited Settings • Prevention of PMTCT • Transmitted Drug Resistance • Acquired Drug Resistance
The views and opinions expressed in this journal are those of the contributors and do not necessarily reflect the views or recommendations of the IAS–USA. The IAS–USA does not own the copyright, permission to reproduce these materials where the IAS–USA does not own the copyright, permission to reproduce these materials must be obtained directly from the original source. For more information about reprints, please send an e-mail to journal@iasusa.org.

Subscription Information
Topics in Antiviral Medicine is published 4 to 6 times a year. To obtain a subscription or notify the IAS–USA of a change in address, please create or update your user profile at www.iasusa.org.

Correspondence
Topics in Antiviral Medicine welcomes editorial correspondence. Address correspondence to:
Editor, Topics in Antiviral Medicine
E-mail: journal@iasusa.org
Mail: IAS–USA
425 California Street, Suite 1450
San Francisco, CA 94104-2120
Phone: (415) 544-9400
Fax: (415) 544-9401
Website: http://www.iasusa.org

On the Web
Current and previous issues of Topics in Antiviral Medicine are available online at www.iasusa.org/pub.
ISSN 2161-5861 (Print)
ISSN 2161-5853 (Online)
Printed in USA on acid-free paper ©2014 IAS–USA. All rights reserved.
Topics in Antiviral Medicine™

A publication of the IAS–USA

Highlights of the 2014 Conference on Retroviruses and Opportunistic Infections

Example of how to cite the CROI 2014 abstracts:

CROI 2014: Basic Science Review 574
Mario Stevenson, PhD

CROI 2014: New Tools to Track the Epidemic and Prevent HIV Infections 579
Susan P. Buchbinder, MD, and Albert Y. Liu, MD, MPH

CROI 2014: Neurologic Complications of HIV Infection 594
Serena S. Spudich, MD

CROI 2014: Complications of HIV Disease, Viral Hepatitis, and Antiretroviral Therapy 602
Anne F. Luetkemeyer, MD, Diane V. Havlir, MD, and Judith S. Currier, MD

CROI 2014: Advances in Antiretroviral Therapy 616
Barbara S. Taylor, MD, MS, Noga Shalev, MD, and Timothy J. Wilkin, MD, MPH

Announcements
Continuing Medical Education Information 572
Educational Programs of the IAS–USA 573
Cases on the Web—Online CME Activities 593
Conference Abstracts Cited in This Issue 632
Guidelines for Authors and Contributors Inside Back Cover

The full text of all abstracts is published online in Topics in Antiviral Medicine, vol. 22, issue e-1, at www.iasusa.org/tam/april-2014.
Topics in Antiviral Medicine™

CME Information

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 enduring material for a maximum of 8.0 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This continuing medical education (CME) activity is offered from May 5, 2014, to May 5, 2015. Participants who successfully complete the activity posttest and submit the evaluation and registration forms are eligible to receive CME credit. Physicians (MDs, DOs, and international equivalents) may receive CME credit for completing this activity. Other health care practitioners will receive a certificate of participation.

Overview

- CME credits available: 8.0 AMA PRA Category 1 Credits™
- Release date: May 5, 2014
- Expiration date: May 5, 2015

This enduring material provides a review of the 2014 Conference on Retroviruses and Opportunistic Infections (CROI). To complete the activity, read the articles, successfully complete the posttest, submit the evaluation, and complete and submit the CME claim form. To claim CME credit, submit the claim form online.

The IAS–USA offers this state-of-the-art activity as part of a nationwide CME effort for physicians on the evolving challenges of managing HIV disease.

Learning Objectives

On completion of this activity, the learner will be able to describe the important new data presented at the 2014 CROI and the potential clinical implications for patients in the areas of:

- Pathogenesis of HIV disease
- Epidemiology of HIV and prevention efforts
- Complications of HIV disease and HIV-related coinfection
- Neurologic disorders in HIV disease and their treatment
- Antiretroviral therapy

Intended Audience

This enduring material is designed for physicians and other health care practitioners who are experienced in the principles of complex chemotherapy (eg, antiretroviral therapy) and are actively treating or will be treating patients with HCV or HIV infection.

This activity is also relevant for other practitioners, including nurse practitioners, nurses, physician assistants, pharmacists, and others.

Disclosure of Financial Interests

In the interest of maintaining the independence of its CME activities, and in accordance with the policies of the Accreditation Council for Continuing Medical Education (ACCME), the IAS–USA requires all persons with control of content (ie, faculty, IAS–USA Board members, and program staff) to disclose any financial relationships that they (or their spouses or partners) have had with commercial companies within the past 12 months. Any real or apparent conflicts of interest of those parties are resolved prior to the continuing medical education activity being delivered. Individuals who refuse to disclose financial interests may not participate in an IAS–USA CME activity.

Financial Affiliations: Dr Stevenson has no relevant financial affiliations to disclose. Dr Buchbinder has been a consultant for Clinical Care Options. Dr Liu has been a consultant for Clinical Care Options. Dr Spudich has received travel support and honoraria from AbbVie, Inc. Dr Luetkemeyer has served as a consultant or advisor to Gilead Sciences, Inc, and has received travel support from Bristol-Myers Squibb and Gilead Sciences, Inc. She has also received grants awarded to her institution from Gilead Sciences, Inc, Janssen Therapeutics, Vertex Pharmaceuticals, Inc, Bristol-Myers Squibb, Pfizer, Inc, and AbbVie. Dr Havlir has no relevant financial affiliations to disclose. Dr Currier has served on an advisory board for ViIV Healthcare and has received grants awarded to her institution from Merck & Co, Inc, and ViIV Healthcare. Dr Wilkin has received research support awarded to Weill Cornell Medical College from Gilead Sciences, Inc, and GlaxoSmithKline/ViIV Healthcare. Dr Taylor has grants under review to be awarded to the University of Texas Health Science Center at San Antonio from the Doris Duke Charitable Foundation and the American Heart Association as of publication. Dr Shaler has no relevant financial affiliations to disclose. Dr Richman has been a consultant to Bristol-Myers Squibb, Chimerix, Gen-Probe, Inc, Gilead Sciences, Inc, Sirenas, Prism, and Monogram Biosciences, Inc. He owns stock in Chimerix. Dr Benson has no relevant financial affiliations to disclose. Disclosure information for her spouse, Robert T. Schooley, MD, is indicated below. Dr Hirsch has no relevant financial affiliations to disclose. Ms Jacobsen has no relevant financial affiliations to disclose. Dr Schooley has received research support from Bristol-Myers Squibb and Boehringer Ingelheim Pharmaceuticals, Inc, and has served as a scientific advisor to CytoDyn and Merck & Co, Inc, as a scientific advisory board member for Gilead Sciences, Inc, Globalmymune, Inc, and Monogram Biosciences, and as a member of data monitoring committees for Axio and Gilead Sciences, Inc. He has stock in Globelmmune, Inc.

Grant Support

This activity is funded through independent, educational grants at a national level from commercial organizations that are committed to supporting high-quality CME. We gratefully acknowledge the supporters of the 2014 Improving the Management of HIV Disease CME program.

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. The views and opinions expressed herein are those of the faculty and do not necessarily represent the opinions or recommendations of the IAS–USA.

Contact Information

If you have any questions about this activity, please contact the IAS–USA.

E-mail: journal@iasusa.org
Phone: 415-544-9400
Mail:  IAS–USA
ViIV Healthcare
1055 California Street, Suite 1450
San Francisco, CA 94104-2120

POST TEST

Please visit our website at www.iasusa.org to complete the posttest and evaluation for this activity and claim CME credit. You can also subscribe or change your mailing address by updating your user profile online.
Spring 2014 Live Continuing Medical Education Courses

IAS–USA CME course announcements are paperless. Please watch for e-mail updates, and visit www.iasusa.org for general course information, agendas, and online registration. Early registration is strongly recommended. These live activities have been approved for AMA PRA Category 1 Credit™.

Improving the Management of HIV Disease®: Full-Day Courses

The annual full-day advanced CME courses continue to focus on cutting-edge, scientifically rigorous issues presented by leading experts in the field, providing the latest insights and data on the full spectrum of HIV- and AIDS-related treatment issues.

- **New York, New York**
  - Tuesday, March 18, 2014
  - Marriott Marquis

- **Atlanta, Georgia**
  - Tuesday, April 1, 2014
  - Cobb Galleria

- **Los Angeles, California**
  - Wednesday, April 23, 2014
  - The Westin Bonaventure

- **San Francisco, California**
  - Friday, May 2, 2014
  - Mission Bay Conference Center

- **Chicago, Illinois**
  - Monday, May 19, 2014
  - Chicago Marriott Downtown

- **Washington, DC, area**
  - Tuesday, June 17, 2014
  - Hyatt Regency Crystal City

Hepatitis C Virus Infection: Looking Beyond the Interferon Alfa Era: Full-Day Courses

The full-day advanced CME courses are designed for clinicians who are experts in the complexities of antiretroviral management and who are well positioned to join their hepatology and gastroenterology colleagues in providing care for hepatitis C virus (HCV)-infected patients, in what has become an exciting new era in HCV care.

- **San Francisco, California**
  - Friday, March 21, 2014
  - Mission Bay Conference Center

- **New York, New York**
  - Wednesday, April 16, 2014
  - Marriott Marquis

Evolving Strategies in Hepatitis C Virus Management: Small-Group Workshops

Part of the IAS–USA focus on the management of HCV infection, these half-day, small-group, intensive CME workshops are presented by leading experts in the field. Attendance is limited to 35 practitioners, so early registration is encouraged.

- **Atlanta, Georgia**
  - Monday, March 31, 2014
  - Cobb Galleria

- **Los Angeles, California**
  - Tuesday, April 22, 2014
  - The Westin Bonaventure

- **Chicago, Illinois**
  - Tuesday, May 20, 2014
  - Chicago Marriott Downtown

- **Washington, DC, area**
  - Monday, June 16, 2014
  - Hyatt Regency Crystal City

**Educational Resources** from past live courses are available on the IAS–USA website at www.iasusa.org, including webcasts (available for CME credit), podcasts, downloadable key slides from lectures, and various presentation handouts.

For information about any of these programs, please contact the IAS–USA.

Phone: (415) 544-9400 • Fax: (415) 544-9402 • E-mail: Registration”at”iasusa.org • website: www.iasusa.org
CROI 2014: Basic Science Review

Mario Stevenson, PhD

In the HIV basic science categories of the 2014 Conference on Retroviruses and Opportunistic Infections, research examining obstacles to viral eradication continued to be a major component. This research encompassed areas of activity from the identification of where virus resides in individuals on suppressive antiretroviral therapy to studies aimed at eliminating long-lived viral reservoirs that persist in the face of therapy. In the area of antiviral restrictions, a number of presentations highlighted the ability of host factors to profoundly shape the interplay between virus and host and, in particular, how innate immune response opposes viral infection through the induction of antiviral restrictions.

**Keywords:** CROI 2014, cure, HIV, pathogenesis, restriction factors, viral reservoirs

**Host Antiviral Restriction Factors**

Infection of human and of nonhuman primates is antagonized by a family of host cell proteins commonly referred to as host restriction factors, a topic discussed in a number of presentations at the 2014 Conference on Retroviruses and Opportunistic Infections (CROI), held from March 3 to 6, 2014. To date, 3 restriction factors that antagonize HIV-1 infection in humans have been identified: the APOBEC (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like) 3 family of cytidine deaminases, tetherin (or BST-2), and SAMHD1 (sterile alpha motif [SAM] domain and histidine–aspartate [HD] domain–containing protein 1). APOBEC 3 proteins are packaged within viral particles and in the target cell, inhibit reverse transcription by a mechanism yet to be elucidated, and induce extensive G-to-A hyper mutation in viral complementary DNA (cDNA). These hypermutated genomes are biologically inactive templates for the generation of progeny virus. Tetherin is a transmembrane protein that, as its name suggests, tethers assembling virions to the surface of the virus-producing cell. These tethered variants are therefore unable to infect other cells. SAMHD1 is a deoxynucleotide triphosphate (dNTP) hydrolase that reduces intracellular dNTP levels, thereby creating suboptimal conditions for reverse transcription of viral cDNA. Given the potent antiviral activity exhibited by these cellular restrictions, why are individuals still susceptible to HIV-1 infection? The answer is that primate lentiviruses have evolved strategies to neutralize these antiviral restrictions and viral accessory proteins are central to the ability of the virus to oppose cellular restrictions. APOBEC 3 is neutralized by the viral infectivity factor (Vif) accessory protein that inactivates APOBEC 3 by inducing its proteosomal degradation. Tetherin is neutralized by the viral protein U (Vpu) protein of HIV-1. HIV-2/simian immunodeficiency virus (SIV) variants that do not encode a Vpu protein use the negative regulatory factor (Nef) protein to counteract the antiviral activity of tetherin. Most studies of how HIV-1 circumvents the action of tetherin have been in the context of Vpu and indicate that interaction of Vpu with tetherin prevents membrane association of tetherin molecules, rendering them unable to interfere with detachment of virions.

In HIV-2 and some SIV variants, the viral protein X (Vpx) protein promotes degradation of SAMHD1 in the 26S proteasome. HIV-1 viral protein R (Vpr) is the counterpart to HIV-2/SIV Vpx, and although HIV-1 infection is antagonized by SAMHD1, there is no strong evidence that HIV-1 Vpr relieves the impact of SAMHD1. Instead, HIV-1 appears to be less sensitive to the antiviral effects of SAMHD1 than HIV-2/SIV, indicating that it has evolved a different strategy with which to deal with this restriction.

In his delivery of the Bernard Fields Lecture at this year’s conference, Bieniasz (Abstract 17) discussed his ongoing research on tetherin and how it counteracts viral replication. To illustrate that the antiviral action of tetherin is simply a consequence of its ability to prevent detachment of virus particles, Bieniasz assembled a synthetic tetherin molecule from the domains of unrelated proteins. The synthetic tetherin, which comprised domains from the transferrin receptor, the dystrophia myotonica protein kinase, and the urokinase plasminogen activator receptor, was very effective in inhibiting HIV-1 particle release, despite the fact that the synthetic tetherin had no sequence homology to the viral tetherin molecule. This set of experiments clearly argues that the antiviral activity of tetherin is based solely on its ability to trap viral particles on the surface of the infected cell. These experiments also demonstrate that the antiviral activity of tetherin does not require specific interaction with viral proteins.

Dr Stevenson is a Professor in the Department of Medicine and Chief of the Division of Infectious Diseases at the University of Miami Medical School in Miami, Florida. Send correspondence to Mario Stevenson, PhD, University of Miami Leonard M. Miller School of Medicine, Life Science Technology Park, 1951 NW 7th Avenue, Rm 2331B, Ste 200, Miami, Florida 33136. Received on March 18, 2014; accepted on March 19, 2014.
Bieniasz described how a better understanding of the mechanisms by which lentiviruses counteract cellular restrictions could aid in the design of HIV-1 variants that replicate in monkeys. The availability of such HIV-1 variants could improve strategies for preclinical evaluation of vaccines and new antiretroviral drugs. However, HIV-1 does not replicate in macaques because the mechanisms it has evolved to counteract antiviral restrictions in human cells are limited in their ability to oppose restrictions in simian cells. For example, HIV-1 Vif does not efficiently neutralize macaque APOBEC3 proteins, and HIV-1 replication in macaque lymphocytes is 4 orders of magnitude less efficient than SIV replication. Bieniasz engineered an HIV-1 variant that contains SIV vif and replicates almost as efficiently as SIV in macaque lymphocytes. This virus has formed the basis for experiments in which HIV-1 variants containing altered envelope genes and SIV vif were adapted to replication in pigtail macaques. Changes appeared in viruses as they evolved to replicate more efficiently in macaques, including changes in envelope that conferred X4 tropism and changes in vpu that conferred the ability to neutralize tetherin. Simian-passaged HIV-1 was able to neutralize tetherin in monkeys, but it simultaneously lost the ability to neutralize tetherin in humans. This was analogous to the series of events that occurred when the HIV-1 ancestor acquired the ability to neutralize human tetherin as it entered its human host. Simian-tropic HIV-1 caused disease in pigtail macaques and recapitulated some key features of AIDS in humans. Although these studies bring us much closer to a simian model for HIV-1, additional blocks to simian-tropic HIV-1 replication in macaques need to be overcome before the adaptation of HIV-1 to its simian host is complete.

In his plenary presentation, Malim (Abstract 119) discussed the impact of type I interferon on HIV-1 infection. All pathogens contain pattern recognition receptors that sense foreign elements in RNA, DNA, and protein. These foreign elements are referred to as pathogen-associated molecular patterns. The components of HIV-1 that are sensed by host pattern recognition receptors to trigger an interferon response have been a topic of intense investigation. In myeloid cells, it is also apparent that HIV-1 escapes the detection of the innate sensing apparatus by cloaking itself. Pathogen-associated recognition receptors in the viral capsid protein are hidden from the innate sensing apparatus because capsid cloaks itself in cellular proteins to evade innate sensing. Mutations in capsid that help uncloak these motifs lead to induction of an interferon response. This theme was expanded on in Session S7. Towers (Abstract 154) described an HIV-1 capsid mutant (P90A) that, unlike its wild-type counterpart, efficiently induced interferon on infection of macrophages. Sensing of the incoming virus appeared to be triggered by viral cDNA or a reverse transcription intermediate. Towers went on to implicate cyclophilin A and cleavage and polyadenylation specific factor 6 (CPSF6) as cellular proteins that cloak capsid from DNA sensors so as to prevent activation of the interferon response. This predicts that agents that uncloak the capsid and expose it to DNA sensors could have utility as antiviral agents. To this point, Towers demonstrated that cyclosporins, which inhibit cyclophilin from binding to capsid, induced an interferon response and inhibited HIV-1 infection in monocyte-derived macrophages. Therefore, the cyclophilin-capsid interface represents a novel target for therapeutic intervention of HIV-1 infection.

There has been much attention focused on the sensors that detect nascent viral cDNA. Malim summarized research implicating cyclic guanosine monophosphate–adenosine monophosphate (cGAMP) synthase (cGAS), an enzyme that resides in the cytosol and recognizes incoming viral cDNA. The action of this enzyme results in the generation of the cyclic dinucleotide cGAMP that binds to and activates stimulator of interferon genes (STING), leading to signaling and induction of type I interferon. However, other sensors have been implicated in the recognition of viral elements, including the recognition of cDNA by host nucleases such as three prime repair exonuclease 1 (TREX1) and the recognition of virion RNA by Toll-like receptor 7 (TLR7). An important question is the extent to which avoidance of DNA-sensing elements impacts HIV-1 infection of T cells.

Identification of host cell factors that are induced by interferon and that mediate the antiviral activity of the interferon response has also been of intense interest. In Abstract 46, Kane and colleagues described research implicating myxovirus resistance 2 (MX2) as an interferon-induced inhibitor of HIV-1 infection. MX2 proteins are interferon-induced, dynamin-like guanosine triphosphatases (GTPases) that inhibit infection of a wide variety of viruses including influenza A virus, measles virus, hepatitis B virus, and vesicular stomatitis virus. MX2 was identified as an inhibitor of HIV-1 replication by comparing gene expression profiles in cell lines that differed in their ability to support the inhibitory action of interferon at the early stages of HIV-1 infection. MX2 was found to act at a stage that followed reverse transcription but preceded nuclear import of viral cDNA. MX2 appears to be required for full antiviral activity of interferon against HIV-1, and neutralization of MX2 using short hairpin RNAs (shRNAs) was sufficient to nullify the inhibitory action of interferon treatment on HIV-1 infection of THP-1 cells. Nuclear localization of MX2 was required for the antiviral action of MX2 and the antiviral activity of MX2 was enhanced when target cell cycles were arrested, suggesting that MX2 prevents the nuclear localization of viral DNA. Furthermore, the antiviral activity of MX2 was mediated by the HIV-1 capsid protein, as some capsid point mutants were insensitive to MX2 inhibition.

Borrow (Abstract 157) discussed how type I interferon response may impact HIV-1 transmission. The majority of heterosexual transmissions is established by a single transmitted founder virus, despite the fact that there is a highly diverse population of viruses in the donor. This suggests either the presence of a barrier that restricts
transmission of the virus or that there are factors within the recipient that restrict the establishment of transmitted viruses. Borrow and colleagues have pursued the hypothesis that innate immune responses mediated by interferons, for example, may exert selective pressure on the transmitted virus. This would seem to predict that interferon-mediated pressure may drive the emergence of interferon-resistant viruses in the acute phase of infection. Primary HIV-1 isolates were generated from cryopreserved plasma by expansion in primary CD4+ T cells and then examined for sensitivity to interferons. HIV-1 isolates derived from acutely infected subjects were found to be more resistant to interferon than viruses obtained from the same patients at the chronic stage of infection. Type I interferon resistance was found to decline rapidly following acute infection and viruses obtained 6 months from the onset of symptoms were found to be substantially less resistant to interferon than viruses obtained in the acute phase of infection. Borrow went on to examine whether the establishment of HIV-1 infection by interferon-resistant viruses was caused by selection of interferon-resistant variants from the donor quasispecies or whether there was preferential transmission of interferon-resistant viruses that preexisted in the donor quasispecies population. Analysis of viruses obtained from an acute-to-acute transmission pair indicated that interferon-resistant viruses in the donor viral quasispecies population were selectively transmitted, supporting the notion that type I interferons contribute to the transmission bottleneck. Viral determinants that mediate the differential resistance to type I interferon are under investigation.

**Viral Reservoirs and Cure Research**

Many sessions and presentations at CROI dealt with issues related to understanding obstacles to viral eradication and attempts to achieve viral eradication in HIV-infected individuals. The scientific rationale for pursuing viral eradication in HIV-1–infected individuals derives from the Berlin patient, Timothy Brown, who in 2007 received a CC chemokine receptor 5 (CCR5)-Δ32 stem cell transplant and has since had undetectable levels of HIV-1 RNA. The stem cell transplant was necessitated after Brown developed acute myelogenous leukemia. He received an allogeneic transplant from a related donor who carried a homozygous deletion in the CCR5 gene. This would seem to predict that interferon resistance was found to decline rapidly following acute infection and viruses obtained 6 months from the onset of symptoms were found to be substantially less resistant to interferon than viruses obtained in the acute phase of infection. Borrow went on to examine whether the establishment of HIV-1 infection by interferon-resistant viruses was caused by selection of interferon-resistant variants from the donor quasispecies or whether there was preferential transmission of interferon-resistant viruses that preexisted in the donor quasispecies population. Analysis of viruses obtained from an acute-to-acute transmission pair indicated that interferon-resistant viruses in the donor viral quasispecies population were selectively transmitted, supporting the notion that type I interferons contribute to the transmission bottleneck. Viral determinants that mediate the differential resistance to type I interferon are under investigation.

AIDS–USA  Topics in Antiviral Medicine

Δzygous CCR5-Δ32 cells did not eliminate all viral reservoirs. One possible explanation is that the reservoirs that maintained HIV-1 in these individuals comprised cells that were long-lived or did not circulate in blood. Drawing conclusions about the source of the virus that persisted in these patients is difficult because of sampling issues with methodologies used to identify infected cells. Sampling of gut and peripheral blood failed to reveal the presence of viral DNA in different memory CD4+ T cell subsets. This begs the question of whether there may be non-CD4+ T cell reservoirs of HIV-1 in individuals on suppressive antiretroviral therapy.

Several presentations offered intriguing evidence that HIV-1 may reside in cells other than CD4+ lymphocytes in aviremic individuals. Wong and colleagues (Session O-12, Abstract 137) examined the distribution of viral DNA in CD4+ T cell subsets in the gut, lymph nodes, and blood of 8 individuals on suppressive antiretroviral therapy. The study subjects underwent leukapheresis and lymph node and rectal biopsy. Cells were separated into naive, central, transitional, and effector memory subpopulations followed by analysis of viral DNA and RNA. Viral distribution was found to be tissue dependent. Viral DNA was most abundant in effector memory cells in rectal tissue, and most of the viral DNA in blood was found in central memory and transitional memory cells. However, levels of viral DNA in cell samples always exceeded the amount that could be accounted for in CD4+ T cell subsets. In cells obtained from rectal tissue, levels of viral DNA in non-CD4+ T cells approached those found in CD4+ T cells. The investigators went on to demonstrate that these cells were macrophages. Although contamination of macrophage cell populations with CD4+ T cells is always a concern in these experiments, the frequencies of viral DNA in macrophages made it unlikely that the signals were caused by contaminating T cells. Abstract 410 described the identification of viral DNA in alveolar macrophages. Of the 22 HIV-1–infected subjects studied, 82% had undetectable plasma HIV-1 RNA levels. Viral DNA was detected in 78% of individuals with undetectable HIV-1 RNA levels, and macrophages from these individuals exhibited impaired phagocytic properties. The half-life of resident tissue macrophages, especially following HIV-1 infection, is relevant to the understanding of how HIV-1 persists in individuals on long-term therapy.

Lichterfeld (Abstract 54) presented evidence for a stem cell reservoir of HIV-1. Stem cells exhibit the greatest longevity due to their ability to undergo cell renewal and homeostatic proliferation, and their ability to resist apoptosis. Lichterfeld presented evidence that CD4+ T memory stem cells are susceptible to HIV-1 infection and harbor high levels of viral DNA.
in infected individuals on suppressive antiretroviral therapy. Viral DNA levels in these CD4+ T memory stem cells were stable over long-term suppressive therapy. It remains to be determined whether the virus present in this cell population is biologically active and is able to drive viral recrudescence in individuals whose therapy is interrupted. Maintenance of viral DNA in stem cells is likely to be a consequence of the intrinsic stability of this cell population. In addition, self-renewal of stem cells followed by duplication of proviruses during mitosis would contribute to maintenance of this reservoir.

Homeostatic proliferation has also been implicated as a mechanism through which the latent CD4+ T cell reservoir is maintained. Evidence for homeostatic maintenance of viral reservoirs is provided indirectly by the nature of viruses that rebound following years of suppressive antiretroviral therapy in which the rebound population has identical viral sequences. This is most likely explained by recrudescence of virus from identical proviruses that were generated through numerous rounds of mitosis. Abstracts 138 and 407LB examined integration sites in individuals on suppressive antiretroviral therapy in order to distinguish whether emergence of identical sequences in individuals whose antiretroviral therapy was interrupted was due to expansion of a population of identical proviruses through homeostatic proliferation, or the rapid outgrowth of a single virus variant with a high fitness advantage.

Hughes (Abstract 407LB) presented evidence that as many as 50% of the integration sites in individuals on suppressive antiretroviral therapy were a result of clonal proviral expansion. Furthermore, the nature of the integration sites indicated that there was some selective pressure exerted by the genetic location of the integration site. Therefore, some integration sites may impact the proliferation and survival of the host cell and promote expansion of that provirus; this would seem counterintuitive as HIV-1 is well recognized for its cytopathic effect on the host cell. It is possible that some expanded proviruses are defective and have little impact on host cell function. Although some duplicated proviruses are clearly capable of driving the synthesis of virions, as evidenced by their appearance in plasma following treatment interruption, it is not known whether proviruses maintained by homeostatic proliferation or by integration site–driven cell proliferation can serve as templates for biologically active viruses that can fuel viral recrudescence in individuals whose therapy is interrupted.

Key elements in the strategy for eradication of long-lived viral reservoirs in HIV-1–infected patients on suppressive antiretroviral therapy include reactivation of viral gene expression and elimination of the reactivated cell through viral cytopathic effects or immune-mediated clearance. Because viral latency is considered to be maintained by the state of chromatin architecture, agents that modify chromatin have been explored for their ability to reactivate latent virus in cellular models of latency in vitro and in HIV-1–infected individuals. Although chromatin modifiers such as histone deacetylase (HDAC) inhibitors can reactivate latent HIV-1 in cell line–based models of viral latency, evidence that these agents can induce HIV-1 in infected individuals on suppressive therapy is lacking. Session P-F9 featured several presentations examining the impact of chromatin-modifying agents on viral and cellular gene expression. Abstract 435LB demonstrated that panobinostat was able to induce HIV-1 transcription as well as plasma viremia in patients on suppressive antiretroviral therapy. In latently infected cell lines, panobinostat exhibited far greater potency than other HDAC inhibitors, such as belinostat or vorinostat. Those findings prompted exploration of panobinostat in HIV-1–infected individuals. The treatment was found to be well tolerated and repeated cycles of panobinostat resulted in episodic induction of viremia.

Results were less encouraging with repeated doses of vorinostat (Abstract 435LB). As has been demonstrated by the Margolis group, a single dose of vorinostat induced cell-associated HIV-1 RNA levels in quiescent T cells from HIV-1–infected individuals on suppressive antiretroviral therapy. However, when vorinostat was administered in weekly cycles, there were limited increases in cell-associated viral RNA and these only occurred in 3 of 5 individuals. In addition, changes in histone acetylation were less apparent following repeated cycles of vorinostat. Therefore, vorinostat may have the capacity to reactivate HIV-1 following a single dose but repeated doses lead to a blunted response. It is unclear whether blunted responses following repeat dosing will apply to other, more potent HDAC inhibitors.

**Immunopathogenesis**

Pathogenic lentivirus infection, such as HIV-1 infection in humans, is distinguishable from nonpathogenic infection, such as SIV infection of sooty mangabeys (SIVsm), by the extent of immune activation. In pathogenic lentivirus infections, there is chronic immune inflammation and this undermines immune homeostasis and likely drives viral persistence. Immune inflammation is associated with disruption of the gastrointestinal epithelial barrier, and this leads to translocation of microbial products, which contributes to immune inflammation and drives AIDS progression. T helper 17 (Th17) cells are important for maintenance of the epithelial barrier and production of cytokines, such as interleukin (IL)-17 and IL-21, and antimicrobial agents, such as defensins. Th17 cells are susceptible to HIV-1 infection and there is a depletion of this cell population in HIV-1–infected individuals.

Abstract 77 presented evidence that early initiation of antiretroviral therapy minimized damage to the mucosal barrier and reduced subsequent T cell activation. Individuals who initiated antiretroviral therapy at Fiebig stages I or II had statistically significantly higher levels of Th17 cells, similar to levels seen in HIV-1–uninfected controls. At 6 months and 24 months posttreatment initiation, subjects at Fiebig stages I or II maintained low levels of
immune activation that were similar to those seen in HIV-seronegative individuals. Recent studies suggest that dysbiosis of commensal microbiota interferes with immunologic reconstitution following antiretroviral treatment. Oral probiotics have previously been shown to increase the extent of gut CD4+ T cell reconstitution but not TH17 recovery in nonhuman primates treated with antiretroviral therapy. Abstract 83 examined the impact of IL-21 administration in SIV-infected macaques receiving probiotic supplementation. The investigators observed that probiotic and IL-21 supplementation of antiretroviral therapy in SIV-infected macaques led to CD4+ T cell reconstitution and increased TH17 frequency but was not associated with increased viral load. This study has important implications for strategies aimed at reversing the damage to the mucosal epithelium by HIV-1 and at improving immune reconstitution during antiretroviral therapy.

Echoing this theme, Abstract 315 explored alterations in gut microflora in HIV-1–infected individuals and whether this was influenced by antiretroviral treatment. Gut microbiota was altered during HIV-1 infection and correlated with immune status. Abstract 317 discussed research aimed at identifying translocating bacteria in SIV-infected macaques. The bacterial population was identified through 454 sequencing of 16S ribosomal DNA. Proteobacteria were found to preferentially translocate from the gastrointestinal tract in SIV-infected macaques. Because some of the translocating bacteria were mobile and flagellated, it is likely that these pathogenic species contribute to immune activation. These studies provide the rationale for monitoring interventions that maintain a healthy gut microbiome, reduce immune activation, and improve disease prognosis.

Financial affiliations in the past 12 months: Dr Stevenson has no relevant financial affiliations to disclose.
CROI 2014: New Tools to Track the Epidemic and Prevent HIV Infections

Susan P. Buchbinder, MD, and Albert Y. Liu, MD, MPH

As discussed at the 2014 Conference on Retroviruses and Opportunistic Infections (CROI), substantial advances have been achieved in using laboratory tools to track the leading edge of HIV transmissions globally. Phylogenetic and phylodynamic studies have identified clusters of new infections occurring along geographic routes and in different groups, including young men who have sex with men. New assays for detecting acute HIV infection are promising; however, additional strategies are needed to increase uptake of HIV testing in a number of populations. Globally, people who inject drugs face numerous barriers to accessing HIV prevention and treatment services and are in need of integrated approaches to deliver services, address stigma and discrimination, and reform drug policies. Young women and individuals in serodiscordant relationships continue to be at high risk for HIV acquisition. Injectable hormonal contraception with progestins may increase the risk of HIV infection. Bacterial vaginosis may also increase HIV acquisition and transmission. Additional evidence suggests antiretroviral therapy lowers HIV transmission in serodiscordant couples, but high levels of diagnosis, linkage, retention, and viral suppression are needed to reduce population-level HIV incidence. Several programs evaluating the implementation of preexposure prophylaxis (PrEP) have shown high uptake in the United States and resource-limited settings. As adherence is a crucial determinant of PrEP efficacy, long-acting PrEP agents are promising approaches being tested.

Keywords: CROI 2014, epidemiology, HIV, injection drug use, phylodynamics, preexposure prophylaxis, PrEP, prevention, seroincidence, TasP, transmission, treatment as prevention

Tracking the Epidemic

This year’s Conference on Retroviruses and Opportunistic Infections (CROI), held from March 3 to 6, 2014, demonstrated the substantial progress that has been made in the implementation of laboratory tools to track the HIV epidemic. Such tools include phylogenetic and phylodynamic mapping of sexual transmission networks and routes, assays to predict HIV seroincidence from cross-sectional population surveys, and identification of acutely infected persons.

Phylogenetic Studies

Several studies have been conducted to track the leading edge of transmission in the United States and identify populations who may benefit most from prevention interventions. Oster and colleagues presented viral sequence data from the US National HIV Surveillance System from 2001 to 2012 (Abstract 211). Of more than 40,000 pol sequences collected from persons aged 13 years or older, 31% were linked to at least 1 other sequence, and 10% were linked to 4 or more other sequences. In multivariable analyses, persons aged 15 years to 29 years, whites, and men who have sex with men (MSM) were more likely to have sequences linked to 4 or more other specimens than were other demographic and risk groups. Similar analyses were conducted in several US cities. Chan and colleagues evaluated sequences from more than 1100 clinic patients in Providence, Rhode Island, who had been diagnosed with HIV infection from 1980 to 2011 (Abstract 212); they found that 31% of viral sequences clustered and that MSM were more likely and injection drug users (IDUs) less likely than heterosexual non-IDUs to belong to a cluster. Using logistic growth modeling, of the 38 members of active clusters with more rapid transmission rates, 90% were MSM and 45% were diagnosed with primary HIV infection.

French and colleagues evaluated 920 newly diagnosed patients in Chicago, Illinois, from 2008 to 2011 and found that viral sequences clustered in 14% (Abstract 210). Similar to the US Centers for Disease Control and Prevention (CDC) study, they found that younger persons and men were more likely to belong to a cluster; unlike the CDC study, French and colleagues found that black MSM were more likely to belong to a cluster than white MSM. The difference between the studies in terms of the association of race with clustering may have been due to the racial makeup of the Chicago cohort (67% black, 23% Hispanic, and 9% white), structural differences in network formation in different
geographic locations, or sampling biases. Both analyses suggest that young MSM are more likely to be part of sexual network clusters, and interventions to increase testing, treatment, and PrEP are particularly important for these groups.

Wertheim and colleagues analyzed sequences from nearly 4000 HIV infected persons diagnosed in New York, New York, from 2005 to 2012 (Abstract 214). Similar to Chan’s analysis of sequences from Providence, Rhode Island, Wertheim’s analysis found that MSM were more likely and IDUs less likely to cluster than heterosexual non-IDUs. They also found that acute or early infections were more likely to cluster than prevalent cases, which may reflect the increased transmissibility of infection during the acute or early phases or confounding by sampling strategies (eg, more frequent sampling and higher proportion of acute diagnoses in more recent years). More than one-quarter of clustered infections was linked to persons who reside outside of but were diagnosed in New York, New York, particularly among MSM. Surprisingly, IDUs were more likely to link with persons from international sites in the Los Alamos Sequence Database. These geographic patterns have numerous implications, including challenges in tracking the impact of local prevention efforts on local HIV incidence among MSM.

Oster and colleagues also evaluated the pairwise connections that exist between their 40,000 sequences from the United States (Abstract 213). Most transmission pairs included at least 1 MSM. Transmission pairs that included blacks were more likely to include same-race pairs (63%) than whites (47%) or Hispanics (27%). These findings highlight the importance of diagnosing and treating MSM to stop transmission within sexual networks. The greater degree of racial homogeneity among black sexual networks may be a factor in the large number of new infections, disproportionate to level of risk, among black men and women.

Little and colleagues took these phylogenetic analyses a step further, assigning each of 478 recently infected patients in San Diego, California, and 170 of their HIV-infected social and sexual contacts a transmission network score (TNS) to quantify the relative interconnectedness of individuals (Abstract 206). In multivariable models, high baseline viral load and high TNS were independently associated with the predicted risk of HIV transmission within 1 year of infection. Additional models suggest that by targeting antiretroviral treatment toward individuals with high TNS, greater reductions could be achieved in lowering HIV transmission rates.

Phyloinformatics, or the quantitative study of epidemiology and evolutionary processes that shape viral phylogenetics, can be used to understand the geographic spread of HIV. Faria and colleagues presented an interesting phylogenetic analysis of HIV transmission from 17 East African regions, including Burundi, Democratic Republic of Congo, Kenya, Rwanda, Republic of Tanzania, and Uganda (Abstract 225). They found that viral transmission was not associated with geographic proximity, nor with train or central highway proximity. However, nearly one-half of the viral migration pathways involved locations situated along or near the northern highway. Such studies may pinpoint geographic hot spots that may help in the development and implementation of innovative prevention strategies. Delaporte and colleagues presented data from more than 3200 blood samples obtained from adults in 26 villages in Cameroon (Abstract 226). In addition to finding clusters linked to a major road for logging transport, they also found several instances of potential new introduction of simian retroviruses other than simian immunodeficiency virus (SIV), raising the concern that conditions for spread of new SIV could exist.

Phylogenetic studies were also conducted to evaluate changes to the HIV epidemic over the past several decades. Bezemer and colleagues presented data on more than 4000 MSM in the Netherlands, and from these isolates identified 91 MSM networks (Abstract 205). Remarkably, 70% of the networks were already circulating before 1996 and 89% of the networks included infections after 2006. Through additional analyses, they estimate that 33% of infections among MSM in the Netherlands were imported and only 6% of these created a local network. They concluded that the subtype B epidemic among MSM in the Netherlands is sustained by numerous, pre-antiretroviral treatment transmission networks and that the widespread introduction of antiretroviral therapy did not bring an end to these networks. Shiino and colleagues found a different epidemic pattern in Japan based on sequences from nearly 4400 newly diagnosed HIV-infected persons from 2003 to 2011 (Abstract 215). They found that subtype B spread through the MSM community mostly in the late 1990s, whereas subtype CRF01_AE spread through heterosexual and IDU routes at the same time. Based on clusters, they report that local heterosexual transmission may have been enhanced by hyperactive male spreaders in that population. They also conclude that CRF01_AE did not spread in the MSM community until the 2000s.

Takebe and colleagues presented data on viral sequences from MSM in China. They reported subclusters that emerged in 1997, 1999, 2005, and 2009, tying this epidemic with MSM epidemics in Japan, Hong Kong, Thailand, Europe, and the United States (Abstract 228). This largely understudied population of MSM in China appears to have been subject to several discrete HIV introductions from geographically diverse areas and presents an important opportunity to prevent further spread within this population.

Several CROI 2014 posters presented data that back-calculate the introduction of HIV into various human populations. Joy and colleagues presented data from more than 7700 patients from British Columbia, Canada (Abstract 230). They suggest that the HIV epidemic originated in 1897 (interquartile range [IQR], 1883-1923); they identify 1941 (IQR, 1923-1958) as the likely introduction of subtype B. Their analysis also confirms an increase in the MSM epidemic in Canada
Incidence Assays

Another strategy for tracking the leading edge of the epidemic and the impact of prevention and treatment interventions is to measure the rate of new infections within a population. Previously, such measures depended on longitudinal cohort studies, which were expensive and unlikely to represent the larger population. Substantial progress has been made over the last several years in developing assays to estimate population HIV incidence based on cross-sectional specimens.

At this year’s CROI, Kassanjee and colleagues performed a head-to-head comparison of 5 assays from more than 2000 subjects in Africa, Brazil, and the United States with well-defined dates of HIV exposure and clinical data (Abstract 1005). All 5 assays (BED, Limiting Antigen–Avidity Enzyme Immunoassay [LAg-Avidity EIA], Detuned Vitros, Vitros Avidity, and Biorad Avidity) misclassified patients with infections of longer than 6 months duration who were virally suppressed, with the proportion misclassified ranging from 27% to 54%. Longosz and colleagues further evaluated the ability of several assays to perform on specimens from 212 subtype A and 298 subtype D infections among adults in Rakai, Uganda (Abstract 1007). They found that the LAg-Avidity assay performed best, but none of the assays performed optimally with subtype D. In a separate analysis, Longosz and colleagues confirmed that those who are misclassified by the LAg-Avidity EIA are likely to be misclassified for the duration of their infection, based on samples from 667 individuals participating in US cohort studies (Abstract 1008). These studies highlight the importance of multiassay algorithms, which use additional assessments (eg, viral load, CD4+ cell count) for more accurate determination of HIV incidence.

Rottinghaus and colleagues compared the performance of the LAg-Avidity EIA on dried blood spots and plasma and found that it performed equally well on both specimens (Abstract 1006). Multiassay algorithms that perform well on dried blood spots allow researchers to take advantage of these specimens often used in surveillance activities in resource-limited settings.

Improving HIV Diagnosis, Including Acute Infection

Identifying newly infected persons is important for individual health (as early treatment may lead to less seeding of viral reservoirs) and public health (as acutely infected persons are highly infectious and may inadvertently expose HIV-uninfected persons prior to diagnosis). Braun and colleagues confirmed that primary HIV infection (PHI; acquired in the previous 6 months) may be difficult to identify based on symptoms alone (Abstract 1001). In their study of 293 patients with PHI enrolled in the Zurich Primary HIV Infection Study, 31% presented without typical symptoms for PHI, a likely overestimate as symptom history was collected retrospectively, after PHI was diagnosed. Powers and colleagues evaluated 342 seroconverters from 9 sites in Africa and found that having a greater number of acute retroviral symptoms was associated with prolonged viremia, but there was substantial variability across subtypes (Abstract 1003).

Several investigators reported on strategies for using antigen-based assays for earlier detection of acute infection in persons with negative results on rapid tests. Eller and colleagues evaluated the proposed CDC algorithm for detection of acute HIV infection (Abstract 619). The fourth-generation Genome Sequencing HIV Combo Antigen/Antibody Enzyme Immunoassay (GS HIV Combo Ag/Ab EIA), followed by the Multispot HIV-1/HIV-2 Rapid Test and nucleic acid testing if required, identified 29 acute infections, using twice-weekly samples from high-risk cohorts in Tanzania, Uganda, Kenya, and Thailand. This algorithm identified acute infections a median of 7 days after the first reactive RNA test, 6 days before peak viral load, and 8 days before third-generation enzyme-linked immunosorbent assay (ELISA) reactivity. The Multispot was not positive until a median of 20 days after the first RNA-positive specimen. Eller and colleagues suggest that their new algorithm enhances detection of acute HIV infection and that optimal detection of acute infection could occur with robust point-of-care viral load testing, to be used for highest-risk cohorts.

Geren and colleagues also evaluated the utility of fourth-generation HIV Ag/Ab testing for screening in an emergency department setting in Phoenix, Arizona (Abstract 618). In screening more than 26,000 patients, they detected 69 previously undiagnosed cases of HIV infection (0.28% positivity), 25% of which were acute infections that were negative or indeterminate on other serologic testing. They suggest that fourth-generation testing is important in identifying persons with acute HIV infection. Hutchinson and colleagues conducted a cost-effectiveness analysis using data from the STOP (Screening Targeted Populations to Interrupt On-Going Chains of Transmission with Enhanced Partner Notification) study, a 12-site prospective study conducted in New York, New York; San Francisco, California; and North Carolina (Abstract 616). Their algorithm called for using a fourth-generation HIV Ag/Ab test on patients with negative results on rapid HIV tests. Of more than 71,000 patients, 963 (1.34%) were HIV seropositive on rapid tests and an additional 127
(0.18%) were HIV seropositive only on the fourth-generation assay. In their costs-effectiveness modeling, screening with the fourth-generation assay was cost-saving (by reducing forward transmission) and remained cost-effective up to a detection rate nearly two-thirds lower than the rate detected in this study.

A cautionary note was added by a poster by Livant and colleagues on the performance of HIV rapid testing in the MTN-003 VOICE (Microbicide Trials Network-003 Vaginal and Oral Interventions to Control the Epidemic) preexposure prophylaxis (PrEP) study (Abstract 617). This study used monthly second-generation rapid tests, followed by confirmatory Western blot and HIV-1 RNA testing as appropriate. In testing more than 5000 women in nearly 78,000 visits at sites in Africa, they found the sensitivity for Determine, Unigold, and OraQuick rapid tests to be 88.78%, 85.86%, and 61.54%, respectively. Because it is important to identify newly infected persons on PrEP as soon as possible to prevent emergence of drug resistance, clinicians must consider testing algorithms that provide sufficient sensitivity to identify acute infection.

Bristow and colleagues presented encouraging data on the sensitivity and specificity of a combined HIV infection and syphilis rapid antibody test (Abstract 627). The group tested several thousand specimens collected from 6 countries at 6 laboratory sites, and found very high sensitivity and specificity, despite diversity in infection rates and antibody profiles. Rollout of this or other combined point-of-care testing for HIV infection or syphilis could improve screening for both infections in resource-limited settings.

HIV Testing and Strategies to Improve Uptake

Cooley and colleagues presented data on HIV testing among MSM in 20 high-prevalence metropolitan statistical areas (defined by the US Office of Management and Budget) in the United States, as measured in the National HIV Behavioral Surveillance System (Abstract 968). Surveys conducted in 2008 and 2011 sampled approximately 8000 MSM. Overall testing rates increased by 9% over that time, with statistically significant increases among blacks, persons of other races and bi- or multiracial persons, and persons aged 20 years or older. Among 18- to 19-year-olds, only blacks were statistically significantly more likely to have tested in 2011 than in 2008. The proportion of persons testing 3 or more times in the previous 2 years also substantially increased, from 37% to 44%. However, two-thirds of all men in the survey had not tested in the previous 12 months, indicating that more work needs to be done to increase testing rates among MSM, for whom the CDC recommends at least annual testing; many jurisdictions recommend at least semiannual testing for MSM.

Malna and colleagues compared data from 2 nationally representative population-based surveys in Kenya (the 2007 and the 2012 Kenya AIDS Indicator Surveys; Abstract 149). In the 2007 survey, only 34% of participants had ever received an HIV antibody test; this increased to 72% in the 2012 survey (P < .001). Similarly, in 2007, only 16% of HIV-seropositive participants were aware of their HIV serostatus compared with 47% in 2012 (P < .001). Although this represents a substantial improvement in overall testing rates, knowledge of HIV serostatus remains relatively low, and additional scale-up is required to identify HIV-seropositive persons.

Novitsky and colleagues presented data on the ability of household-based HIV testing campaigns to reach populations at risk of HIV infection in Mochudi, Botswana (Abstract 1043). They surveyed more than 6000 16- to 64-year-olds in northeastern Mochudi; HIV prevalence was 20%. By comparing these data with data from the United Nations, they estimate having reached 88% of women but only approximately half of men and approximately 40% of men aged 25 years to 44 years through this testing campaign. Alternative strategies are needed to increase the uptake of testing among men. Brunie and colleagues presented data from a pilot study in Uganda of integrating HIV testing and counseling services into village health teams, which provide community-based health services, including family planning (Abstract 1042). They were able to conduct 647 HIV-testing visits in the first 3 months of 2015 at 4 clinics; 80% of visits included men and 50% included women. More than one-quarter of those participating had never previously tested, and more than 90% said they would like to test again through the village health teams. This presents one possible approach to increasing HIV testing in men.

Mehta and colleagues pointed to the crucial role that HIV testing plays in the treatment cascade. Theirs was one of several presentations from a large cross-sectional survey of more than 12,000 MSM and 14,000 IDUs across 26 cities in India (Abstract 1065). HIV prevalence was 18% among IDUs and 6% among MSM, with substantial variability by study site. The most substantial drop-off in the treatment cascade was in the proportion of HIV-seropositive persons who were diagnosed: among IDUs, 41% of HIV-seropositive persons were diagnosed (3%-92% by site) and among MSM, 30% were diagnosed (0%-90% by site). The proportion of HIV-seropositive persons diagnosed was higher among participants who were older; had higher educational levels; and received other services, such as IDUs and MSM with previous tuberculosis diagnoses, MSM diagnosed with a sexually transmitted infection (STI), and IDUs receiving opiate substitution therapy. This suggests that integrating HIV testing with other clinical services may reach persons at risk but that substantial additional efforts must be made to increase HIV testing nationally.

HIV Self-Testing

Several investigators at CROI 2014 reported on the use of HIV self-testing in the United States and internationally. Nunn and colleagues presented on hypothetical willingness to use the FDA-approved OraQuick in-home HIV test, the first over-the-counter self-test kit, among approximately 1000 residents
participating in an HIV and hepatitis C virus (HCV) testing program in Philadelphia, Pennsylvania (Abstract 971). Their survey was conducted in areas with high HIV prevalence (estimated 3% of adult population), but with limited HIV testing and treatment services. Stated willingness to use the test kit was high (91%), and more than half were willing to pay, but only 14% were willing to pay current market price.

Marlin and colleagues presented data on use of a paper voucher system for free OraQuick in-home HIV tests at 12 Walgreens pharmacies in Los Angeles, California (Abstract 969). They distributed more than 600 vouchers through community-based organizations, student distributors, a clinic, and survey recruitment flyers; 49 vouchers were redeemed for test kits. The most frequently cited barrier was difficulty in travel to available pharmacies, and there were substantial differences in store procedures, some of which caused discomfort for the potential users (eg, needing the store manager to be involved). Three persons reported a positive test and being linked to care; 2 additional persons declined to report test results but also stated they had engaged in follow-up care. The investigators suggest that this mechanism may be used to newly identify HIV-infected persons and link them to care. Myers and colleagues presented data on a survey of 361 pharmacies in New York, New York, in summer of 2013 (Abstract 970). They found that test kits were available in 84% of chain pharmacies but only 9% of independent pharmacies, and kits were kept behind the pharmacy counter in 77% of high-morbidity neighborhoods (based on HIV diagnosis rate) and 55% of low-morbidity neighborhoods (P < .03). Only 80% of pharmacists correctly stated kit availability, and two-thirds of kits were sold above the manufacturer’s suggested retail price of $39.99, identifying potential barriers to use of self-test kits that should be addressed.

Choko and colleagues presented data from a cluster randomized trial of 16,660 adults from 14 high-density neighborhoods (HIV prevalence 18.5%) in Malawi (Abstract 147). Half of the communities received an HIV self-testing intervention that included distribution of self-test kits by 2 trained residents, with linkage to care for those who tested seropositive for HIV. Overall uptake in the intervention neighborhoods was 76%, including 67% of all men and 93% of all 16- to 19-year-olds. In total, 9% reported positive HIV test results, 78% of whom accessed HIV care. No suicides or assaults were reported, but 147 men and 119 women reported coercion to test, mostly by partners. Cambiano and colleagues presented a cost-effectiveness analysis of HIV self-testing in resource-limited settings (Abstract 1045). Using Zimbabwe as an example, they estimated that the introduction of self-testing would be cost-saving, with an estimated savings of $53 million dollars during a 20-year period. This was based on a decrease in the proportion not willing to be HIV tested from 5% to 2.5%, and an increase in first-time and repeat testing of 20%. Because of the substantial uncertainties in many of the inputs into this model, additional data on uptake of HIV self-testing and linkage to care are required to determine whether this may be a feasible and affordable strategy to increase testing in resource-limited settings.

Partner Notification Services

Peters and colleagues compared partners of 579 newly diagnosed persons with established HIV infection with 110 newly diagnosed persons with acute HIV infection in New York, New York; North Carolina; and San Francisco, California (Abstract 1030). Overall, 58% of partners had previously diagnosed infection, 11% were newly diagnosed, and 45% were HIV seronegative, with no difference in partners of persons with acute versus established infections. In addition to linking newly diagnosed persons into care, partner notification services presents the opportunity to ensure that partners with established infection are linked to care and treatment, to reduce further transmission from those partners. In addition, nearly half of the newly diagnosed index cases declined partner notification services, suggesting that new strategies are needed to reach partners of newly diagnosed persons.

Risk Factors for HIV Transmission and Acquisition

Sex

Women bear a disproportionate burden of HIV infection globally, and several epidemiologic studies presented at this year’s conference further elucidated this increased risk. Good news came from Jonas and colleagues who demonstrated a stable HIV prevalence among women aged 15 years to 49 years in Namibia (Abstract 1039). Among women aged 15 years to 24 years, prevalence appears to have decreased by approximately 8%, signaling a likely decrease in HIV incidence in this population of young women. Mills and colleagues found no sex-based differences in HIV incidence in a community-wide, home-based testing campaign in rural, western Kenya reporting an overall incidence of 1.2 per 100 person-years of observation (Abstract 1025). Of more concern were data presented by Huerga and colleagues from a population-based survey in rural Kwazulu-Natal (Abstract 152LB) showing an overall HIV prevalence of 25%; women had twice the prevalence of men (31% vs 16%, respectively) and a 2.5 times higher incidence than men (1.6 per 100 person-years of observation vs 0.6 per 100 person-years of observation, respectively). Antiretroviral therapy coverage was higher for women than men (79% vs 64%, respectively), which may further fuel sex disparities in HIV acquisition in this population, if leaving men untreated makes them more infectious. Incidence differences between women and men were particularly pronounced in the 20- to 29-year-old age group (4 per 100 person-years of observation vs 1 per 100 person-years of observation, respectively), pointing to the need for prevention interventions for young women.

Nair and colleagues presented risk factors for HIV acquisition in the
HIV in younger women. Harling and colleagues presented data from a population-based cohort of more than 5000 women in rural KwaZulu-Natal, South Africa, from January 2005 to June 2012 (Abstract 145). Overall HIV incidence was 7.75 per 100 person-years of observation, but having an older partner was not associated with increased incidence among women younger than 30 years of age. Among women aged 30 years and older, HIV incidence fell as partner age rose, suggesting that public health campaigns encouraging women to avoid older male partners could be harmful for older women and may not be helpful for younger women.

Nerlander and colleagues analyzed 2009 US National HIV Behavioral Surveillance (NHBS) data on women who inject drugs to identify risk practices and undiagnosed HIV infection in this population in 20 US cities with high AIDS prevalence (Abstract 1037). They found that approximately one-third of these women exchanged sex and that women who exchanged sex were statistically significantly more likely than women who did not exchange sex to have sex without a condom (88% vs 65%, respectively) and to have a shared injection equipment (56% vs 30%, respectively) in the past 12 months. A small proportion of women who did and did not exchange sex were HIV seropositive and unaware of their status (5% vs 3%, respectively), but only somewhat more than one-half of each group had tested for HIV in the past 12 months. These data point to the need for interventions (including regular HIV testing) that specifically target women who inject drugs, with a special focus on women who also exchange sex. Lucas and colleagues presented data from respondent-driven sampling that recruited nearly 15,000 IDUs at 15 sites in India (Abstract 1036). Overall prevalence was 18%, but women had a fourfold greater odds of HIV infection and were statistically significantly less likely than men to report ever accessing needle exchange or opiate substitution programs. Thus, women who inject drugs may have dual disparities (injection and sexual) for HIV acquisition; women-specific programs are needed to curb the spread of HIV in these populations.

**Hormonal Contraception**

Session 10 was a themed discussion focusing on the impact of reproductive hormones on the risk for HIV acquisition and transmission. Cu-Uvin opened the session by reviewing observational data suggesting a potential increased risk of HIV acquisition with the use of injectable contraceptives (depot medroxyprogesterone acetate [DMPA]) but not oral contraceptives. The World Health Organization (WHO) convened an expert panel to review the epide-miologic literature and issued a statement in February 2012 that available evidence was inconclusive and there should continue to be no restrictions on the use of any hormonal contraceptive for at-risk women. Cu-Uvin reviewed possible biologic mechanisms for increased HIV acquisition and transmission with the use of hormonal contraceptives, including changes in vaginal and cervical structure, changes in local and systemic immunity, and heightened STI risk and alterations in vaginal flora.

In this session, Roxby and colleagues presented data on the impact of DMPA on effector molecules of the innate immune response in cervicovaginal secretions in high- and low-risk HIV-uninfected women (Abstract 846). Among 160 HIV-exposed, seronegative women in serodiscordant relationships and 73 low-risk control women in Kenya, DMPA users had statistically significantly higher mean concentrations of the cationic polypeptides HNP1-3 and LL37. These molecules are potent recruiters of target cells for HIV infection, and it was hypothesized that upregulation of these polypeptides may lead to recruitment of dendritic cells susceptible to HIV infection.

Noguchi and colleagues compared the impact of DMPA with that of nor-ethisterone enanthate (NET-EN), another injectable hormonal contraceptive, on HIV acquisition among women enrolled in the MTN-003 VOICE trial (Abstract 847). Of 3163 injectable hormonal contraceptive users, 65% used DMPA and 43% used NET-EN during follow-up (8% overall used both DMPA and NET-EN). Compared with NET-EN users, DMPA users were older, more likely to be married and to have children, more likely to test seropositive for HSV-2 at baseline, and less likely to report more than 1 sex partner. In adjusted analyses, DMPA users had a higher risk of HIV acquisition than NET-EN users (hazard ratio [HR], 1.42; 95% CI, 1.03-1.97; P = .034). This relationship was modified by HSV-2 status, with an increased risk of HIV acquisition seen only among women who were HSV-2 seropositive at baseline (adjusted HR, 2.02; 95% CI, 1.11-3.66; P = .021). Noguchi pointed out that the lack of a nonhormonal contraceptive comparator group in this analysis prevented estimation of the impact of DMPA or NET-EN use versus nonuse on HIV acquisition. These findings support current WHO recommenda-tions that women using injectable contraceptives containing progestins should use other preventive measures against HIV infection.

Radzio and colleagues reported that DMPA did not affect simian-human immunodeficiency virus (SHIV) viremia nor genital shedding in a randomized, controlled pigtail macaque challenge study using 6 animals on DMPA and 6 controls (Abstract 844). These findings suggest that DMPA may not increase...
HIV infectivity in HIV-seropositive women. During the discussion period, several attendees made the point that additional data are needed on the risk associated with different hormonal contraception methods, discussing whether randomized controlled trial data are needed to better understand the risk associated with injectable hormonal contraceptives. The WHO will convene a meeting shortly to review emerging data and their recommendations on hormonal contraception. Overall, there was agreement on the importance of expanding contraceptive options for women.

Two posters evaluated whether the coadministration of hormonal contraception and PrEP diminished the efficacy of either intervention in the Partners PrEP study of serodiscordant couples. Heffron and colleagues demonstrated high PrEP efficacy (71%) among women who used DMPA and men whose female partners used DMPA (90% efficacy), with no difference when compared with women and men not exposed to hormonal contraception (Abstract 950). The authors conclude that PrEP use could counterbalance the potential increased risk of HIV acquisition in women using DPMA. Murnane and colleagues compared contraceptive effectiveness in the PrEP arm with that in the placebo arm in the Partners PrEP study (Abstract 957). Women using injectable and implantable contraception had a substantial reduction in pregnancy rates that did not differ by randomization arm. Similar to previous studies, oral contraceptives did not result in substantial reductions in pregnancy incidence, possibly due to low adherence rates. These results suggest that a combination of injectable or implantable hormonal contraception and PrEP could provide effective prevention for pregnancy and HIV acquisition.

Sexually Transmitted Infections

In a symposium on intimate infections (Session S9), Myer reviewed the evidence for the role of bacterial vaginosis (BV) in HIV acquisition and transmission. He highlighted that our basic insights into normal and abnormal vaginal flora are rapidly evolving. Currently, BV is thought of as a polymicrobial condition in which normal vaginal Lactobacillus species are replaced by diverse bacterial communities of anaerobes and facultative anaerobes. BV is clinically characterized by the loss of normal acidic pH and the presence of epithelial cells covered with anaerobes (clue cells). Several factors, including immunologic impairment (eg, advanced HIV disease), changes in hormone levels, cervical and vaginal infections (eg, HSV-2, Trichomonas), and intravaginal practices (eg, douching) may facilitate the development of BV. Although BV is consistently associated with high-risk sexual behaviors, a specific sexually transmitted etiologic agent has not been identified.

BV prevalence is higher in HIV-infected than in HIV-seronegative women, and in a meta-analysis of 3 prospective studies, BV was associated with increased HIV acquisition in women (risk ratio [RR], 1.61; 95% CI, 1.21-2.13). Potential mechanisms behind this increase include loss of healthy mucosal defenses and local inflammation in the vaginal mucosa. BV has also been associated with increased HIV shedding in cervicovaginal specimens of HIV-infected women, and a recent study among serodiscordant couples in Africa demonstrated that BV was associated with increased female-to-male HIV transmission. Treatment of BV can be challenging, as there is a 50% to 50% recurrence rate after standard treatment. Furthermore, treating BV in HIV-infected women has had limited impact on HIV shedding. New BV treatment strategies are emerging, with interventions focused on promoting healthy vaginal flora. Myer recommends future research into the mechanisms through which normal and abnormal vaginal flora affect HIV transmission, and the drivers of the onset and persistence of abnormal vaginal flora.

Racial Disparities

A number of presentations and posters highlighted the racial and ethnic disparities in new HIV infections in the United States. Rosenberg and colleagues presented data from the InvolvEMEnT study, a longitudinal cohort of black and white MSM in Atlanta (Abstract 38). Of the more than 800 men enrolled, HIV prevalence was 44% in black MSM and 15% in white MSM. HIV prevalence increased with age and was higher in black MSM (34% at 25 years, 45% by 30 years, and 60% if older than 30 years of age) than white MSM at all ages except 18- to 19-year-olds. HIV incidence was 9.6 per 100 person-years of observation among black MSM younger than 25 years; no infections were seen in white MSM in this age group. A change-in-hazard approach was undertaken and it was found that the racial disparity in HIV incidence may be explained by poverty and partner race but not employment, insertive versus receptive sex roles, known serodiscordant partners, drug use, arrest, or homelessness.

Serodiscordant Couples

A central question of the HIV epidemic is what accounts for the substantial differences in HIV prevalence in different countries in sub-Saharan Africa. Bellan and colleagues addressed this question using data from 40,000 couples in 25 countries (Abstract 1041). They developed a couples transmission model to assess whether this variation was due to differences in sexual networks (eg, concurrency) or transmissibility (eg, differences in host or viral characteristics, or sexual practices), concluding that the substantial difference in HIV prevalence (ranging from 1% to 30%) is explained by transmissibility differences and not by differences in sexual networks.

Rodger and colleagues presented data on an interim analysis from the PARTNER Study conducted in 14 European countries whose aim is to assess transmission rates between serodiscordant couples when the HIV-seropositive partner is on suppressive antiretroviral therapy (Abstract 153LB). They noted that data on condomless sex between serodiscordant couples are limited, with only 330 cumulative
couple-years of data in the published literature. In addition, the HPTN (HIV Prevention Trials Network) 052 study demonstrated a substantial reduction in the risk of transmission from HIV-seropositive partners in stable serodiscordant relationships, but only 2% of the study population were MSM couples. This PARTNER Study interim analysis included 767 couples (including 282 MSM couples) in whom the HIV-infected partner was on antiretroviral therapy with a plasma HIV RNA level less than 200 copies/mL, the HIV-seronegative partner was not on PrEP or postexposure prophylaxis (PEP), and the couple engaged in condomless sex. As of this interim analysis, no linked transmissions have occurred. The upper 95% confidence limit on this 0% estimate for a 10-year period is 4% for all condomless sex, 10% for anal sex, and 32% for receptive anal sex with ejaculation.

Although the lack of linked transmissions is an encouraging sign, the investigators pointed out that couples enrolled in the study had already been in stable relationships for some time prior to entering the study (1.5 years for MSM couples, 3 years for heterosexual couples), which may have preferentially selected for couples in whom transmission is a less common occurrence. MSM were more likely than heterosexual couples to report having an STI during the study (16% vs 5%, respectively) and to report having an outside sex partner (34% vs 3%, respectively); no data are yet available on any transmissions that may have come from outside partners.

Several studies addressed prevention issues related to stable heterosexual couples in Africa. Grabowski evaluated the introduction of HIV into stable, seronegative heterosexual partnerships in the Rakai Community Cohort Study from rural Uganda (Abstract 146). Their data included 4570 initially HIV-serocordant couples followed up annually from 1997 to 2011, including periods before and after the introduction of combination antiretroviral therapy. In total, 135 infections were introduced into couples; in 21% of these, the second partner seroconverted during the same interval. Although self-reported extra-couple relationships were strongly associated with the introduction of HIV into the couples, only 22% of women and 70% of men admitted to having external sex partners.

Waruiru and colleagues presented data from the population-based, 2012 Kenya AIDS Indicator Survey (Abstract 1029). Based on these data, the investigators estimated that there are 260,000 serodiscordant couples in Kenya. Risk factors for serodiscordancy included a higher number of lifetime sex partners for women, and outside sex partners and lack of male circumcision for men. HIV treatment was relatively uncommon across all serodiscordant partnerships (24%) but was substantially greater (64%) among those couples in whom the HIV-infected partner was aware of his or her HIV serostatus. These 2 studies point to the importance of HIV testing and knowledge of serostatus among couples and the need for prevention interventions (male circumcision for HIV-seronegative men, treatment for HIV-seropositive partners, and other interventions such as PrEP) to reduce transmission within serodiscordant partnerships and to prevent the introduction of HIV into stable, concordant HIV-seronegative partnerships.

Emerson and colleagues presented data from the 2010 through 2011 SHIMS (Swaziland HIV Incidence Measurement Survey), a population-based longitudinal cohort analysis (Abstract 1027). Overall, 21% of the nearly 10,000 households surveyed were HIV serodiscordant at baseline. Over follow-up, HIV incidence was 3.1% for women and 1.7% for men; 40% of seroconversions occurred within serodiscordant households. For women, having an HIV-infected male household member was strongly associated with seroconversion (odds ratio [OR], 3.3). Men were at increased risk based on outside sex partners (1 partner: OR, 2.1; 2 or more partners: OR, 4.6) but were not at increased risk from an HIV-infected, stable partner. The investigators suggest that in this context, identifying women in serodiscordant relationships allows for efficient targeting of prevention strategies, but for men, having outside relationships remains the greatest HIV risk.

Risk Practices Among HIV-Seropositive Persons

Kuhn and colleagues presented data from 269 interviews of HIV-infected MSM in Germany to explore risk practices and serocommunication strategies among men following the viral load strategy (VLS; Abstract 1040). VLS is patterned after the so-called Swiss Statement that HIV transmission is unlikely to occur within monogamous couples when HIV viral load is stably suppressed for 6 months and no other STIs are present. Kuhn reported that approximately 10% of the men in this study followed VLS but that in addition to being more likely than others to report condomless anal sex (insertive and receptive), they were also more likely to engage in anonymous sex and less likely to disclose their HIV serostatus to sex partners, particularly in anonymous settings. These authors caution against the use of the VLS outside of monogamous relationships, where other STIs may occur and thus increase the risk of HIV transmission.

Mattson and colleagues presented data from the national Medical Monitoring Project, evaluating factors associated with nondisclosure of serostatus among HIV-infected individuals (Abstract 1033). In multivariable analysis, heterosexual men and women were more likely than MSM to inform all partners of their HIV serostatus, as were white compared with black and Latino patients. Substance use (binge drinking, noninjection drug use), homelessness, and condomless sex were also more likely to be associated with nondisclosure of HIV serostatus.

Lin and colleagues presented data on risk factors for condomless anal sex among HIV-infected MSM using data from the CDC Medical Monitoring Project (Abstract 1038). Overall, 56% of MSM reported condomless anal sex. In multivariable analysis, independent risk factors associated with condomless sex included use of erectile
dysfunction drugs (adjusted prevalence ratio [aPR], 1.2), white race (aPR, 1.3), 3 to 5 sex partners (aPR, 1.5), 6 or more partners (aPR, 1.6), use of illicit drugs before or during sex (aPR, 1.3), and depression (aPR, 1.2). However, of the 13% of sexually active MSM prescribed erectile dysfunction drugs, only 40% received STI or HIV risk reduction counseling from their practitioner in the previous 12 months. The investigators highlighted the need for practitioners to counsel patients for whom they prescribe erectile dysfunction drugs about strategies to reduce the risk of HIV and STI transmission.

**Injection Drug Use**

The topic of injection drug use was featured more prominently at this year’s conference than in previous years. Kamarulzaman presented a plenary providing an update on the epidemiology of new infections and drivers of the epidemic among IDUs. She presented data from the Joint United Nations Programme on HIV/AIDS (UNAIDS) Global AIDS Report noting that illicit drugs are one of the largest contributors to disability among men and in countries where HIV incidence is increasing, 70% to 80% of HIV infections are occurring among IDUs. Despite numerous studies that support the effectiveness of opiate substitution therapy and needle and syringe exchange programs in reducing HIV acquisition, only 8 of every 100 IDUs are receiving opiate substitution therapy and only 2 needles are exchanged per IDU per month. In countries reporting IDUs, 86 countries have no opiate substitution therapy programs and 76 countries have no needle and syringe exchange programs. Kamarulzaman reviewed progress following the 2010 publication of a *Lancet* review article highlighting punitive drug laws in several countries. Since that time, China, Vietnam, Malaysia, and Ukraine have reduced punitive laws and/or increased access to opiate substitution therapy and/or needle and syringe exchange programs. However, the United States has reinstated its ban on funding for needle and syringe exchange programs, and Russia has reduced the number of IDUs receiving needle and syringe exchange services by 60%.

Among IDUs, women have a much higher prevalence than men, exacerbated by intimate partner violence, sex imbalances in power, sex work, and lack of woman-specific services in many places. Adolescents may also be particularly vulnerable, as estimates are unavailable in many countries, and where data are available, needle sharing appears to be particularly high but access to services is low. Among MSM, use of injection drugs is often episodic but appears to be higher among young and urban men and may be exacerbated by co-use of club drugs, which are increasingly more likely to be injected. IDUs are likely to be incarcerated in many countries, and new data are confirming the danger of increased needle sharing and decreased access to antiretroviral therapy among incarcerated populations, which raise HIV transmission risk.

Studies from several countries have documented the worsening treatment cascade among IDUs. Data from the ALIVE (AIDS Linked to the IntraVenous Experience) cohort of IDUs in Baltimore, Maryland, showed that only 8% of HIV-infected participants were fully virally suppressed, and lack of retention in care and of viral suppression were each associated with lack of consistency in HIV care practitioners, incarceration, and active use of injection drugs. Studies in Central Asia also demonstrate low levels of antiretroviral treatment, due in part to practitioners’ reluctance to prescribe antiretroviral drugs among active IDUs. Providing opiate substitution therapy can increase adherence to antiretroviral treatment, with improvement in viral suppression. Integrating HIV infection, STI, and tuberculosis care has been shown to improve health outcomes in Ukraine. A World Bank study of the cost of scaling up of combination prevention efforts (needle and syringe exchange programs, medically assisted therapy, HIV counseling and testing, and antiretroviral treatment) compared with the status quo in Ukraine, Pakistan, Thailand, and Kenya found that the cost per infection averted was $400 to $1600, highly cost-effective.

The Global Commission on Drug Policy makes the case that the criminalization of drug use fuels the HIV pandemic. Despite enormous funds spent on the criminal justice system and a declared “war on drugs,” the global heroin supply has increased by 380% from 1980 to 2010. A modeling study suggests that eliminating laws against opiate substitution therapy and scaling up needle and syringe exchange programs and opiate substitution therapy to 80% coverage could eliminate 29% of new infections in Nairobi. Portugal decriminalized all illicit drugs in 2001 while continuing to prosecute dealers and traffickers. They scaled up treatment and harm reduction, while guaranteeing a minimum income, and saw a dramatic reduction in the incidence of HIV infection among drug users by more than 75%. A recent editorial in the *Journal of the American Medical Association* pointed out the stigma associated with opiate addiction—rather than recognizing it as a medical disorder—and a failure to attend to other associated mental health and medical issues.

In her plenary, Kamarulzaman called for combination, multilevel prevention integrated with treatment, addressing stigma and discrimination (beginning with the medical and scientific community), and reforming drug policies worldwide.

Mitsch and colleagues presented national data on trends in HIV diagnoses among IDUs in the United States (Abstract 1034). Using data reported to the CDC, they estimate that the number of new HIV diagnoses attributable to injection drugs was down by 10.5% among men and by 12.2% among women from 2008 to 2011. Despite this improvement, IDUs continue to bear a disproportionate burden of HIV infection (6 times higher than overall prevalence), and prevalence does not appear to be increasing, a possible sign of relatively high mortality among this population. Approximately 15% of persons with heterosexually acquired infection were likely to have become infected through sexual contact with IDUs, underscoring the need to
prevent, diagnose, and treat HIV infection among IDUs to improve the health and well-being of this population and their sex partners.

**Prevention Strategies**

**Preexposure Prophylaxis**

Clinical trials have demonstrated the safety and efficacy of daily oral PrEP in several populations, whereas other trials have shown no efficacy. New data on PrEP presented at CROI 2014 focused on understanding efficacy, adherence, and resistance data from completed PrEP trials; describing PrEP implementation efforts and rollout strategies to maximize PrEP’s public health impact; and evaluating long-acting formulations of PrEP to overcome adherence challenges.

Baeten and colleagues presented data from the Partners PrEP study comparing the efficacy of single-agent tenofovir PrEP with dual-agent emtricitabine plus tenofovir PrEP in heterosexual serodiscordant couples (Abstract 43). After the primary study results were released in July 2011 demonstrating a preventive efficacy of 67% for tenofovir and 75% for emtricitabine plus tenofovir, placebo-arm participants were offered rerandomization to tenofovir or emtricitabine plus tenofovir. Data through December 2012 showed that efficacy for tenofovir was 33% lower than efficacy for emtricitabine plus tenofovir alone, although this was not statistically significantly different (HR, 0.67; 95% CI, 0.39-1.17). Estimated PrEP efficacy was high among participants with detectable plasma drug levels in both treatment arms (85% in the tenofovir and 90% in the emtricitabine plus tenofovir arm), and safety outcomes were similar between treatment arms. These results suggest that once-daily tenofovir and emtricitabine plus tenofovir are safe and provide substantial preventive benefit with comparable efficacy.

Several presentations focused on understanding and validating adherence measures used in PrEP trials. van der Straten and colleagues presented data comparing behavioral and pharmacokinetic measures of adherence in the VOICE trial (Abstract 44). This trial in African women did not demonstrate efficacy of daily oral tenofovir, daily oral emtricitabine plus tenofovir, and 1% vaginal tenofovir gel, due in part to low product use as evidenced by low rates of drug detection in trial participants. In their analysis, van der Straten and colleagues compared behavioral measures of adherence (including face-to-face interviews, clinic pill counts, and audio–computer assisted self-interview) with pharmacokinetic measures of adherence (tenofovir concentrations in plasma and vaginal swabs). Pharmacokinetic nonadherence was defined as having a drug level below a threshold concentration reflecting no dosing in the past week. Although pharmacokinetic nonadherence was high in the oral arms (69%) and the gel arm (64%), rates of nonadherence were lower for the behavioral measures (6% to 49%). Nonadherence detected via behavioral measures did predict pharmacokinetic nonadherence, but this population represented a small proportion of the overall cohort. In logistic regression models to estimate predictive ability, none of the behavioral measures performed well in predicting pharmacokinetic nonadherence and provided only slightly better prediction than a coin toss.

These results highlight the importance of developing accurate real-time, low-cost objective and biologic measures of adherence for use in PrEP trials. Baxi and colleagues presented data evaluating the correlation among pharmacokinetic measures (plasma, intracellular, and hair PrEP drug levels) and traditional measures of adherence (self-report and medication electronic monitoring system [MEMS] counts of medication bottle openings) in 2 intermittent PrEP trials in Africa (Abstract 953). Hair drug levels and MEMS counts were strongly associated, with hair tenofovir and emtricitabine concentrations increasing by 8% to 10% for every 10% increase in MEMS counts; plasma levels and peripheral blood mononuclear cell (PBMC) levels were also associated with MEMS counts. Hair levels and self-reported adherence were only weakly associated, highlighting the limitations of self-reported adherence data for PrEP.

To help inform the use of pharmacokinetic assessments as quantitative, objective measures of PrEP adherence and to guide the evaluation of intermittent PrEP dosing strategies, Hendrix and colleagues presented data on drug concentrations associated with varying dosing patterns in the HPTN 066 study (Abstract 104). In this phase I pharmacokinetic study, HIV-seronegative men and women were randomized to receive directly observed oral emtricitabine plus tenofovir with different dosing frequencies ranging from once a week to daily dosing (100% adherence). Steady-state levels of tenofovir diphosphate were achieved within 1 week of dosing in all blood analytes including PBMCs, which was earlier than predicted based on previous pharmacokinetic studies in HIV-seropositive individuals. Tissue drug concentrations were higher in colon than in vaginal tissue in almost all cases and were generally higher with increasing doses per week. However, dose proportionality was demonstrated only for PBMC tenofovir diphosphate and these findings were inconsistent, with variability by visit week. Steady-state plasma tenofovir concentrations from daily dosing in HPTN 066 were consistent with concentrations reported in trials with high PrEP efficacy and higher than concentrations observed in trials demonstrating moderate or no efficacy. These results suggest that data from smaller pharmacokinetic studies can be used as a benchmark for interpreting drug concentrations and PrEP outcomes in larger efficacy trials.

Similar to the VOICE trial, the FEM-PrEP (Preexposure Prophylaxis Trial for HIV Prevention among African Women) did not demonstrate efficacy of emtricitabine plus tenofovir PrEP among African women, attributable in part to low study product adherence. Corneli and colleagues presented qualitative and quantitative data from a follow-up study with...
As resistance testing using standard consensus sequencing can only detect resistance at frequencies above 20%, Lehman and colleagues utilized 454 ultradeep sequencing to detect resistance at frequencies as low as 1% in the Partners PrEP study (Abstract 590LB). Among 121 seroconverters tested, 9 (7.4%) had PrEP-related resistance mutations (K65R, K70E, or M184I/V) detected above 1%, only 2 of which had previously been detected using standard sequencing. Resistance was detected in virus in 3 of 12 (25%) individuals acutely infected at enrollment and randomized to receive active product, and in virus in 4 of 51 (8%) participants in the active arms who became infected after enrollment. Virus in 2 of 58 (3%) placebo arm participants had evidence of M184I/V resistance. Resistance was highest (5 of 25 [20%]) among seroconverters in the emtricitabine plus tenofovir arm (4 M184I/V, 1 M184I/V/K65R). In the tenofovir arm, virus in 2 of 38 (5.3%) participants had resistance detected (1 K65R/K70E, 1 M184I/V). The detection of a PrEP drug in plasma was associated with an increased risk of resistance. Although overall selection of resistance was rare, this finding suggests that acquired resistance was more likely to occur in the presence of PrEP exposure.

Several posters described early PrEP implementation efforts in demonstration projects and open-label studies to evaluate PrEP uptake and delivery in the United States and in resource-limited settings. Cohen and colleagues described high levels of uptake among a diverse population of MSM offered PrEP in STI clinics and a community health center in 3 US cities (Abstract 954). Overall PrEP uptake was 60% among potentially eligible individuals and was associated with study site (higher in Miami, Florida, and Washington, DC, than in San Francisco, California), having prior PrEP awareness, being self-referred to the PrEP project, and reporting higher-risk sexual behaviors at baseline. Tenofovir diphosphate levels in dried blood spots were tested at week 4 and were detected in 98% of samples, with most participants (77%) having a tenofovir diphosphate level consistent with taking at least 4 doses a week. Relatively few transgender women and young MSM of color were assessed for participation and enrolled in the program, highlighting the need for strategies to increase community awareness and engage these populations in PrEP programs.

Hosek and colleagues presented data on PrEP uptake and adherence in the iPrEx OLE (Pre-Exposure Prophylaxis Initiative Open Label Extension) among young MSM in the United States who were previously in a randomized pilot study of PrEP feasibility and acceptability (Abstract 951). Approximately two-thirds of eligible young MSM enrolled in iPrEx OLE, and of those, 70% chose to take PrEP. Tenofovir detection in plasma increased from 45% during the randomized phase to 58% in iPrEx OLE. Participants reported numerous social benefits from study participation, and the majority (70%) expressed interest in future use of PrEP if available.

Mayer and colleagues described prevalence and correlates of PrEP use among an online sample of 9179 US MSM using a networking site for seeking a sex partner (Abstract 952). Only 1.2% reported PrEP use. Having a college education, reporting a prior STI, being comfortable talking with their practitioner about sex, and previous use of PEP were associated with prior PrEP use. These results highlight the need for educating health care practitioners on providing culturally competent care and facilitating discussions about sexual health and the potential role of PrEP in reducing HIV risk.

In a symposium on PrEP (Session S3), Mugo presented insights into implementing PrEP in resource-limited settings (Abstract 62). Currently, access to PrEP is limited to demonstration projects in these regions. Demonstration projects can help determine priority populations for PrEP, identify optimal delivery systems, and help evaluate cost-effectiveness and overall public health impact. Mugo pointed to a number of PrEP demonstration projects being planned in resource-limited settings; however, only 1 of these projects is currently under way.
She, along with Heffron and colleagues, presented preliminary findings from the Partners Demonstration Project in HIV-serodiscordant couples in Kenya and Uganda (Abstract 949). In this study, PrEP is used as a bridge to antiretroviral treatment use and is offered to couples in whom the HIV-infected partner declines, delays, or is not eligible for antiretroviral treatment; PrEP discontinuation is recommended after 6 months of antiretroviral treatment when viral suppression is achieved. PrEP uptake was 95% among HIV-seronegative partners at enrollment, and antiretroviral treatment was initiated in 75% of eligible HIV-infected partners. The majority of couples were willing to stop PrEP 6 months after their partner initiated antiretroviral treatment. Although demonstration projects will provide important insights into PrEP implementation, Mugo highlighted the need to expand PrEP access beyond these projects to achieve maximal public health impact.

Also in Session S3, Glidden presented strategies for prioritizing PrEP to have the maximal public health impact (Abstract 64). He described 2 epidemiologic constructs, the number needed to treat (NNT) and population attributable fraction (PAF), to identify populations who may benefit the most from PrEP. The NNT indicates the number of MSM and transgender women who would need to take PrEP for 1 year to prevent 1 HIV infection and is particularly useful for practitioners deciding on whether to initiate PrEP in a patient. At a population level, PAF can be used to identify subpopulations accounting for the largest proportion of new infections and thereby guide programmatic decisions on how to roll out PrEP to maximize population level impact. These 2 variables are plotted against each other in Figure 1: desirable targeting strategies include subpopulations with high PAF and low NNT (lower right quadrant), whereas those less desirable include subpopulations with low PAF but high NNT (upper left quadrant).

As seen in a secondary analysis of data from the iPrEx trial, self-reported receptive anal sex without a condom had the highest PAF and one of the lowest NNT. NNT was also low for MSM and transgender women reporting cocaine use or an STI. In this study population, having a single HIV-seropositive partner accounted for only 2% of new infections; prioritizing serodiscordant MSM couples without including those contributing to the largest number of infections reduces overall population impact. These results suggest that prioritizing PrEP for MSM and transgender women who report condomless receptive anal sex could help achieve maximal impact of PrEP. Unfortunately, among young women in sub-Saharan Africa, risk factors associated with a high PAF (being young and unmarried) were associated with low adherence, and therefore a high NNT. Strategies are needed to improve efficacy of PrEP and other prevention strategies among this very vulnerable population of young women.

Long-Acting Antiretroviral Agents and Microbicides

Given the crucial relationship between PrEP adherence and efficacy, several presentations focused on evaluating long-acting systems for delivering PrEP agents to overcome adherence challenges with daily dosing. Andrew and colleagues presented follow-up data on GSK744LA, a long-acting injectable nanosuspension previously shown to be effective against low-dose intrarectal SHIV challenge in rhesus macaques (Abstract 39). In this study, a single intramuscular (IM) injection of GSK744LA given 1 week prior to first virus exposure protected 12 of 12 macaques for at least 5 weekly challenges and delayed infection by 5 to 10 challenges compared with 12 controls (all of which became infected within 8 weeks). GSK744 plasma concentrations of greater than 3x protein-adjusted IC$_{90}$ (PAIC$_{90}$)
resulted in 100% protection and greater than or equal to 1x PASTD, resulted in 97% protection; these levels can be readily achieved in humans with quarterly 800 mg IM injections. These data support moving GSK744LA forward into phase II PrEP clinical trials that will launch later this year.

Garcia-Lerma and colleagues presented data on the prophylactic efficacy of GSK744LA against vaginal infection in female pigtail macaques (Abstract 40LB). Pigtail macaques have menstrual cycles similar to women and can become infected with doses of SHIV that more closely mimic those that occur in HIV acquisition. None of the 6 animals treated with 3 monthly GSK744LA injections became infected during twice-weekly, low-dose vaginal challenges or 16 weeks after the last viral challenge, whereas all 6 controls became infected. Plasma drug concentrations in macaques were within the range reported in humans receiving GSK744LA 800 mg IM, but vaginal drug concentrations were four- to fivefold lower than plasma, suggesting a contribution of systemic drug to the observed protection. In a related poster, Andrews and colleagues evaluated the efficacy of GSK744LA in protecting macaques against high-dose intravaginal challenge (Abstract 941LB). Macaques were treated with DMPA to simulate the menstrual cycle and thin the cervicovaginal epithelium. Although all 4 control animals became infected after a single high-dose SHIV challenge, 6 of 8 macaques treated with 2 monthly doses of GSK744LA were protected against 3 virus challenges at weeks 1, 5, and 7. Drug concentrations in the 2 treated animals that became infected had fallen below 4x and 1x PAIIC50, respectively, at the time of first virus detection. Together, these results support further clinical investigation of GSK744LA as PrEP in women at risk for HIV acquisition.

Vaginal rings are also promising candidates for providing sustained delivery of antiretroviral-based microbicides. Chen and colleagues presented data from a phase I study on the safety, pharmacokinetics, and pharmacodynamics of vaginal rings containing dapivirine and maraviroc, either alone or in combination, compared with placebo (Abstract 41). Dapivirine, a potent NNRTI, is currently in phase 3 trials for HIV prevention in women, and maraviroc, an antagonist to CC chemokine receptor 5 (CCR5), has been approved for HIV treatment but has not been previously evaluated for intravaginal use. In this trial of 48 HIV-seronegative, sexually abstinent women in the United States, all vaginal rings were found to be safe and well tolerated after 1 month of use. Dapivirine levels were detectable in all compartments and were substantially higher in vaginal fluid and cervical tissue than in plasma. In contrast, maraviroc was detected at lower levels in vaginal fluid and was undetectable in plasma and most cervical tissue samples. In an explant model, dapivirine concentrations in fresh cervical tissue correlated with protection against HIV replication, whereas tissue levels of maraviroc were too low to show protection. These results support the delivery of NNRTIs via vaginal rings for HIV prevention.

There has been growing interest in delivering topical microbicides as films, which are inexpensive, scalable, and more discreet, portable, and easier to store than gels. Film formulations also do not require an applicator and minimize drug leakage after use, and their small volume may decrease dilution of innate immune defenses in vaginal fluid compared with gels. Bunge and colleagues presented results from a phase I trial to assess the safety, pharmacokinetics, and pharmacodynamics of gel and film formulations of dapivirine in 60 HIV-seronegative women (Abstract 42LB). Participants were randomized to 7-day use of 1 of 4 study products: dapivirine gel, placebo gel, dapivirine film, or placebo film. The dapivirine gel was found to be safe, with no difference in genitourinary adverse events between arms. Five of 29 women in the film arms were noted to have visible film on the external genitalia at the time of genital biopsy, indicating poor film placement. Comparable dapivirine plasma levels were achieved in the film and gel arms; however, tissue concentrations were higher in the gel users than the film users, possibly due to residual drug adhering to the tissue surface. Importantly, tissue drug concentrations in cervical and vaginal tissues after dapivirine film use were comparable to tissue levels observed after 1 month of intravaginal ring use. Both the dapivirine gel and film were protective against ex vivo HIV-1 challenge in vaginal tissue. This first-in-human trial of dapivirine film provides proof of concept that quick-dissolving films can effectively deliver antiretroviral drugs to genital tissues; the size and shape of the film have been modified to address film placement issues.

**Postexposure Prophylaxis**

Postexposure prophylaxis (PEP), that is, a 28-day course of antiretroviral medication started as soon as possible within 72 hours of high-risk exposure, is recommended after occupational and nonoccupational exposures to HIV. Several posters presented new data on PEP at this year’s conference, focusing on evaluating new PEP agents, use of PEP after infected blood transfusion, and strategies to facilitate PEP completion.

Fatkenheuer and colleagues presented data from an open-label, randomized, noninferiority trial comparing ritonavir-boosted (r) darunavir with standard-of-care (SOC) PEP (mainly lopinavir/r) following high-risk HIV exposure in Germany (Abstract 948). For the 312 patients enrolled, the median time to PEP initiation after exposure was 2.5 hours for occupational exposures (22% of cases) and 14 hours for nonoccupational exposures (78% of cases). Early PEP discontinuation occurred in 6.5% of patients in the darunavir/r arm and 11.3% in the SOC arm. Both regimens were well tolerated, with fewer gastrointestinal adverse drug reactions in the darunavir/r group (21 vs 49, respectively; P = .0007). No seroconversions were observed in either arm of the trial. The investigators concluded that darunavir/r-based PEP was noninferior to SOC PEP with lopinavir/r and can serve as an alternative PEP regimen.
Hajjar and colleagues reported a case of PEP preventing HIV transmission after a transfusion with HIV-infected blood (Abstract 960). A 12-year-old girl with sickle cell crisis inadvertently received 1 unit of packed red blood cells from an HIV-infected donor not on antiretroviral therapy (plasma HIV RNA level was 9740 copies/mL). One day after the transfusion, the recipient had a positive HIV ELISA and Western blot (with bands identical to the donor), but negative HIV DNA by polymerase chain reaction testing. The patient was started on tenofovir, emtricitabine, darunavir/r (subsequently switched to lopinavir/r), and raltegravir 22 hours after transfusion and continued antiretroviral treatment for 13 weeks. Longitudinal HIV RNA and DNA measurements by standard and highly sensitive assays remained negative during and 3 months after stopping antiretroviral treatment, and HIV-1–specific antibodies declined to undetectable levels 6 months after transfusion. Although this may be further evidence that treatment administered shortly after exposure can abort infection, the investigators caution that positive HIV serologies in recipients determined shortly after transfusion with HIV-infected blood may not represent true HIV infection.

Landovitz and colleagues presented results from a randomized controlled trial evaluating contingency management to improve PEP outcomes among stimulant-using MSM (Abstract 961). Participants were randomized to contingency management (with escalating voucher-based incentives) or a noncontingent control group. Contingency management participants were more likely to complete the PEP course than were controls (adjusted OR[aOR], 7.2; 95% CI, 1.1–47.9). There was a trend toward increased self-reported medication adherence in the contingency management group (aOR, 4.3; 95% CI, 0.8–21.9). Contingency management participants were also more likely to have stimulant-free urine samples than were controls (incidence rate ratio [IRR], 1.57; 95% CI, 1.22–2.22), and there was a trend toward fewer episodes of condomless anal sex in the contingency management group (IRR, 0.34; 95% CI, 0.11–1.08). These findings suggest that contingency management may be a useful strategy to support PEP and potentially other biomedical prevention strategies among stimulant-using MSM.

**Treatment as Prevention**

Phillips presented data suggesting that despite high rates of diagnosis and viral suppression among MSM in the United Kingdom, HIV infections have been rising in number since the late 2000s (Abstract 116). He pointed to numerous modeling studies that suggest that increased HIV testing and treatment should lead to overall reductions in HIV incidence. To evaluate potential explanations for increased HIV infections in the United Kingdom, Phillips created a model that was fit to what is known about the natural history of HIV and the effect of antiretroviral treatment on transmission rates. Based on these models, Phillips suggests that this increased HIV incidence is due to increases in condomless sex. He suggests that testing and immediate treatment could substantially reduce transmission rates in future but that adherence and retention on antiretroviral therapy and rates of condomless sex will determine the extent of that reduction. He projects that approximately 90% of HIV-infected persons would need to be virally suppressed to reduce HIV incidence to less than 0.1 per 100 person-years. This would require that approximately 90% of HIV-infected persons be diagnosed within 1 year of infection (although the current estimate is less than 50%); linkage, adherence, and retention remain high; antiretroviral treatment be initiated immediately upon diagnosis; and levels of condomless sex increase no further.

**Medical Male Circumcision**

Although voluntary medical male circumcision has been shown to reduce the risk of HIV acquisition among HIV uninfected men, the rate of HIV transmission to female partners was increased when HIV-infected men resumed sexual intercourse prior to wound healing after circumcision. Toblan and colleagues evaluated the time course of HIV shedding postcircumcision among HIV-infected men in Rakai, Uganda (Abstract 966). HIV shedding was detected in 11% of men prior to circumcision but in 60% of men during surgery after foreskin removal. Compared with precircumcision levels, the probability of HIV shedding was increased from week 1 to week 3, declining to baseline levels by week 4. This identifies a period of increased risk postcircumcision for female partners. The importance of condom use during this 4-week period should be emphasized for HIV-infected men and their sex partners.

**Financial affiliations in the past 12 months:** Dr Buchbinder has been a consultant for Clinical Care Options. Dr Liu has been a consultant for Clinical Care Options.

**A list of all cited abstracts appears on pages 632-638 of this issue. Abstracts are published in Top Antivir Med. 2014;22(e-1):1-570, a special online issue available at www.iasusa.org/pub.**

**Additional References**


CROI 2014: Neurologic Complications of HIV Infection

Serena S. Spudich, MD

A shift in focus in the field of neuroHIV was clearly manifest at the 2014 Conference on Retroviruses and Opportunistic Infections (CROI), where a major emphasis was on the milder forms of neurologic morbidity, including cognitive impairment, seen in well-treated patients. Mechanisms of this persistent abnormality were investigated, including extensive analysis of the prevalence and associations of persistent HIV detection in cerebrospinal fluid (CSF) and characterization of persistent CNS immune activation. Another key emphasis was the early establishment of HIV replication and inflammation within the central nervous system (CNS) and the potentially salutary effect of very early HIV diagnosis and treatment in protecting the CNS from HIV-related injury. Mitochondrial function was identified as a potential mediator of a number of aspects of HIV-associated CNS dysfunction, including neurotoxicity associated with efavirenz, host genetic determinants of HIV-associated neurocognitive disorders (HAND), associations with direct measures of mitochondria in CSF, and metabolomic screening of CSF in HIV-infected subjects and those with HAND. Many studies employed laboratory rather than neuropsychologic end points, with a major focus on CSF biomarkers. Overall, neuroHIV presentations at CROI 2014 provided new insights into pathogenesis and treatment of the CNS, raising new challenges for researchers and practitioners aiming to optimize the status of the brain in people living with HIV infection.

Keywords: biomarker, central nervous system, CROI 2014, dementia, HAND, HIV, HIV-associated neurocognitive disorder, neuroimaging, neurology, neuropathy, viral escape

Mechanisms of Persistent CNS Injury on Antiretroviral Therapy

As highlighted in a plenary talk on neuroHIV (Abstract 66), a major theme of the scientific presentations at the 2014 Conference on Retroviruses and Opportunistic Infections (CROI), held March 3 to 6, 2014, was the characterization and investigation of central nervous system (CNS) perturbation during antiretroviral therapy. A number of lines of evidence suggest that the CNS may exhibit persistent abnormalities in patients on antiretroviral therapy. For example, several studies report neuropsychologic testing performance in an impaired range in a higher proportion of HIV-infected persons on antiretroviral therapy than uninfected persons, with the proportions of impaired subjects in distinct studies ranging from 18% to 80% depending on the demographics of the subject populations and the uninfected control groups employed for comparison. Additionally, brain imaging and cerebrospinal fluid (CSF) biomarkers suggest neuronal injury in a proportion of treated patients. Notably, in these investigations, many study volunteers with HIV infection manifest neuropsychologic performance, imaging, and CSF markers that are within the normal range, suggesting that not all patients with HIV infection are living with CNS injury. However, research is needed to explain, and address, the CNS injury detected in some individuals who appear to be optimally treated for HIV infection with antiretroviral therapy.

CSF HIV Escape or CSF/Plasma HIV Discordance in Patients on Antiretroviral Therapy

A variety of factors may underlie detection of abnormality in the CNS in some patients treated with antiretroviral therapy. One possibility is that viral replication may not be completely suppressed by antiretroviral therapy within the CNS compartment, or that HIV persistence within cells of the CNS contributes to intermittent release of virus and thus a cascade of events in the CNS that allows for ongoing damage despite antiretroviral therapy. Despite early findings that the CNS responds very favorably to antiretroviral therapy, as reflected by dramatic improvement of signs and symptoms of severe dementia in many patients and typical reduction of CSF HIV RNA levels, recent evidence suggests that with more sensitive testing, the CNS may be a site of continued viral release or replication in some patients even when the periphery is controlled. Detection of HIV in the CSF despite antiretroviral therapy that successfully suppresses plasma HIV RNA levels has been described in neurologically asymptomatic research subjects and neurologically symptomatic patients.

The phenomenon of CNS viral escape from antiretroviral therapy—defined in different studies as detectable CSF HIV RNA in the presence of undetectable plasma HIV RNA, a discordance of greater than 0.5 log10 copies/mL or more between CSF and plasma HIV RNA levels in fairly well-suppressed patients, or most strictly, greater than 50 copies/mL in CSF with less than 50 copies/mL in plasma—was described in numerous studies at CROI 2014 and was the focus of a themed discussion (Session 15). Nightingale

Dr Spudich is Associate Professor of Neurology at Yale University in New Haven, Connecticut. Send correspondence to Serena S. Spudich, MD, Yale University Department of Neurology, PO Box 208018, New Haven, CT 06520. Received on March 24, 2014; accepted on March 24, 2014.
and colleagues (Abstract 442) presented findings from the PARTITION (Penetration of Antiretroviral Therapy into the Nervous System) study in the United Kingdom. This study evaluated subjects with signs or symptoms of possible neurologic disease (typically headache or cognitive impairment) or with unexplained plasma HIV RNA levels greater than 50 copies/mL to assess whether either of these phenomena might associate with CSF/plasma discordance. In their study, discordance—defined as CSF HIV RNA levels more than 0.5 log₁₀ copies/mL higher than plasma levels—was found in 13.1% of 145 subjects and associated with longer duration of HIV infection and lower nadir CD4⁺ cell count. Low-level detection of HIV RNA in CSF was more frequent in subjects with blood plasma residual viremia (detectable HIV RNA levels between 10 copies/mL and 49 copies/mL), though whether CSF HIV is a consequence or cause of residual viremia in the plasma is unclear.

Importantly, despite low median CSF HIV RNA levels in the discordant subjects, CSF from the 4 subjects who underwent HIV genotyping demonstrated resistance mutations, including subjects with levels of only 138 copies/mL and 162 copies/mL in CSF, suggesting that these may have been biologically relevant levels of CSF viral escape from antiretroviral therapy. Pinnetti and colleagues (Abstract 445) examined 75 subjects in a longitudinal cohort who had plasma HIV RNA levels less than 50 copies/mL at enrollment. Of these subjects, 23% had CSF HIV RNA levels greater than 50 copies/mL detected during at least 1 study visit. Only 3% had CSF viral escape by this definition in consecutive samples, perhaps indicating persistent replication within the CNS versus intermittent detection of HIV in this compartment, possibly equivalent to a plasma “blip.” Although CSF neopterin, a pteridine marker of intrathecal immune activation, was higher in the subjects with detectable versus undetectable CSF HIV RNA, a biomarker of active neuronal injury, CSF neopterin was not different between these 2 groups. These findings suggest that viral detection and immune activation in the CNS during antiretroviral therapy are linked, CNS persistence, at least by this measure, may not be a cause of neuronal injury detected during antiretroviral therapy.

Overall, the clinical and biologic significance of asymptomatic CSF viral escape or discordance remains unclear. Hammond and colleagues (Abstract 33) presented an analysis of CSF and mood data from the CHARTER (CNS HIV Anti-Retroviral Therapy Effects Research) study to examine whether signs or symptoms of depression may associate with detectable CSF HIV RNA in treated subjects. Subjects were included in the current analysis if they did not have depression at baseline and also had a number of CSF samples available. Using the Beck Depression Inventory to assess mood and a cutoff of 17 points or greater on this evaluation as a marker of moderate to severe depression, these investigators found that 14.4% had CSF HIV RNA levels greater than 50 copies/mL at the baseline visit. Participants with a detectable CSF HIV RNA at any visit had a 4.7x greater risk than those with consistently undetectable CSF HIV RNA for developing new onset of moderate to severe depression during the course of the study. Although cause and effect cannot be clearly established in this study, which may be affected by potential effects of variable adherence and other issues, these findings are provocative in suggesting that depression in HIV-infected persons may have a neuroinflammatory or virologic basis and that CSF viral escape may have clinical consequences.

**Persistent CNS Immune Activation During Antiretroviral Therapy**

Viral persistence may be related to or independent from smoldering, low-grade immune activation detected within the CNS during antiretroviral therapy in some patients.⁷,⁸ This immune activation, considered the substrate of HIV-associated neurocognitive disorder (HAND), may thus perpetuate progressive neuronal injury despite treatment. Several presentations at this year’s CROI explored the nature of and mechanisms underlying persistent immune activation on antiretroviral therapy. Abstract 445, as noted, confirmed prior findings that low-level CSF HIV RNA in the setting of antiretroviral therapy associates with CSF neopterin.

Eden and colleagues (Abstract 490) presented a separate study of 100 subjects with plasma viral suppression on antiretroviral therapy identified through the multisite CHARTER study and the HIV Neurobehavioral Research Center in San Diego, California. CSF markers, including CSF neopterin and CSF NFL, were compared between subjects classified as neuropsychologically normal (NPN) and those identified as having neuropsychologic impairment—either asymptomatic neurocognitive impairment or mild neurocognitive disorder. CSF neopterin was associated with impairment, with median levels in the impaired group (7.3 nmol/L) statistically significantly elevated compared with median levels in the NPN group, and higher than the upper limit of normal reference value (5.8 nmol/L). This is one of the first studies to correlate persistent immune activation with neuropsychologic outcomes, suggesting that inflammation may indeed produce neurologic damage and measurable reduction in...
Potentially novel biomarkers of immune activation, which may reveal information about not only viral persistence but mechanisms of ongoing inflammation, was another topic of presentation at CROI 2014. Perez-Santiago and colleagues (Abstract 446) presented a study of cell-free mitochondrial DNA (mtDNA) in CSF, measured by droplet digital polymerase chain reaction (PCR), from 28 HIV-infected individuals. These investigators found that in individuals with impairment, higher levels of mtDNA were associated with neurocognitive impairment and levels of inflammation. These investigators also demonstrated that mtDNA rose after treatment interruption in the CSF prior to increases in CSF white blood cell count, supporting the concept that mtDNA detected in CSF is not simply a proxy for pleocytosis in HIV infection. These investigators posit that mtDNA detected in the CSF in HIV-infected individuals might reflect the breakdown of neurons or might potentiate inflammation within the CNS during HIV infection.

Another potentially novel biomarker was presented by Vera and colleagues (Abstract 486LB), who demonstrated abnormal levels of brain uptake of \(^{[11C]}\text{PBR28}\), a radioligand that recognizes a receptor for a translocator protein expressed on microglia, in 12 asymptomatic HIV-infected subjects on suppressive antiretroviral therapy versus 10 -uninfected controls. Greater volume of distribution \((V_t)\) of the radioligand, interpreted as a measure of microglial activation, associated with plasma HIV RNA levels prior to antiretroviral therapy and inversely associated with performance in specific neuropsychologic domains. Longitudinal follow-up of subjects assessed with this positron emission tomography imaging marker should reveal whether elevated \(^{[11C]}\text{PBR28} V_t\) observed in HIV-infected subjects has a predictive value in the development of neurocognitive impairment.

**Vascular Pathology, Aging, and CNS Injury in HIV Infection**

Excess cardiovascular disease has been noted in well-treated HIV-infected patients, leading investigators in the field of neuroHIV to explore whether vascular pathology, likely related to chronic low-grade systemic immune activation, may be a new mechanism underlying neurologic injury in the antiretroviral therapy era that is largely distinct from the classic mechanisms of HIV pathogenesis seen in the pre–antiretroviral therapy era. Several prior studies found markers of vascular disease or classic vascular risk factors to be greater predictors of HAND in subjects treated with antiretroviral therapy than HIV disease factors or even HIV se-rostatus.\(^9,10\) Other recent research has highlighted an increased risk of overt ischemic stroke in persons with HIV infection, perhaps disproportionately affecting young people and women.\(^11,12\)

Soontornniyomkij and colleagues (Abstract 35) examined the relationship between cerebral small vessel disease and HAND in subjects treated with antiretroviral therapy. These investigators examined brain tissue specimens from 144 deceased, mostly male, chronically HIV-infected tissue donors for research purposes. Most subjects had neuropsychologic testing prior to death, and 44% had been on what was considered combination antiretroviral therapy prior to death. Cerebral small vessel disease was assessed in white matter brain tissue and defined on histopathology as absent, mild (reflecting partial-thickness involvement of vessel walls), or moderate to severe (full-thickness involvement). Histopathology evidence of mild cerebral small vessel disease was associated with diagnosis of HAND during life. Mild and moderate to severe cerebral small vessel disease was associated with protease inhibitor (PI)-based combination antiretroviral therapy prior to death. These findings are compelling in that they suggest that cognitive impairment seen in HIV-infected subjects may be directly associated with vascular disease in the era of antiretroviral therapy and, further, that PI treatment may contribute to the presence of this vascular disease independent of the effects of classic risk factors such as diabetes and hypertension.
Urday and colleagues (Abstract 463) presented data from a small study investigating correlations between neuropsychologic testing performance and vascular measures during primary HIV infection. In 15 subjects enrolled at a median of 3 months postinfection, associations were examined between neuropsychologic testing performance and vascular measures available from corresponding time points, including brachial artery flow-mediated dilation, carotid intima-media thickness, and a putative blood biomarker of endothelial dysfunction, asymmetric dimethylarginine (ADMA). In this pilot study, higher ADMA levels tended to correlate with poorer neuropsychologic performance, a novel finding that might suggest a role of this inhibitor of nitric oxide synthase in HAND, either through vascular damage or loss of neuroprotection. Carotid intima-media thickness, considered a marker of vascular pathology, correlated with better performance on neuropsychologic testing in this study, contrary to the relationship observed in prior studies in chronic HIV infection. These findings warrant further evaluation in a larger group of subjects.

Several studies investigated the status of the CNS in aging HIV-infected populations on stable antiretroviral therapy. Magnus and colleagues (Abstract 449) employed functional magnetic resonance imaging (MRI) to assess the effects of suppressive antiretroviral therapy on brain structure and function among HIV-infected subjects aged 50 years and older. These investigators measured cerebral white matter volumes and brain activity in response to a task switch in 10 HIV-infected individuals, comparing these with measures in 5 age-matched -uninfected controls. In the HIV-infected subjects, although neuropsychologic testing performance was only mildly impaired, white matter brain volume was reduced, and task switching led to increased brain activity detected on functional MRI, implying that a greater impact was associated with the task switch in these subjects. Additionally, HIV-infected subjects demonstrated a higher number of detectable responses to irrelevant stimuli, interpreted as decreased inhibition in these networks. These findings confirm prior reports that functional MRI is a sensitive marker that may reveal pathology and also potential pathways of subtle neurologic injury in antiretroviral therapy– suppressed subjects with HIV infection.

Nowak and colleagues (Abstract 450) longitudinally assessed cortical brain volumes using structural MRI imaging in a group of 18 subjects with a baseline median age of 48.4 years, demonstrating statistically significant atrophy over a 1-year period in patients on stable antiretroviral therapy. Although no HIV-infected control subjects were available for comparison of cortical atrophy over this period, a strong correlation between nadir CD4+ cell count and cortical atrophy in numerous brain regions suggests that prior immunologic injury may be a determinant of subsequent atrophy in HIV-infected persons despite stabilization of virologic and immunologic parameters. Becker and colleagues (Abstract 448) also examined HIV- and age-related brain atrophy using structural MRI, comparing cross-sectional, whole-brain volumes in 186 HIV-infected and 142 -uninfected men enrolled at a median age of 57.5 years in MACS (Multicenter AIDS Cohort Study). In this study, HIV-infection and age were associated with reduced whole-brain volumes, though the effect of age was stronger than that of HIV serostatus. Importantly, no clear interaction was noted in whole-brain volumes between age and infection with HIV, implying that an accelerated aging phenotype was not revealed by this brain measure.

CSF hyperphosphorylated tau (p-tau) was examined as a potential biomarker for neurologic aging in subjects with HIV infection and comparison control subjects in a study by Krut and colleagues (Abstract 453). CSF p-tau, a neural marker used in the diagnosis of Alzheimer’s disease and other neurodegenerative dementias, is a microtubule-associated protein that serves to stabilize axons. These investigators examined p-tau levels across the age spectrum in 291 HIV-uninfected controls, 172 HIV-infected neuroasymptomatic subjects off antiretroviral therapy, 68 HIV-infected subjects on antiretroviral therapy with plasma HIV RNA levels less than 50 copies/mL, and 33 subjects with HIV-associated dementia. In the HIV-infected subjects, p-tau levels correlated statistically significantly with age only in those on suppressive antiretroviral therapy, perhaps suggesting that p-tau increases in untreated HIV-infected subjects are a consequence of neuropathologic mechanisms distinct from aging. Further examination of CSF p-tau as a possible predictive measure of neurologic status or HAND in HIV-infected individuals may reveal a utility for this biomarker in neurologic assessment in this population.

**CNS Consequences of Antiretroviral Therapy Exposure and Toxicity**

A key question in the field of neuro-HIV remains whether antiretroviral therapy exposure within the CNS contributes importantly to the abnormalities detected in HIV-infected subjects who appear to be successfully treated from a systemic standpoint. The concept that better versus poorer CNS penetration and effectiveness of antiretroviral medications might differentially impact the efficacy of treatment in the brain versus the periphery has been the subject of intensive scrutiny over the past 10 years.15,14 One new concern related to this fundamental issue is that although subjects on reduced-drug regimens designed to limit systemic toxicity, cost, and nonadherence associated with combination antiretroviral therapy may do well from a systemic virologic standpoint, it is possible that these regimens may not adequately suppress HIV in the CNS compartment. Stephan and colleagues (Abstract 473) studied 24 subjects on boosted, dual PI therapy and 131 subjects on classic triple-therapy regimens followed in the Frankfurt HIV Treatment Cohort. The median CSF HIV RNA level in the dual PI group was 600 copies/mL versus 50 copies/mL in the triple-therapy group. Although
a lower proportion of subjects in the dual PI group had plasma HIV RNA levels less than 50 copies/mL, the CSF-to-plasma HIV RNA ratios were higher in the dual PI group. Furthermore, HIV RNA increased in CSF over time in the dual PI group, raising the question of whether dual PI therapy may allow for progressive viral escape in the CNS during long-term antiretroviral treatment.

To examine whether a regimen with presumed better penetration and effectiveness in the CNS may have beneficial effects in the CNS, Tiraboschi and colleagues (Abstract 492) assessed 12 subjects with plasma HIV RNA levels less than 40 copies/mL (median suppression duration, 6.5 years) and neurocognitive impairment for baseline CSF measures while on tenofovir, emtricitabine, and efavirenz, and 9 of these subjects after a change to abacavir, lamivudine, and maraviroc. CSF parameters included HIV RNA measured using an assay with a lower limit of detection of 2.5 copies/mL and inflammatory and neural biomarkers including neopterin, TNF-α, monocyte chemoattractant protein (MCP)-1, and total tau. CSF HIV RNA on this highly sensitive assay was noted to decline after a switch in antiretroviral regimens in subjects with detectable levels of HIV RNA, though the difference was not statistically significant. Of the inflammatory and neural markers, the change in regimens was associated with a modest, nonstatistically significant decline in CSF neopterin and reduced levels of CSF TNF-α. Whether these findings are associated with reduced neurotoxicity or improved efficacy of these antiretroviral regimens within the CNS is unclear, but these preliminary findings suggest the need for further close examination of CNS end points in switch studies of patients on distinct antiretroviral regimens.

The possibility that certain antiretroviral medications may be toxic to the brain has been a subject of concern since the advent of antiretroviral treatments. Although the consensus of experts in the field is that given current data, the benefits of suppressive antiretroviral therapy in the CNS far outweigh possible risks, evidence has emerged in recent years that certain antiretroviral therapies may cause neurologic morbidity in some individuals. As noted above, Abstract 35 suggests that PI therapy may be associated with increased vascular pathology that in turn correlates with presence of neurologic impairment in HIV-infected persons.

The HIV nonnucleoside reverse transcriptase inhibitor (NNRTI) efavirenz has also been recognized as being associated with neurologic impairment that may lead to intolerable adverse effects in some individuals. The mechanisms behind efavirenz-related neurotoxicity are poorly understood. Funes and colleagues (Abstract 454) performed a study investigating whether interference with mitochondrial function, thought to mediate efavirenz-associated cellular toxicity in liver cells, may also underlie neuronal dysfunction in the setting of efavirenz. Their in vitro experiments assessing the effects of efavirenz on glial cells and neurons derived from human cell lines indicate that cellular oxygen consumption, cell viability, and intracellular adenosine triphosphate (ATP) production were reduced in the presence of efavirenz and that these effects were more profound in neurons than in astrocytes. Primary cultures of rat neurons also showed decreased ATP production and overall cell number if treated with efavirenz. These investigators conclude that because of the efavirenz-mediated effects noted on cell bioenergetic pathways, mitochondrial inhibition may be a key aspect of CNS toxicity due to efavirenz and that selectively more profound effects may be noted in neurons than in glial cells in the brain.

Potential Significance of Early HIV Infection and Treatment to CNS Injury

Abnormalities detected in persons on suppressive antiretroviral therapy who were started on treatment during chronic HIV infection may reflect processes such as viral persistence, ongoing low-level inflammation, progressive vascular disease, and other active processes. However, an alternate or additional possibility is that some damage was accrued in the nervous system prior to the start of HIV treatment that was incompletely reversed by antiretroviral therapy. Studies have indicated that HIV invades the nervous system in the first weeks of infection, accompanied by immune activation that likely establishes a substrate for local CNS infection and pathogenesis. However, only limited studies have examined whether local replication in the CNS may exist during the first years after infection.

Sturdevant and colleagues (Abstract 32) examined paired CSF and plasma samples from 72 subjects with primary HIV infection in the PISCES (Primary Infection CNS Events Study) cohort recruited at a median of 3.5 months after infection and longitudinally followed up for as long as 2 years. Using single-genome amplification of the envelope (env) gene, they identified distinct patterns of phylogenetic relationships between the CNS compartment and the blood and found evidence of viral compartmentalization based on sequences in 12% of subjects. In serial sampling, they found that viral compartmentalization or marked pleocytosis suggestive of ongoing replication was maintained over time in 20% of subjects, and diversification of CSF variants was also observed over time, indicating viral evolution locally within the CNS in the first 2 years of HIV infection. These locally evolving CNS HIV variants, as well as all plasma and CSF env, when analyzed with an affinofile cell entry assay, appeared adapted to replicate in cells with high CD4 receptor density, suggestive of T lymphocytes. These data suggest that even within the first 2 years of infection, HIV can establish an autonomous infection within the CNS compartment in some HIV-infected individuals.

Another study of subjects from the PISCES cohort examined the effect of antiretroviral therapy initiated in the first year after HIV infection on CSF and blood biomarkers associated with CNS disease in HIV infection. Peterson and colleagues (Abstract 30) studied
26 men enrolled in an observational study at a median of 4.5 months after initial HIV exposure who subsequently started combination antiretroviral therapy for reasons outside of the protocol at a median of approximately 8 months after infection. Laboratory biomarkers were assessed pretreatment and 6 months to 12 months (median 9 months) posttreatment. Improvements were noted in all biomarkers of intrathecal immune activation, including CSF neopterin, and infection. Importantly, all CSF measures, including CSF neopterin, normalized in comparison with an age-matched control group of 20 HIV-uninfected people, and in contrast to findings of persistently elevated CSF immune activation markers in subjects starting treatment during chronic infection. These findings suggest that early identification of HIV infection and prompt initiation of antiretroviral therapy may prevent or reduce signs of intrathecal immune activation, the pathologic substrate of HAND, to normal levels.

In a related study, Peluso and colleagues (Abstract 31) examined the effect of immediate antiretroviral treatment during acute infection on NFL, the protein product released during degeneration of myelinated axons that has been examined as a marker of active neuronal injury in neurodegenerative dementias and HIV infection. In Bangkok, Thailand, 32 subjects with acute HIV infection (median 18 days postinfection) and 33 subjects with chronic HIV infection had initial blood and CSF sampling at enrollment, prior to antiretroviral treatment. Although at this visit, HIV was detected in most subjects in blood and CSF, NFL was elevated above expected values for age in 10 of 33 chronic but only 1 of 32 acute subjects, suggesting that acute HIV infection is not typically characterized by neuronal injury. All subjects in both groups initiated immediate combination antiretroviral therapy. After 48 weeks of treatment in the chronic group, 5 of 10 subjects with samples available had elevated CSF NFL for age; only 1 of 26 in the acute group manifested this abnormality after 24 weeks. These findings thus imply that very early initiation of antiretroviral therapy may halt processes that facilitate development or persistence of neuronal injury in chronic infection on antiretroviral therapy.

Examining data from the same cohort in Bangkok, Thailand, Valcour and colleagues (Abstract 447) examined whether in those subjects with acute HIV infection, treatment with standard combination antiretroviral regimens of efavirenz, emtricitabine, and tenofovir versus standard regimens plus maraviroc and raltegravir had a differential effect on neurologic outcomes. Sixty-two subjects with a median duration of 17 days of HIV infection at enrollment were randomized to the 2 study arms. From baseline (pre–antiretroviral therapy) to 24-month follow-up, the subset of subjects with samples available had improvement in all CSF (total n = 16), neuropsychologic (total n = 62), and magnetic resonance spectroscopy (total n = 43) measures, with no difference in improvement by study arm. Although for some of these end points, sample size may not have been adequately powered at this stage of the study to detect differences between arms, these data so far suggest that no CNS benefit is conferred by intensification with a C-C chemokine receptor type 5 (CCR5) inhibitor and an integrase inhibitor during acute HIV infection.

Ndhlovu and colleagues (Abstract 444) described patterns in blood monocyte phenotype evident in 17 subjects with acute HIV infection in this same cohort in Bangkok, Thailand prior to antiretroviral therapy initiation. Detection of nonclassic monocytes (CD14+ CD16++) was statistically significantly higher in Fiebig I versus Fiebig III infection. As these investigators have previously found that HIV DNA burden in monocytes correlates with the presence of HAND in chronic HIV infection, it is likely that this early activation and dynamic alteration in monocyte phenotypes in subjects in the earliest stages of infection sets the stage for important aspects of the neuropathogenesis of HIV.

**Novel Alternative Mechanisms of HIV Neuropathogenesis**

Although HIV-related neurologic injury is associated with pathologic immune activation in the CNS that can be improved if not always ameliorated by antiretroviral therapy, many key aspects of the specific pathways and mechanisms of this damage are yet to be elucidated. Several presentations at CROI 2014 suggested alternate or novel mechanisms of HAND neuropathogenesis.

Kallianpur and colleagues (Abstract 458) examined whether brain iron deficiency, defined by increased RNA expression of the transferrin receptor, associated with neuropsychologic performance. In 274 donors from the National NeuroAIDS Tissue Consortium (NNTC) who were neuropsychologically evaluated within 6 months prior to death, RNA expression of the transferrin receptor was measured in brain autopsy tissue (frontal cortex). In this subject group with a very high rate of HAND diagnoses (85%), presence of milder and more severe forms of HAND and performance on specific neuropsychologic tests independently correlated with transferrin receptor RNA expression. Thus, iron transport or iron deficiency in the brain may relate to neurologic injury in HIV-infected persons.

In a related study, Kallianpur and colleagues (Abstract 489) examined the relationship between red blood cell (RBC) indices and presence of cognitive impairment in 1235 subjects from the CHARTER study. RBC count, mean cell volume, mean cell hemoglobin, and hemoglobin were each associated with measures of neuropsychologic performance or detection of impairment. As these cell indices may reflect iron status and are reduced in the presence of chronic inflammation, these results may directly implicate iron deficiency in the pathogenesis of HAND or, alternately, may demonstrate changes in iron status in concert with neurologic dysfunction through a common pathway of chronic inflammation.

Cassol and colleagues (Abstract 34) employed metabolite profiling, or
metabolomics, of CSF samples derived from 46 HIV-infected subjects enrolled in the NNTC or CHARTER studies and 54 -uninfected controls to identify metabolites associated with HIV infection. Of the 107 named metabolites identified, 15 metabolites distinguished HIV-infected subjects on antiretroviral therapy from -uninfected controls. Using pathway analysis, these 15 metabolites associated with alterations in pathways associated with neurotransmitter production, mitochondrial function, oxidative stress, and accumulation of metabolic waste. Interestingly, some of these altered metabolite pathways overlapped with pathways altered in aging HIV-uninfected subjects. Further, a more circumscribed set of metabolites associated with the presence of HAND, including markers of glial cell activation and systemic and intra-thecal markers of immune activation. Overall, this study approach yielded possible new mechanisms of pathogenesis in HAND, providing potential new biomarkers for investigation and targets for therapeutic strategies to ameliorate CNS injury in HIV infection.

In an investigation of a potential novel host determinant of HIV-related neurologic dysfunction, Hulgan and colleagues (Abstract 465) examined mtDNA haplotypes, patterns of single nucleotide polymorphisms in mtDNA associated with mitochondrial function in 1046 predominantly antiretroviral therapy–treated subjects enrolled in the CHARTER study. These mtDNA haplotypes were identified and distinct haplotypes were then correlated with the presence of neurocognitive impairment, assuming that differential rates of HAND may associate with distinct bioenergetics and oxidative stress related to the different haplotypes. One of the haplogroups identified, considered to be a Native American mtDNA haplogroup, was found in Hispanic participants to be associated with statistically significantly lower risk of neurocognitive impairment. This finding suggests that a potential genetic determinant for risk of HAND may be altered mitochondrial function, leading to altered neuro-immune activation or bioenergetics in the face of HIV infection.

Although host genetics likely plays a role in response to HIV infection, viral genetics, including within-compartment viral diversity and viral compartmentalization within the CNS, has been recognized as being associated with HAND. Wagner and colleagues (Abstract 471) used next generation sequencing (454 platform) of HIV-1 DNA derived from peripheral blood mononuclear cells to assess for dual HIV infection in 16 neurocognitively normal and 18 impaired HIV-infected subjects on antiretroviral therapy enrolled in the CHARTER study. Based on their criteria requiring divergent populations with bootstrap values of 90% or higher, 7 of 18 subjects with impairment versus only 1 of 16 neurocognitively normal subjects had dual HIV infection, suggesting a role for dual infection itself or very high within-compartment diversity in the pathogenesis of HAND. Evering and colleagues (Abstract 472) focused more specifically on differences between paired blood and CSF samples in subjects with chronic HIV infection in the CHARTER study. They used single genome amplification and sequencing of env to compare HIV variants in the blood and CSF of 15 subjects, identifying distinct patterns of compartmentalization across disease states. They then identified specific positions at which there were statistically distinct amino acids in the CSF versus blood to generate hot spots that might be more intensively examined in larger numbers of subjects as potential CSF compartmentalization–specific patterns or amino acids determining specific neurotropism or local viral evolution.

Conclusion
Neurologic presentations garnered a great deal of interest at CROI 2014, galvanized by the recognition that the CNS is likely still a site of perturbation in some HIV-infected persons despite successful antiretroviral therapy. An additional frontier of neuroHIV research is a focus on whether the CNS may serve as a reservoir of persistent and either latent or smoldering HIV infection that may be an impediment or consideration in some people in efforts to eradicate or cure HIV infection. A single small study by Rasmussen and colleagues (Abstract 482) assessing the effect of panobinostat, a potent histone deacetylase (HDAC)-inhibitor, on CSF markers is an initial step to examine the potential beneficial versus injurious effects of targeted cure strategies on the CNS. In 11 subjects treated with panobinostat who consented to lumbar puncture for CSF collection, no rise in CSF HIV RNA levels (measured using an assay with a limit of detection of 3.8 copies/mL) nor change in neuro-rural marker or immune activation levels was noted in the final dosing week after a round of 3 cycles of every other week panobinostat. These preliminary findings in a small number of subjects, though reassuring, provide evidence for the feasibility of CNS monitoring during such eradication approaches that should likely be considered in planning and implementing future cure studies.

Financial affiliations in the past 12 months: Dr Spudich has received travel support and honoraria from AbbVie, Inc.

A list of all cited abstracts appears on pages 632-638 of this issue. Abstracts are published in Top Antivir Med. 2014;22(e-1):1-570, a special online issue available at www.iasusa.org/pub.

Additional References


CROI 2014: Viral Hepatitis and Complications of HIV Disease and Antiretroviral Therapy

Anne F. Luetkemeyer, MD; Diane V. Havlir, MD; and Judith S. Currier, MD

The remarkable advances in interferon-sparing, all-oral hepatitis C virus (HCV) treatment were a highlight of the 2014 Conference on Retroviruses and Opportunistic Infections (CROI). The backbone of the nucleotide inhibitor sofosbuvir and the nonstructural protein 5A (NS5A) inhibitor ledipasvir with an additional third agent (HCV protease inhibitor or HCV nonnucleoside reverse transcriptase inhibitor) led to a sustained virologic response (SVR) rate 12 weeks after cessation of treatment of 95% to 100% after only 6 weeks of treatment. These results demonstrate the potential of combination direct-acting antiviral (DAA) therapy for abbreviated, well-tolerated, and highly effective HCV treatment. Two triple-drug regimens that comprised 12 weeks of an NS5A inhibitor, an HCV protease inhibitor, and a nonnucleoside inhibitor also resulted in SVRs of more than 90% in patients with HCV genotype 1. HCV coinfection does not appear to negatively impact response to DAA-based HCV therapy, as evidenced by similar response rates in HIV/HCV-coinfected patients compared with HCV-monoinfected patients receiving interferon-sparing or -containing regimens. There was continued emphasis at CROI 2014 on non-AIDS complications of HIV infection, specifically cardiovascular disease, renal insufficiency, and bone and endocrine disorders that persist among patients with treated HIV disease and contribute to morbidity and mortality. Finally, new data on novel drugs and combinations for treatment of tuberculosis (TB), patient outcomes using new rapid TB diagnostics, and a short-course TB prevention strategy were presented.

Keywords: CROI 2014, HIV, hepatitis C virus, HCV, direct-acting antivirals, antiretroviral therapy, coinfection, comorbidities, cardiovascular disease, bone, aging, Kaposi sarcoma, tuberculosis

Overview of Hepatitis C Virus Direct-Acting Antiviral Drugs: Present and Future

Dramatic advances in the treatment of hepatitis C virus (HCV) with short, well-tolerated, highly effective oral regimens were a highlight of the 2014 Conference on Retroviruses and Opportunistic Infections (CROI), held from March 3 to 6, 2014. A summary of the current classes of direct-acting antiviral (DAA) drugs and their sites of action during HCV replication are presented in Figure 1. Pawlotsky gave a comprehensive overview of DAAs and the anticipated pathways for use of all-oral DAA therapy in HCV infection (Abstract 60), highlighting 2 key summary points.

First, HIV/HCV-coinfected patients have demonstrated an excellent and generally equivalent response to DAA regimens. Thus, coinfected patients should no longer be expected to have a suboptimal response on the basis of HCV coinfection, as was the case in the pre-DAA, interferon-based treatment era. It will still be important to evaluate HCV regimens in coinfected patients to ensure that there are no adverse interactions between antiretroviral and DAA drugs, and to confirm that HIV is not negatively impacting response to novel HCV combinations. Second, Pawlotsky outlined 3 main pathways for use of all-oral DAA drugs, and to confirm that HIV is not negatively impacting response to novel HCV combinations.

Nucleos(t)ide Inhibitor-Based Regimens

The National Institutes of Health SYNERGY study evaluated a fixed-dose, once-daily combination of the nucleotide analogue NS5B polymerase inhibitor sofosbuvir and the investigational NS5A inhibitor ledipasvir in a US urban population with genotype 1 HCV infection (Abstract 27LB). Subjects were characterized by a high proportion of risk factors traditionally predictive of poor response to HCV treatment; 88% of subjects were African American, 70% had HCV genotype 1a, 70% had HCV RNA levels above 800,000 IU/mL, and 80% had less favorable IL28b non-CC genotypes. In arm A of the study, sofosbuvir and ledipasvir given for 12 weeks led to a sustained virologic response (SVR) rate 12 weeks after cessation of treatment (SVR12) of 100% (20 of 20). Arm A permitted subjects with cirrhosis (15% with Knodell fibrosis scores of 4), and arms B and C of the study excluded subjects with cirrhosis (15% with Knodell fibrosis scores of 4).
cirrhosis. In arm B, sofosbuvir and ledipasvir given with the nonnucleoside inhibitor GS-9669 for 6 weeks resulted in an SVR12 of 95% (19 of 20) with 1 subject relapsing at week 4 after therapy. In arm C, sofosbuvir and ledipasvir given with the HCV PI GS-9451 for 6 weeks resulted in an SVR12 of 100% (20 of 20). Treatment was generally well tolerated with the most common adverse effects being headache, fatigue, and diarrhea. There were no discontinuations or serious adverse events related to study medications. The 6-week regimens of sofosbuvir and ledipasvir used with either an HCV PI or a nonnucleoside inhibitor are currently being evaluated in subjects with cirrhosis, and a 4-week regimen is also being evaluated.

SYNERGY represents a remarkable step forward in HCV treatment, with near universal cure rates in a relatively hard-to-treat population using 6 weeks of all-oral, well-tolerated therapy that did not include interferon or ribavirin. These results raise the possibility of shortening HCV therapy even further (ie, 4 weeks), potentially with the addition of a fourth agent (an HCV PI or a nonnucleoside inhibitor). Of note, sofosbuvir has been approved for use by the US by Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Ledipasvir in combination with sofosbuvir is under FDA review.

Additional results were presented from the PHOTON-1 study (Abstract 26), evaluating the use of sofosbuvir with weight-based ribavirin in HIV/HCV-coinfected patients. Raltegravir, rilpivirine, ronivir-boostered (r) darunavir, atazanavir/r, efavirenz, and emtricitabine plus tenofovir were permitted as antiretroviral therapy. For HCV treatment-naive patients, SVR12 rates were 76% (87 of 114) in patients with HCV genotype 1 infection who received 24 weeks of treatment, 88% (23 of 26) in patients with HCV genotype 2 infection who received 12 weeks of treatment, and 67% (28 of 42) in patients with HCV genotype 3 who received 12 weeks of treatment. Among these treatment-naive subjects, 25 with HCV genotype 1 and 12 with HCV genotype 3 had confirmed virologic relapse; no patients with HCV genotype 2 experienced relapse. No sofosbuvir resistance was documented in the relapers.

For treatment-experienced patients, the SVR12 rate for those with HCV genotype 2 was 92% (22 of 24) and was 94% (16 of 17) for those with HCV genotype 3, each with 24 weeks of therapy. It is notable that the SVR rate was considerably higher in treatment-experienced patients with HCV genotype 3 than was seen in the VALENCE study, which also investigated sofosbuvir and ribavirin for 24 weeks in HCV genotype 3—monoinfected patients. In the VALENCE study, SVR12 rates were 87% (87 of 100) in treatment-experienced patients without cirrhosis and 60% (27 of 45) in treatment-experienced patients with cirrhosis. Twenty-four percent (10 of 41) of treatment-experienced subjects with HCV genotype 2 or 3 in the PHOTON-1 study had cirrhosis; however, data on SVR12 rates in patients with HCV genotype 3 was not broken down into those who had cirrhosis and those who did not have cirrhosis. In terms of tolerability, most subjects experienced some adverse effects, most commonly fatigue, insomnia, headache, nausea, and diarrhea. Grade 3 or 4 adverse events occurred in 10% to 12% of participants, with treatment-limiting adverse effects occurring in 3% to 4%.

In general, response rates in the PHOTON-1 study are very similar to
those seen in HIV-uninfected patients, providing additional evidence that HIV is no longer a risk factor for poor response to HCV treatment in the current DAA treatment era. Sofosbuvir plus ribavirin is a currently available treatment option that produces excellent SVR rates with 12 weeks of therapy in patients with HCV genotype 2 infection. Treatment should be extended to 24 weeks in patients with HCV genotypes 1 or 3. The PHOTON-I study did not evaluate sofosbuvir and ribavirin in treatment-experienced patients with HCV genotype 1 infection.

**Nucleoside-Sparing Regimens: Triple Therapy**

The A443-014 study (Abstract 25) evaluated HCV-monoinfected treatment-naive patients with HCV genotype 1 (9% with cirrhosis) who were treated with 12 weeks of an investigational, twice-daily regimen of the NS5A inhibitor daclatasvir, the HCV PI asunaprevir, and the nonnucleoside polymerase inhibitor BMS-791325 (dosed at 75 mg or 150 mg daily). SVR12 rates were 92.2% with 75 mg of BMS-791325 and 91.7% with 150 mg of BMS-791325. Response rates were generally similar between subjects with or without cirrhosis, with a marginally lower response rate in subjects with HCV genotype 1a (91%) than in those with genotype 1b (94% to 100%), and in those with the less favorable IL28B non-CC genotypes (89% to 91%) than in those with the favorable IL28b CC genotype (96%). Of note, all on-treatment virologic breakthroughs (5 of 166) and post-treatment relapses (6 of 166) occurred in participants with HCV genotype 1a infection. Of the 11 failures, 6 had HCV virus resistant to all 3 HCV DAAs and 5 had virus resistant to daclatasvir and asunaprevir. Baseline polymorphisms associated with resistance were not associated with treatment failure in patients with HCV genotype 1a.

Although treatment failure was uncommon, association of failure with 2- or 3-class resistance has important implications for subsequent HCV retreatment, which at least in the short term would need to exclude NS5A, HCV PI, and nonnucleoside inhibitor use due to anticipated cross-resistance within these classes with most drugs currently in development. The most common adverse effects were headache, diarrhea, fatigue, and nausea, with no treatment-related serious or grade 3 or 4 adverse events. This triple-therapy, all-oral regimen is promising for genotype 1 HCV infection, with the caveat that patients with genotype 1a may be more vulnerable to treatment failure with emergence of HCV resistance. More data are needed to understand the duration of HCV resistance mutations after treatment failure and the implications for cross-resistance with newer DAAs in development.

Another promising triple-drug regimen in development is the investigational combination of the HCV PI ABT 450/ft, coformulated in a single pill with the NSSA inhibitor ABT-267, and the nonnucleoside polymerase inhibitor ABT-333, given with or without ribavirin, evaluated in the PEARL-III study. HCV-monoinfected, treatment-naive participants who did not have cirrhosis were randomized to receive triple therapy, with or without ribavirin, for 12 weeks (Abstract 29LB). SVR12 rates were 99.5% with ribavirin and 99% without ribavirin, suggesting that ribavirin is not a necessary component for patients with HCV genotype 1b infection. Similar results were obtained in the PEARL-II study, with HCV genotype 1b-infected, treatment-experienced patients attaining SVR12 rates of 97% with ribavirin and 100% without ribavirin. In the PEARL-IV study, this triple-drug regimen led to SVR12 rates of 97% with ribavirin and 90% without ribavirin, indicating that ribavirin may be more important for curative therapy of subjects with genotyping 1a.

In the current PEARL-III study, there were no virologic failures in the arm that did not contain ribavirin and 1 virologic rebound posttreatment in the ribavirin-containing arm, with emergence of an NSSA resistance mutation (Y93H). The most common adverse effects were headache and fatigue; anemia occurred in the ribavirin-containing arm only. There were no treatment-related study discontinuations.

The same triple-drug regimen plus ribavirin was evaluated in an open-label study, M14-105, of treatment-naive or -experienced HCV genotype 1-monoinfected patients who did not have cirrhosis and were on stable opiate replacement therapy with buprenorphine (19 of 38) or methadone (19 of 38) (Abstract 662LB). The SVR12 rate was 97.4% (37 of 38), which is comparable to SVR rates attained in other studies of this triple-drug regimen in treatment-naive and -experienced patients with HCV genotype 1 infection. One participant discontinued early because of stroke and a high-grade sarcoma diagnosis that were judged unrelated to study treatment. There were no virologic failures and no patients required changes in dosage of methadone or buprenorphine. This study provides promising pilot data to support use of this triple-drug regimen in patients on opiate substitution therapy, which is common in the HCV-infected population.

The nucleoside-sparing dual therapy of daclatasvir and the HCV PI simeprevir, given with or without ribavirin, was evaluated in the LEAGUE-1 study (Abstract 28LB). HCV genotype 1-monoinfected patients who were either treatment naive or had prior null responses were randomized to receive daclatasvir and simeprevir with or without ribavirin. Patients with HCV genotype 1a received 24 weeks of treatment and patients with genotype 1b were randomized to 12 weeks or 24 weeks of treatment. Importantly, daclatasvir was dosed at 50 mg, a dose reduction based on healthy volunteer data indicating that simeprevir coadministration led to a 2-fold decrease in daclatasvir concentrations. On-study daclatasvir concentrations were lower than anticipated and may have affected the efficacy of this regimen. Treatment-naive patients with HCV genotype 1a had an SVR12 rate of 67% (8 of 12), with 33% (4 of 12) experiencing virologic breakthrough on treatment. Resistance data were not presented. The first 5 HCV genotype 1a–infected patients with prior...
null response enrolled in the study all experienced virologic breakthrough and were offered peginterferon alfa and ribavirin in addition to daclatasvir and simeprevir. Treatment-naive participants with HCV genotype 1b infection fared better, attaining SVR12 rates of 83% with 12 weeks and 89% with 24 weeks of treatment with daclatasvir and simeprevir without ribavirin; SVR12 rates were 75% and 74%, respectively, with the addition of ribavirin. Thus, in treatment-naive patients with HCV genotype 1b, ribavirin did not improve SVR, and extending therapy to 24 weeks only marginally improved response. However, in patients with prior null response (never achieved a ≥ 2 log_{10} IU/mL drop in HCV RNA level after ≥ 12 weeks of prior treatment) ribavirin did impact cure, with ribavirin-sparring therapy yielding SVR12 rates of 83% with 12 weeks of treatment and 50% with 24 weeks of treatment compared with ribavirin-containing therapy that yielded SVR12 rates of 100% and 89%, respectively. Overall, these data indicate that the likely suboptimal dosing of 30 mg of daclatasvir coadministered with simeprevir is generally not sufficiently potent for patients with HCV genotype 1a but works well for patients with HCV genotype 1b. However, HCV genotype 1b–infected patients with prior null response may benefit from the addition of ribavirin. There did not appear to be a benefit to extending treatment to 24 weeks in patients with HCV genotype 1b. It is not known if increasing daclatasvir dose when given with simeprevir would have improved the regimen potency, particularly in subjects with HCV genotype 1a.

**Second-Generation Combination Strategies**

Data were presented from part B of the C-WORTHY study, evaluating the second-generation investigational HCV PI MK-5172, which has shown a higher barrier to resistance than earlier HCV PIs, coadministered with the investigational NSSA inhibitor MK-8742 in a once-daily oral regimen (Abstract 654LB). Part A of this trial demonstrated SVR24 rates of 89% to 100% with 12 weeks of treatment with MK-5172 and MK-8742 given with or without ribavirin in HCV-monoinfected, treatment-naive patients with HCV genotype 1a or 1b who did not have cirrhosis. Part B evaluated 12 weeks of MK-5172 and MK-8742 given with or without ribavirin in 59 HIV/HCV-coinfected patients. Response rates were compared with those of 65 HCV-monoinfected patients enrolled in part A of the study. Both groups had HCV genotype 1, were treatment-naive, and did not have cirrhosis. Permitted antiretroviral therapy was raltegravir and 2 nucleos(t)ide reverse transcriptase inhibitors (nRTIs).

At the end of 12 weeks of treatment with MK-5172 and MK-8742 plus ribavirin, virologic response (HCV RNA level < 25 IU/mL) by intent-to-treat analysis was attained in 100% (29 of 29) of HIV/HCV-coinfected participants and in 94% (49 of 52) of HCV-monoinfected participants. Treatment with MK-5172 and MK-8742 alone produced virologic response in 90% (26 of 29) of HIV/HCV-coinfected participants and in 100% (13 of 13) of HCV-monoinfected participants. Two HIV-HCV-coinfected patients experienced HCV virologic breakthrough in the ribavirin-sparring arm and both patients had low MK-5172 and MK-8742 levels on treatment. SVR12 data are not yet available. There did not appear to be a difference in response between HIV-infected and -uninfected subjects. Virologic breakthrough only occurred in 2 HIV-infected subjects and the numbers are too small to conclude whether HIV infection increases the risk of virologic breakthrough. Healthy volunteer pharmacokinetic data found no meaningful drug interactions between MK-5172 or MK-8742 coadministered with raltegravir or tenofovir (Abstracts 498 and 500). Thus, it seems unlikely that raltegravir or NRTIs led to suboptimal MK-5172 and MK-8742 concentrations. Treatment was well tolerated and the most common adverse effects were fatigue, headache, nausea, and diarrhea; no subjects discontinued therapy due to treatment-associated adverse events.

**Peginterferon Alfa–Containing Regimens**

Given the remarkable efficacy of all-oral, peginterferon alfa–sparing regimens, there is a limited role for the current use of peginterferon alfa because of the duration required and the considerable associated toxicity; it is anticipated that there will be no role for peginterferon alfa–containing regimens in the future. Because lower SVR rates (68% to 72%) were attained with 24 weeks of treatment with sofosbuvir and weight-based ribavirin (PHOTON-1 [Abstract 26] and SPARE trials) than with sofosbuvir plus peginterferon alfa and ribavirin, 12 weeks of peginterferon alfa and ribavirin with sofosbuvir may be preferable for eligible patients with HCV genotype 1 infection until more DAAs become available, particularly for those who are treatment experienced. Although peginterferon alfa–based regimens will be of limited use as availability of interferon-sparing regimens increases, data from interferon-containing regimens can still provide insight into efficacy, tolerability, and comparative performance in HIV-infected and -uninfected individuals. The C212 study evaluated the HCV PI simeprevir, which is currently approved for use by the FDA (Abstract 24). One hundred six HIV/HCV-coinfected participants with HCV genotype 1 infection received 12 weeks of once-daily simeprevir. Treatment-naive patients and those with prior relapse received 24 weeks to 48 weeks of accompanying peginterferon alfa and ribavirin, depending on treatment response. Treatment-experienced patients (partial and null response) and those with cirrhosis received 48 weeks of peginterferon alfa and ribavirin. Because simeprevir is metabolized by cytochrome P450 3A4, antiretroviral therapy was restricted to raltegravir, rilpivirine, maraviroc, enfuvirtide, and NRTIs. SVR12 rate was 74% overall, 79% in treatment-naive patients, 87% in those with prior relapse, 70% in those with prior partial response, and 57% in those with prior null response. These SVR rates are comparable to those of HCV-monoinfected patients (80%-81%...
in treatment-naive patients, 79%-88% in those with prior relapse, 65%-86% in those with prior partial response, and 58% in those with null response. As seen with previous peginterferon alfa and ribavirin regimens, IL28B status affected response. The favorable IL28B CC allele was associated with a 96% SVR12 rate, whereas SVR12 rates with the less favorable alleles were 68% (CT) and 61% (TT). There was a trend toward decreased SVR12 rates with more advanced fibrosis (64% with Metavir score F3-F4 vs 80% with F0-F2) and with HCV genotype 1a compared with genotype 1b (71% vs 89%, respectively). Of note, baseline presence of the HCV protease Q80K polymorphism was not associated with a substantially decreased SVR12 rate (67% in those with Q80K vs 72% in those without Q80K), despite a previous association of Q80K with a 26% decrease in SVR12 rates in HCV monoinfection studies of simeprevir with peginterferon alfa and ribavirin in patients with HCV genotype 1.

The safety profile was similar to other peginterferon alfa–based regimens, with 10% of patients experiencing serious adverse events. Simeprevir is associated with rash, pruritus, photosensitivity which can be severe, and elevated bilirubin levels. Overall, the C212 study demonstrates that HIV/HCV-coinfected patients can attain cure rates equivalent to their HCV-monoinfected counterparts, which has been shown with other HCV PIs when given with peginterferon alfa and ribavirin. Although simeprevir use with peginterferon alfa and ribavirin will be limited by interferon-related toxicity and lengthy treatment duration, simeprevir is under investigation as part of all-oral, interferon-sparring regimens, including simeprevir with sofosbuvir (COSMOS [Combination of Simeprevir and Sofosbuvir in HCV Genotype 1 Infected Patients] study) and simeprevir with daclatasvir (LEAGUE-1 study).

The STARTVerso 4 study evaluated the investigational HCV PI faldaprevir, also given in combination with peginterferon alfa and ribavirin, in HIV/HCV-coinfected patients with HCV genotype 1 (Abstract 23). Three hundred nine subjects received 12 weeks to 24 weeks of faldaprevir in conjunction with 24 weeks to 48 weeks of peginterferon alfa and ribavirin, depending on treatment response: 17% had fibrosis (F4). Permitted antiretroviral therapy was raltegravir, maraviroc, efavirenz, darunavir/ritonavir, atazanavir/ritonavir, and NRTIs. Because of anticipated drug interactions, faldaprevir was dosed at 240 mg with efavirenz, 120 mg with the HIV PIs, and patients were randomized to 120 mg or 240 mg with raltegravir and maraviroc. The overall SVR12 rate was 72%, with 80% of patients qualifying for short-enned therapy (24 weeks) and 89% of these attaining SVR. Interestingly, the SVR12 rate was higher in those with prior relapse than in those who were treatment naive (83% vs 69%, respectively; \( P = .02 \)). HCV genotype 1a, cirrhosis, or the presence of the Q80K polymorphism did not negatively impact SVR12 rates. The safety profile was similar to other interferon-containing regimens, with adverse events triggering discontinuation in 7% of patients. As with simeprevir plus peginterferon alfa and ribavirin, SVR12 rates with faldaprevir plus peginterferon alfa and ribavirin were nearly identical to what has been seen in the HCV-monoinfected population, reiterating that HIV does not appear to negatively impact response with DAA-based therapy.

Pharmacokinetic data from the STARTVerso 4 study found that faldaprevir reduced mean darunavir trough levels, reduced raltegravir concentrations only when faldaprevir was dosed at 240 mg daily, and had no notable effect on efavirenz or atazanavir; the investigators indicated that the impact on antiretroviral therapy is not clinically significant (Abstract 497). Interestingly, raltegravir drug concentrations were increased 2.7-fold by faldaprevir 240 mg daily in a study of healthy volunteers, suggesting that pharmacokinetic interactions in HIV-uninfected volunteers on single-drug HCV or HIV therapy cannot always be generalized to HIV-infected patients on combination antiretroviral therapy (Abstract 501).

Complications of HCV Infection

The systemic impact of HCV beyond strictly liver-related complications is increasingly recognized. In an observational cohort of US veterans, patients with detectable HCV RNA levels and unfavorable lipid profiles had a 22% to 64% increased risk of myocardial infarction (MI). Individuals with undetectable HCV RNA levels had a less pronounced increase in coronary artery disease risk at each unfavorable lipid stratum, suggesting that chronic HCV infection contributes to coronary disease risk (Abstract 685). In another US veteran cohort analysis, HIV/HCV coinfection was associated with higher risks of stroke, congestive heart failure, and venous thromboembolism than were seen with HIV or HCV monoinfection, after adjusting for traditional cardiovascular risk factors (Abstract 688).

HCV infection was independently associated with low bone mineral density (BMD) at hip, spine, and femoral neck, which may be mediated through elevated levels of regulatory cytokines receptor activator of nuclear factor kappa-B ligand (RANKL) and osteoprotegerin (OPG) suppressing bone turnover. The investigators suggested that this is a different pathophysiologic mechanism than HIV-associated low BMD, which may be mediated in part by high bone turnover and tenofovir use. HCV-associated low BMD was not correlated with hepatic fibrosis, as assessed by aspartate aminotransferase (AST)-to-platelet ratio index (APRI) (Abstract 785). In terms of liver-related mortality, a EuroSIDA analysis demonstrated that liver-related deaths accounted for 27% of all deaths in HIV/HCV-coinfected patients, which was similar to the AIDS-related death rate (Abstract 652). Predictors of liver-related mortality included fibrosis of F2 or more (adjusted subhazard ratio [sHR] 28.3; \( P < .024 \)), low CD4+ cell count, and hepatitis B virus (HBV) coinfection (sHR 6.57; \( P = .013 \)). HCV viremia and duration of infection were also statistically significantly associated with increased risk of non–liver-related death (sHR 1.54 and 1.34 per 5 years, respectively). In
a French cohort, HIV/HCV-coinfected individuals had a higher hazard ratio (HR) of all-cause mortality of 1.79 ($P < .001$) than HIV-monoinfected patients (Abstract 690). Non–liver-related mortality (HR 1.4; $P < .001$) and non-liver, non–AIDS-related mortality (HR 1.47; $P < .001$) were also statistically significantly increased in HIV/HCV coinfection. Collectively, these data are an important reminder of the systemic impact that chronic HCV infection can have on hepatic, cardiovascular, and skeletal health, and of the impact of HCV on overall mortality, including non–liver-related death. The emerging availability of shorter, better-tolerated, and highly effective HCV curative therapy has enormous potential to impact the morbidity and mortality associated with HCV.

Hepatitis B Virus and Hepatitis Delta Virus

Currently, active HBV drugs are nucleos(t)ides that target the HBV polymerase or the immune modulator interferon. There is a marked need for drugs with other HBV targets, to improve control of HBV viremia and perhaps ultimately eradicate HBV, which is not possible with current therapies.

Kottilill gave an excellent talk reviewing a number of HBV drugs in development with novel targets of action, including HBV entry inhibitors (Myrcludex-B), covalently closed circular DNA inhibitors or silencers (zinc finger motifs), HBV capsid inhibitors (BAY 41-4109), hepatitis B surface antigen secretion inhibitors (HBF-0259), and host-directed therapies such as Toll-like receptor 7 agonists (GS-9620), programmed cell death 1 (PD-1)/programmed death ligand 1 (PD-L1) antibodies, and therapeutic vaccination (Abstract 58). These therapies are all particularly in development but hold promise for more robust HBV treatment in the future.

Isolated HBV core antigen positivity presents a challenge to the treating clinician as it may represent resolved HBV infection with undetectable hepatitis B surface antibody level, the window period in acute HBV infection, a false positive test result, or clinically significant occult HBV infection. One abstract found an association between isolated HBV core antibody positivity and advanced fibrosis (assessed by FIB-4 or APRI) in HIV/HCV-coinfected patients (Abstract 695). This association was not seen in HIV/HCV-coinfected patients from the WIHS (Women’s Interagency HIV Study) cohort, where fibrosis was assessed by enhanced liver fibrosis (ELF) markers (Abstract 696). Further data are needed to identify which HIV-infected patients with isolated HBV core antibody positivity are truly at risk for progression of fibrosis.

Hepatitis delta virus (HDV) superinfection of HBV can lead to severe liver fibrosis, and there are limitations to treatment with peginterferon alfa. In a cohort of 19 HIV/HBV/HDV-coinfected patients who received a median of 58 months of tenofovir as part of their HIV treatment, 100% attained undetectable HBV DNA levels and 53% (10 of 19) had HDV RNA levels below 10 copies/mL (Abstract 700). Substantial liver fibrosis regression (defined as a 30% reduction in hepatic stiffness measured by elastography) occurred in 60% (6 of 10) of patients with undetectable HDV RNA levels and did not occur in 9 patients with persistent HDV viremia. These data suggest that tenofovir may play an important role in the control of HDV infection, although treatment was not sufficient to suppress HDV in all patients during the 3- to 7-year study period.

Hepatitis E Virus

Hepatitis E virus (HEV) is found worldwide and is typically an acute, self-limiting viral hepatitis. However, HEV infection is increasingly recognized as a cause of chronic viral disease, particularly in immunosuppressed individuals, and can lead to liver fibrosis and decompensation. Sherman comprehensively reviewed HEV (Abstract 57). Transmission of HEV genotypes 1, 2, and 4 is associated with poor sanitation and contaminated water. However, HEV genotype 3 is transmitted via contact with pigs and pork products, deer, shellfish, and through parenteral exposure. Diagnosis of HEV can be challenging—there is no FDA approved test for HEV, and there is a short duration of immunoglobulin M (IgM) positivity and HEV RNA viremia during acute illness, which limits the window for diagnosis. HEV should be in the differential for acute hepatitis in HIV infection—it was detected in 3% to 4% of acute hepatitis episodes in a US study of HIV-infected individuals and in 2% to 9% in European studies—and may lead to hepatic decompensation in the setting of acute or chronic disease. Diagnoses of HEV infection were made through detection of HEV IgM, IgG, and RNA.

Chronic HEV infection is uncommon but can occur in patients with HIV coinfection, those who have received a solid organ transplant, or those with hematologic malignancy, and may be an underrecognized cause of transaminitis and hepatic decompensation. A study in northern Spain found an HEV seroprevalence of 9.8% in HIV-infected patients, with none developing chronic HEV infection (Abstract 633). A second study, in southern Spain, found an HEV seroprevalence of 17.2%; HEV seropositivity was associated with elevated transaminases, and only 1 patient had detectable HEV RNA levels (Abstract 634). These data are a reminder that HEV infection may play a role in HIV-infected patients and should be a consideration in the setting of acute or chronic hepatitis that is not attributable to HBV or HCV infection.

Complications of HIV Infection

Non-AIDS complications, specifically cardiovascular disease (CVD), renal insufficiency, and bone and endocrine disorders persist among patients with treated HIV disease and contribute to morbidity and mortality. Research in this area remains focused on the epidemiology and risk factors for these problems, identifying the contributions of HIV-related immunopathology to specific and collective end-organ diseases, and evaluating interventions to prevent or reduce the morbidity associated with these conditions. CROI
2014 provided new insights into all of these areas.

**Evolution of Mortality Due to Non-AIDS Events Over the Past Decade**

Between 2000 and 2010, investigators from the Centers for Disease Control and Prevention (CDC) examined causes of death among HIV-seropositive patients aged 30 years to 39 years and 50 years to 69 years, and examined the coefficients of association between co-factors such as alcohol use and HIV disease and the need for further intervention studies in this area.

In the general population, soluble measures of inflammation are increased among patients with obesity, diabetes, and those who smoke. However, the relationship between these risk factors and measures of inflammation in treated and suppressed HIV patients has not been fully explored. AIDS Clinical Trials Group (ACTG) investigators reported correlations between IL-6, D-dimer, soluble (s) tumor necrosis factor receptor 1 (sTNFR1), gamma interferon–induced protein 10 (sTNFRP1), and sCD14 and metabolic and anthropometric factors (Abstract 757). Increased age, central obesity, smoking, and elevated triglyceride levels were all associated with sCD14, IL-6, and sTNFR1, whereas none of the metabolic or anthropometric measures appeared to correlate to D-Dimer or IP-10.

Data from the SUN study (Abstract 732) found associations between current smoking and higher levels of sCD14, whereas heavy alcohol use was associated with lower D-dimer levels. In a Swiss HIV Cohort study, low to moderate alcohol use—defined as up to 29 grams per day for women and 39 grams per day for men, or approximately 2 drinks per day—was associated with lower rates of CVD (Abstract 731), but whether this benefit is mediated by the effects of alcohol on coagulation warrants further investigation.
The Impact of Antiretroviral Therapy on Inflammatory Biomarkers

It is known that measures of inflammation decline when effective antiretroviral therapy is initiated and plasma HIV RNA level decreases, but how this varies with specific regimens and among subgroups of patients is not yet fully defined. It has also been well documented that women tend to have higher CD4+ cell counts and lower HIV RNA levels than men during early HIV infection, although they progress at a similar rate without treatment. Using samples from a completed international ACTG treatment trial, Mathad and colleagues (Abstract 853) observed that before initiating antiretroviral therapy, women had lower levels of hsCRP and sCD14, and a lower percentage had detectable lipopolysaccharide, and higher levels of endotoxin core antibody (EndoCAb) than men. After 48 weeks of antiretroviral therapy, among those who achieved viral suppression, men had a greater decrease in sCD14 level that seemed to plateau after 24 weeks to 48 weeks of antiretroviral therapy, although they plateau after 24 weeks to 48 weeks after stopping. The mechanism of the protective effect of TMP-SMX requires further investigation.

CVD

Risk Factors and Rates of CVD

Traditional risk factors for CVD remain prevalent among patients with HIV infection, and several studies at CROI 2014 reported on the contributions of specific risk factor to rates of CVD. Analysis of data from the Veterans Aging Cohort Study (VACS) found that even when traditional risk factors are managed, patients with HIV infection appear to still be at twice the risk for MI compared with HIV-uninfected patients (Abstract 736). A second VACS study demonstrated that HIV is an independent risk factor for CVD among women and, as has been previously noted, that the magnitude of the effect of HIV on this cohort is greater among women (3-fold) than was previously reported among men (1.5- to 2-fold) (Abstract 734). Investigators working with the Partners HealthCare System database reported on rates of major adverse cardiac events during the period from 2000 to 2009 and observed that HIV-infected individuals had higher rates of individual events (MI, stroke, angina, revascularization) and a composite end point that includes all of these diagnoses (Abstract 738). More encouraging news came from Klein and colleagues who reported that patients with HIV infection managed in the Kaiser Permanente California health system from 2010 to 2011 did not have higher rates of MI than those seen in age-matched, HIV-uninfected controls; this occurred despite the higher prevalence of smoking, hypertension, and low-high-density lipoprotein (HDL) cholesterol levels among the HIV-infected patients (Abstract 737). Investigators from the multicenter Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort confirmed the importance of Framingham risk score covariates (age, smoking, total and HDL cholesterol, and systolic blood pressure) in predicting MI risk in patients with HIV infection but also found that HIV-associated factors, specifically lower CD4+ cell count and higher level of HIV RNA, remain independent risk factors (Abstract 739), highlighting the important role that immunodeficiency and viral replication may play in the observed increased risk for CVD in HIV infection. Lower CD4+ cell counts were also found to be associated with the risk of ischemic stroke in another report from Kaiser Permanente California investigators (Abstract 741). Finally, work from the MACS (Multicenter AIDS Cohort Study) highlighted the possible contribution of heavy nitrate inhalant use to risk for cardiovascular and renal events (Abstract 740).

Coronary Plaque Associations With Inflammation

At prior CROI meetings, the use of novel imaging methods (computed tomography [CT] angiography to examine features of plaque and 18F-2-deoxy-D-glucose positron emission tomography [18F-FDG-PET] to examine arterial inflammation) for the study of atherosclerosis in HIV disease were discussed. This year 2 groups reported data from further studies employing these methodologies. Zanni, Tawakol, and colleagues (Abstract 130) described the interrelationship between arterial inflammation and high-risk plaque morphology in a study in which participants who had previously undergone CT angiography underwent 18F-FDG-PET and were characterized as having either high or low levels of arterial inflammation (measured from the degree of aortic inflammation over background, known as aortic tissue-to-background ratio [TBR]). Participants with higher levels of aortic inflammation had a higher number of plaques and a greater amount of what is considered to be high-risk morphology.
plaque (low attenuation and positive remodeling) than those with lower levels of aortic inflammation. In another study Hsue, Tawakol, and colleagues used 18F-FDG-PET to investigate the relationship between arterial inflammation and splenic and bone marrow activity, hypothesizing that if macrophages contribute to the development of arterial inflammation in HIV, an increase in splenic and bone marrow FDG uptake might be expected (Abstract 131). They found once again that virologically suppressed, HIV-infected patients had higher levels of arterial inflammation than -uninfected controls and higher levels of FDG uptake in spleen and bone marrow but not in muscle tissue, suggesting that immune cell activity may be contributing to this inflammation. Together, these findings suggest a possible link between vascular inflammation and high-risk plaque and, possibly, immune cell activation that warrants further investigation. These findings also highlight the potential use of 18F-FDG-PET scanning as a research tool in studies evaluating potential interventions to reduce the development of atherosclerosis in HIV disease.

Investigators from the MACS presented further evidence supporting the role of monocyte activation in CVD in a cross-sectional study of virally suppressed HIV-infected patients and -uninfected controls who underwent coronary artery calcium scanning and CT angiography (Abstract 730). Among HIV-infected patients, sCD163 but not sCD14 was associated with plaque. In contrast, T cell activation was higher in the HIV-infected group and was not associated with coronary atherosclerosis in either group.

The contribution of HIV persistence—determined by measurement of ultrasensitive HIV RNA levels (<0.5 copies/mL by single-copy assay) and proviral DNA in peripheral blood mononuclear cells—to endothelial dysfunction was evaluated by University of California San Francisco investigators in a study measuring endothelial function by flow-mediated dilatation (FMD) (Abstracts 727 and 729). In HIV-infected study subjects with low HIV RNA levels, traditional risk factors and cell-associated HIV RNA levels correlated with worsened FMD, raising questions about the role of HIV replication in the pathogenesis of CVD. This issue was further explored in a small pilot study of elite controllers, compared with viremic controllers and noncontrollers, investigating the impact of antiretroviral therapy on FMD (Abstract 729). Twenty-four weeks of antiretroviral therapy resulted in reductions in ultrasensitive HIV RNA levels in the elite controllers and an improvement in T cell activation. However, FMD did not improve in the small sample evaluated; given the known variability of FMD, these pilot data support further investigation into the role of HIV persistence in the pathogenesis of vascular disease.

**Heart Failure**

Growth stimulation–expressed gene 2 (ST2; a member of the IL-1 receptor family) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP), biomarkers of cardiac dysfunction that are predictive of heart failure and mortality in the general population, were previously reported to be higher in patients with HIV infection and associated with mortality. The findings were extended by data confirming that higher mortality was predicted by NT-proBNP levels among women with HIV infection (Abstract 723) and by a study that demonstrated that ST2 and growth differentiation factor 15 (GDF-15), which is involved in regulating inflammation, were independent predictors of mortality and, in the case of ST2, diastolic dysfunction (Abstract 725). The clinical role of these biomarkers remains to be determined. Cardiac steatosis, measured by magnetic resonance spectroscopy, was shown to be 38% higher in HIV-infected patients than in -uninfected controls. Among HIV-infected patients, female sex and higher amounts of visceral fat were associated with increased cardiac steatosis (Abstract 724).

**Lipids, CVD Risk, and Antiretroviral Therapy**

There are numerous species of lipids that can be measured in plasma using mass spectrometry, and changes in the lipidome have been used to stratify patients’ future cardiovascular risk. Data on lipid profiles were reported by Australian investigators. They noted adverse lipid profiles in patients randomized to either efavirenz- or atazanavir-based regimens (Abstract 742) and the ability of plasma lipid profiling to identify patients at higher risk for coronary artery disease events in a case-control study (Abstract 748).

The association between recent abacavir use and risk for MI remains controversial. Investigators from the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study reported a decline in the use of abacavir among patients at high and moderate risk for CVD since the association between abacavir and MI was first reported in 2008. They note that the association between abacavir use and MI persists in more recent years, despite this change in prescribing patterns. (Abstract 747LB). One potential mechanism to explain the link between abacavir and MI is changes in platelet function after abacavir exposure. Using samples from the SWIFT study, in which patients were randomized to switch from abacavir and lamivudine to tenofovir and emtricitabine or to remain on abacavir and lamivudine, O’Halloran and colleagues (Abstract 749LB) measured changes in markers of platelet activation in the 2 groups and found an increase in soluble glycoprotein VI (sGPVI) among those who switched from abacavir- to tenofovir-based treatment, whereas no changes in soluble P-selectin were observed. It remains to be clarified whether this change in platelet function could contribute to MI risk during abacavir-based therapy.

**Fat**

Obesity remains an important problem that contributes to other comorbidities, including hypertension and
CVD, and complicates the management of HIV disease. Not surprisingly, a body mass index (BMI) of 30 kg/m² or higher was a risk factor for developing hypertension in a study of South Africans initiating antiretroviral therapy (Abstract 759). Lower pre-antiretroviral therapy CD4+ cell count and female sex were risk factors for developing obesity among 3000 treatment-naive patients followed in the ACTG Longitudinal Linked Randomized Trials (ALLRT) cohort (Abstract 802). A higher rate of mortality 48 months after initiation of antiretroviral therapy was observed in obese (BMI ≥ 30 kg/m²) South African subjects than in those with normal BMIs (18 kg/m²-24.9 kg/m²); however, loss to follow-up was lower in the obese group than in the group with normal BMIs (Abstract 803).

Tesamorelin, a synthetic growth hormone–releasing hormone agonist, has been FDA approved for the treatment of HIV-related lipodystrophy. Grinspoon and colleagues reported the effects of tesamorelin on hepatic fat in a randomized, placebo-controlled trial conducted in HIV-infected patients who had evidence of abdominal fat accumulation. After 6 months of treatment with subcutaneous tesamorelin 2 mg, compared with placebo, visceral adipose tissue and hepatic lipid measurements decreased substantially (Abstract 135). Whether tesamorelin can reduce hepatic steatosis remains to be demonstrated but seems very important to investigate given the currently limited available treatment options for this condition.

**Statins**

There continues to be great interest in the role of statin drugs in the management of HIV-related cardiovascular risk. Several new developments from ongoing clinical trials of statin use in HIV-infected patients were reported this year. Rosuvastatin was previously shown to reduce low-density lipoprotein (LDL) cholesterol and measures of monocyte immune activation in HIV-infected patients. At CROI 2014, McComsey and colleagues reported a decline in oxidative LDL with rosuvastatin treatment (Abstract 134); however, this did not correlate with reductions in other markers of inflammation. In addition, they reported an increase in total hip and trochanter BMD among SATURN-HIV (Stopping Atherosclerosis and Treating Unhealthy Bone With Rosuvastatin in HIV) trial participants randomized to receive rosuvastatin. However, markers of insulin resistance also worsened substantially in this group, with 1 subject developing diabetes. These findings suggest that rosuvastatin use in patients with HIV should include monitoring for diabetes. The 52-week results of the INTREPID study of pitavastatin 4 mg compared with pravastatin 40 mg showed the continued superiority of pitavastatin in lowering LDL at 52 weeks of follow-up; safety appeared similar in both study groups, and there were no reports of diabetes (Abstract 751LB).

**Renal Disease**

The long-term outcomes after development of chronic renal impairment on antiretroviral therapy have not been well described in prior studies. D:A:D investigators performed a detailed analysis of the outcomes of participants who had a confirmed decline in estimated glomerular filtration rate (≤70 mL/min/1.73 m²) (Abstract 792). After the development of renal impairment while on antiretroviral therapy, 23% of patients improved, 69% stabilized, and 7.8% worsened. Older age, diabetes, and the use of tenofovir or ritonavir-boosted PIs were associated with a lower chance of improvement, but there was some evidence that discontinuation of tenofovir before the development of chronic renal impairment was associated with better outcomes. A chronic kidney disease risk score reported by Scherzer and colleagues that incorporates traditional risk factors for renal disease (age, glucose levels, systolic blood pressure, hypertension, triglyceride levels, and proteinuria) may prove useful in identifying patients in whom tenofovir use should be avoided (Abstract 798). Genetic markers for tenofovir proximal tubular dysfunction were also reported (Abstract 799).

Immune complex kidney disease (ICKD) has been less studied than HIV-associated nephropathy HIVAN. Investigators from the UK demonstrated that HIV viremia was a risk factor for ICKD and, compared with HIVAN, ICKD was associated with less advanced immunodeficiency; black race remained a strong risk factor for both ICKD and HIVAN (Abstract 793).

**Pulmonary Disease**

A Themed Discussion session at CROI 2014 focused on pulmonary disease, and results from ongoing cohort studies aimed at investigating the relationship between HIV and lung diseases were showcased. Investigators from the ALIVE (AIDS Linked to the Inflammatory Experience) study reported that HIV infection was independently associated with increased risk of acute exacerbations of chronic obstructive pulmonary disease (COPD) (Abstract 773), and the ANRS (Agence Nationale de Recherche sur le Sida et les Hépatites Virales) HIV CHEST study identified a high prevalence of COPD among HIV-infected patients, with marijuana use as a possible risk factor (Abstract 776). EXHALE (Examinations of HIV-Associated Lung Emphysema) investigators noted an association between HIV infection and decline in lung function that appeared to be mediated by elevations in sCD14 levels in HIV-infected subjects (Abstract 774), and an association between HIV infection and the development of emphysema (Abstract 775).

**Bone**

Examination of the risk factors and pathogenesis of bone loss in HIV disease remains an important area of investigation. At CROI 2014, more information on possible interventions to prevent or treat bone loss was presented.

The finding that HIV infection early in life appears to be associated with replicative senescence and lower
numbers of bone precursor cells was reported by Yin and colleagues from a study that included perinatally HIV-infected men compared with -uninfected men (Abstract 132).

Data from 2 CDC cohort studies demonstrated that in HIV-infected patients, low BMD (measured by dual-energy x-ray absorptiometry [DXA] scans) and older age were associated with the risk of future fracture (Abstract 781). These data confirm the utility of DXA scans for predicting fracture risk in patients with HIV infection. Concurrent use of daily calcium (1000 mg of calcium carbonate) and vitamin D (4000 IU of vitamin D$_3$) supplements in patients starting treatment with efavirenz, tenofovir, and emtricitabine mitigated the loss of hip BMD in a placebo-controlled ACTG trial (Abstract 133). Treatment was safe and well tolerated and is something that can be incorporated into clinical practice for patients who initiate this antiretroviral regimen. In another ACTG trial, 96-week BMD losses in lumbar spine and total hip were statistically significantly lower among patients randomized to receive raltegravir than among those randomized to receive atazanavir/r or darunavir/r (Abstract 779LB). Finally, a small, randomized pilot study suggested that biennial doses of zoledronic acid in HIV-infected patients may provide a similar benefit to annual administration of the drug in improving BMD (Abstract 782).

**Frailty and Aging**

Geriatric syndromes were reported to be more common among HIV-infected patients than among -uninfected controls in several studies (Abstracts 766 and 767). Immunologic profiles that have been developed for the study of aging are being increasingly applied to populations of patients with HIV infection. Ndumbi and colleagues examined the prevalence of the immune-risk phenotype that predicts mortality in elderly individuals in a group of successfully treated HIV-infected patients. They found a higher prevalence of features of the immune-risk phenotype in the HIV-infected group than in -uninfected controls (Abstract 765). In addition, they noted that within the HIV-infected group, median telomere length was shorter, although it did not reach statistical significance.

Investigators from the ALIVE cohort applied a validated index that measures inflammation and predicts the risk of mortality among adults aged older than 65 years to a population of HIV-infected patients and examined whether measures of inflammation added to the predictive value of a frailty index. The inflammatory index included measurement of IL-6 and sTNFR1 levels and frailty measurement included the presence of 3 or more of the following: weakness, slow gait, weight loss, low physical activity, and exhaustion. Investigators found strong associations between measures of inflammation and the presence of frailty. However, in models, controlling for sociodemographic characteristics, comorbidity, HIV infection, and frailty, the inflammatory index remained statistically significantly associated with mortality (Abstract 762). These results suggest that interventions to reduce inflammation in the setting of treated HIV infection may have the potential to improve long-term outcomes. One such intervention may be exercise. Longo and colleagues demonstrated that moderate-intensity exercise (walking, with or without strength exercises, 3 times/week) improved aerobic fitness, metabolic markers, and measures of inflammation in antiretroviral therapy–treated HIV infection (Abstract 763).

**Kaposi Sarcoma**

**HIV PIs—Effect on Clinical Kaposi Sarcoma?**

HIV PIs exhibit antiangiogenesis and antiviral activity against Kaposi sarcoma (KS)-associated herpesvirus (KSHV) in vitro, but the clinical relevance of these observations is unknown. Chiao and Kowalkowski examined clinical KS infection risk in a cohort of 25,529 US veterans receiving combination antiretroviral therapy. There was a 4% reduction in risk for new KS infections among those receiving a PI compared with risk among those on a nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimen; KS infection risk for the subset of patients receiving nefilnavir- was actually 4% higher than for those receiving NNRTI-based regimens (Abstract 708). Martin and colleagues evaluated clinical outcomes among Ugandan patients with KS in a randomized study comparing lopinavir/r with efavirenz-based antiretroviral therapy (Abstract 710). The 224 patients enrolled had clinical evidence of KS but did not yet meet the clinical indications for chemotherapy according to Ugandan guidelines; however, many patients had very extensive cutaneous disease. At 1 year, there was no difference between study arms in death or disease progression, and the 1-year mortality rate for the cohort was 18%. Despite the biologic plausibility of HIV PIs in prevention or treatment of KSHV disease, these studies suggest that treatment with HIV PIs is not more beneficial than treatment with NNRTIs in patients with KS. The alarming mortality rates for KS in the Ugandan study call for more intensive treatment for these patients.

**KICS**

KSHV inflammatory cytokine syndrome (KICS) is a newly described clinical syndrome characterized by multiorgan KSHV-associated tumors and elevated cytokines that is distinct from classic HIV-associated KS, primary effusion lymphoma, or multicentric Castleman disease. Polizzotto and colleagues extended prior descriptions of this syndrome by comparing 10 patients meeting KICS criteria with KSHV/HIV-coinfected patients and HIV-monoinfected patients with or without virologic suppression (Abstract 101). The patients with KICS had, in addition to greater multiorgan involvement, higher levels of anemia, leukopenia, thrombocytopenia, CRP, IL-6, and IL-10 than the comparator groups. Six of the 10 patients with KICS died despite treatment. This report highlights the high level of morbidity and mortality.
associated with KICS and the need for new therapeutic approaches.

**Tuberculosis**

New data on novel drugs and combinations for the treatment of tuberculosis (TB), patient outcomes using new rapid TB diagnostics, and a short-course TB prevention strategy were among the highlights of CROI 2014. In the TB symposium (Session S4), Murray showcased the genetics and pathogenesis of TB drug resistance mutations (Abstract 107), Karakousis challenged the current concept of TB latency (Abstract 108), Barry proposed high-tech imaging methods (PET and CT) to understand TB response during new drug development (Abstract 109), and Godfrey-Faussett offered population-based strategies for control of HIV-related TB (Abstract 110).

**New TB Drugs and Shorter Regimens—Combining and Defining Activity**

New TB drugs are being combined to evaluate potency and prospects for treatment shortening. Bedaquiline, an inhibitor of adenosine triphosphate (ATP) synthetase, has already been FDA approved for use in treatment of drug-resistant TB, and the investigational drug PA-824, a cell wall inhibitor, shows strong anti-TB activity in short-term studies in humans. Studies of animal models suggest that combining these 2 agents with a third drug such as pyrazinamide or clofazimine achieves rapid and sterilizing responses. Diácon and colleagues presented the results of a 7-arm study evaluating the use of pyrazinamide or clofazimine alone or in combination with PA-824 and bedaquiline (Abstract 97LB). One hundred five subjects with smear-positive TB were enrolled in this 14-day study. The primary end point was early bactericidal activity (EBA). The 3-drug combination of PA-824, bedaquiline, and pyrazinamide showed an EBA of 0.167 (95% confidence interval [CI], 0.078, 0.256), similar to a standard 4-drug TB regimen (EBA 0.151; 95% CI, 0.70, 0.231). This combination will be studied on a larger scale for longer durations. Clofazimine showed no activity in this study when administered alone, nor any additional activity when combined with PA-824, bedaquiline, and pyrazinamide. Although some argue that 2 weeks is an insufficient time period to observe the activity of clofazimine, others interpret these data as strong evidence that clofazimine adds only toxicity and not activity to TB treatment.

**Moxifloxacin and Rifapentine in Combination**

Moxifloxacin and rifapentine, both of which are efficacious in combination TB treatment, are being evaluated for use in treatment-shortening regimens. Dorman and colleagues presented the results of a phase II study of patients randomized to receive a standard 4-drug TB regimen (isoniazid, rifampin, ethambutol, and pyrazinamide) compared with an investigational regimen of moxifloxacin, rifapentine, ethambutol, and pyrazinamide (Abstract 93). This was a “double-switch” study in which isoniazid and rifapentine were replaced with moxifloxacin and rifapentine. Rifapentine was dosed at 7.5 mg/kg daily. The proportion of patients with culture conversion using solid media after the induction phase was similar in the 2 arms (85% in the investigational arm vs 86% in the control arm). Higher rates of culture conversion were achieved on liquid media in the investigational arm than in the control arm (85% vs 69%, respectively; P = .08). Four patients in the investigational arm and 2 patients in the control arm changed therapy because of toxicity. Investigators concluded that this investigational TB regimen is safe, well tolerated, and efficacious and that these data support the evaluation of rifapentine- and moxifloxacin-containing regimens for treatment shortening in a larger phase III study.

**HIV and TB Drug Interactions—More Data and More Options**

As new drugs become available for prevention and treatment of TB, it is essential that potential drug interactions are understood in order to avoid jeopardizing efficacy or patient safety of TB or HIV treatment during cotreatment of HIV and TB. In an ongoing study of TB prevention regimens, specifically a 1-month course of rifapentine (10 mg/kg) and isoniazid (300 mg) compared with 9 months of isoniazid alone, investigators reported the effect of rifapentine, a cytochrome P450 inducer, on efavirenz exposure (Abstract 105). Clearance of efavirenz in the presence or absence of rifapentine was equivalent, providing reassurance that these drugs can be safely co-administered at these doses. For TB treatment, Reynolds and colleagues reported results of an intensive pharmacokinetic study, which suggests that the raltegravir dose should be doubled from 400 mg to 800 mg twice daily in persons receiving thrice-weekly rifampin, in order to achieve raltegravir drug exposure levels comparable to those seen in persons not receiving rifampin (Abstract 496). This study did not include viral load data; however, results are similar to those from other studies that have examined interactions between daily rifampin and raltegravir.

**Xpert MTB/RIF Assay—Rollout in South Africa Hits Road Bumps**

In 2010, the World Health Organization endorsed a rapid combined TB and resistance to rifampicin assay (Xpert MTB/RIF) as a first-line test for TB diagnosis. This molecular-based assay has a sensitivity that exceeds the routine smear for acid-fast bacilli (AFB), provides a readout in approximately 2 hours, and can detect most cases of rifampin resistance. In 2011, South Africa made the bold policy move of replacing the routine AFB smear with Xpert MTB/RIF as the first-line diagnostic test for patients with suspected TB. The South African government and donors equipped central laboratories with hundreds of new machines in a phased implementation plan. Churchyard, Fielding, and colleagues presented early readouts from the rollout of this much anticipated new technology (Abstracts 95 and 96LB).
The XTEND study, a pragmatic, cluster-randomized trial, addressed the following questions: Were more cases of TB detected with access to the Xpert MTB/RIF assay? Did more patients diagnosed with TB start TB therapy? Was there any reduction in TB-associated mortality? In this study, 20 laboratories were randomized to immediate or delayed access to Xpert MTB/RIF. Patients from 2 primary health centers served by these labs were approached for enrollment in this TB screening evaluation study. Patients attending clinics in the immediate access arm were evaluated for TB with the Xpert MTB/RIF test. Patients attending clinics in the delayed access arm were evaluated with routine AFB smear. There were 4412 evaluable laboratory tests. The yield for TB diagnosis was higher with Xpert MTB/RIF use (9.2%) than with AFB smear (7.8%). In their model, Xpert MTB/RIF testing increased yield of TB detection by 49%. However, there was no difference between the groups in terms of number of persons started on TB therapy (10.8% for the Xpert MTB/RIF arm vs 12.5% for the routine AFB smear arm). Likewise, mortality did not differ between the 2 arms (3.9% in the Xpert MTB/RIF arm vs 5.0% in the routine AFB smear arm). Among persons self-reported as HIV infected, mortality was lower with use of Xpert MTB/RIF (5.6%) compared with controls (1.6%).

The major conclusion from this study was that scaling up new interventions like the Xpert MTB/RIF assay requires strengthening and coordination of health systems to reach maximal benefit. In the XPERT study, test results from both Xpert MTB/RIF tests and AFB smears were returned to the provider in an average of 2 days. Providing the results of new TB diagnoses to patients fell short of targets and subsequent steps, such as the initiation of antiretroviral therapy for HIV-infected persons, were also often not done in a timely fashion. According to Churchyard, the South African government was disappointed with the findings, but remains supportive of the Xpert MTB/RIF assay for first-line TB diagnosis and is designing a corrective plan for health care system deficiencies.

**Urinary Lipoarabinomannan Assay—High Yield in Hospitalized Patients in South Africa**

TB is often undiagnosed and a cause of mortality in African patients with advanced AIDS. Disseminated TB has nonspecific symptoms and smear tests may be positive in less than half of cases. Last year, studies presented at CROI showed that the rapid, low cost, lateral flow, point-of-care, urinary lipoarabinomannan (LAM) test is a valuable diagnostic tool for patients with low CD4+ cell counts. This year, Lawn and colleagues reported the performance of urinary LAM testing among adult HIV-infected patients admitted to a district hospital in South Africa (Abstract 811LB). Sputum, blood, and urine exams were sent within 24 hours of admission for all adult HIV-infected patients. After excluding those with a known TB diagnosis, 139 of 427 patients were diagnosed with TB. Adding urinary LAM testing to Xpert MTB/RIF testing increased rapid detection from 26.6% to 80.6%, and urinary LAM testing detected 85% of TB cases in persons with CD4+ cell counts below 100/µL. Urinary LAM testing detects disseminated TB, and in regions like South Africa where TB rates are extraordinarily high, screening all ill, HIV-infected persons who require hospitalization for TB using both Xpert MTB/RIF and LAM assays makes good sense. Rapid TB and the initiation of antiretroviral therapy in these patients could have a high impact on mortality.

**Short-Course TB Prevention**

Three months of once-weekly rifapentine plus isoniazid (900 mg) is comparable to 9 months of daily isoniazid (300 mg) for TB prevention and is now a recommended option by the CDC. However, it is unknown whether this short-course regimen provides the same protection to HIV-infected persons as longer treatment with isoniazid alone. Sterling and colleagues presented data from analysis of the 399 HIV-infected persons enrolled in the randomized trial that was the basis for the new recommendation on short-course preventive TB therapy (Abstract 817). Participants were followed for 33 months and the noninferiority margin was 0.75%. Regimen completion rate was higher in the short-course treatment arm (88%) compared with the standard treatment arm (64%). There were only 8 cases of TB total, and the cumulative rates of TB were similar between the 2 arms (1.01% in the short-course arm vs 3.69% in the standard arm). Drug discontinuations were low and rates were similar between the arms (3.4% in the short-course arm vs 4.2% in the standard arm). The overall number of TB cases was low in this study, reflecting the epidemiology of TB in this population. Nevertheless, the study provides reassurance that a short-course, once-weekly regimen can be safely used in HIV-infected patients.

**Financial affiliations in the past 12 months:** Dr Luetkemeyer has served as a consultant or advisor to Gilead Sciences, Inc, and has received travel support from Bristol-Myers Squibb and Gilead Sciences, Inc. She has also received grants awarded to her institution from Gilead Sciences, Inc, Janssen Therapeutics, Vertex Pharmaceuticals, Inc, Bristol-Myers Squibb, Pfizer, Inc, and AbbVie. Dr Havlir has received a grant awarded to her institution from Gilead Sciences, Inc, to support drug donations for a clinical program. Dr Currier has served on an advisory board for ViV Healthcare and has received grants awarded to her institution from Merck & Co, Inc, and ViV Healthcare.

A list of all cited abstracts appears on pages 632-638 of this issue. Abstracts are published in *Top Antivir Med.* 2014;22(e-1):1-570, a special online issue available at www.iasusa.org/pub.

**Additional References**

2. AbbVie. AbbVie completes largest phase III program of an all-oral, interferon-free therapy for the treatment of hepatitis C.


CROI 2014: Advances in Antiretroviral Therapy

Barbara S. Taylor, MD, MS, Noga Shalev, MD, and Timothy J. Wilkin, MD, MPH

The 2014 Conference on Retroviruses and Opportunistic Infections (CROI) highlighted important advances in antiretroviral therapy, with an emphasis on HIV eradication strategies. Follow-up information about the Mississippi baby who remains free of HIV infection off antiretroviral therapy was presented, and a second baby and 1 adult may also have been cured with very early initiation of antiretroviral therapy. The HIV care cascade was again a major focus of the conference. Investigators from around the world presented data on the implementation, and limitations, of the care cascade paradigm. Scale-up of antiretroviral therapy continues and a number of presentations featured optimal ways to measure the impact of these efforts by applying lessons from implementation science and health care economics. Encouraging results from expanded prevention of mother-to-child transmission programs, especially Option B+, were highlighted. Extensive data on transmitted (primary) drug resistance in the United States and Europe were presented.

Keywords: cascade of care, CROI 2014, cure, HIV, resource limited, treatment

Clinical Studies Investigating HIV-1 Cure

Persaud and colleagues presented further data on the Mississippi child thought to be cured of HIV infection and a second baby with a possible cure (Abstract 75LB) at the 2014 Conference on Retroviruses and Opportunistic Infections (CROI), held from March 3 to 6, 2014. The Mississippi child has been described previously. This child remains off antiretroviral therapy with undetectable plasma HIV-1 RNA through 41 months of age (23 months after stopping antiretroviral therapy). Trace levels of HIV-1 DNA remain in peripheral blood mononuclear cells (PBMCs), but no replication-competent virus could be found and no HIV-1 DNA could be identified in PBMCs with the sensitive droplet digital polymerase chain reaction (PCR) assay. HIV-specific cellular and humoral responses are not detectable.

The investigators also reported on a second baby who was born to a mother who did not receive prenatal antiretroviral therapy. The baby started combination antiretroviral therapy at 4 hours of life. The baby had detectable HIV-1 DNA in the peripheral blood at 4 hours of life and detectable plasma HIV-1 RNA (217 copies/mL) at 36 hours. Plasma HIV-1 RNA was undetectable by day 11 and has remained undetectable through 9 months. HIV-1 DNA was undetectable at day 6 by droplet digital PCR and has remained undetectable. HIV-1 RNA was detected at day 6 in cerebrospinal fluid obtained from a lumbar puncture during evaluation for possible sepsis. No replication-competent virus was recovered at 1, 3, and 9 months of life. Noninduced proviral genomes were detected by droplet digital PCR in stimulated T cells at 1 month, but not at 3 months or 9 months. HIV antibody status was indeterminate at 3 months and negative at 9 months.

The infant remains on combination antiretroviral therapy in contrast to the Mississippi child who has remained off antiretroviral therapy. Planned clinical trials will try to replicate these observations in other infants.

Hatano and colleagues presented data on an adult who started tenofovir/emtricitabine for preexposure prophylaxis (PrEP) and was subsequently found to have had low-level plasma HIV-1 RNA at the time of PrEP initiation (Abstract 397LB). This patient was intensified to a standard 3-drug antiretroviral regimen. Two additional measurements after PrEP initiation showed detectable plasma HIV-1 RNA. All assays for HIV-1 DNA were negative. A plasma HIV outgrowth assay was negative for inducible viruses. An HIV Western blot was initially indeterminate and subsequently became negative. A treatment interruption is planned after 1 year of antiretroviral therapy.

Treatment Intensification With or Without Therapeutic HIV-1 Vaccination

Murphy and colleagues presented data on ERAMUNE-02, a pilot clinical trial that investigated whether intensification of suppressive antiretroviral therapy with maraviroc/raltegravir with or without therapeutic HIV-1 vaccination would decrease the HIV-1 latent reservoir as assessed by measuring HIV-1 DNA levels (Abstract 422). All participants underwent intensified antiretroviral therapy with maraviroc/raltegravir at baseline for 8 weeks; participants were then randomized to continue either intensified antiretroviral therapy alone (n = 14) or with therapeutic HIV-1 vaccination.

Dr Taylor is Assistant Professor of Infectious Diseases at the University of Texas Health Science Center at San Antonio. Dr Shalev is Assistant Professor of Clinical Medicine at the Columbia University College of Physicians and Surgeons in New York, New York. Dr Wilkin is Associate Professor of Medicine at the Weill Cornell Medical College in New York, New York. Send correspondence to Timothy J. Wilkin, MD, MPH, Division of Infectious Diseases, Weill Cornell Medical College, 53 West 23rd Street, 6th Floor, New York, NY 10010. Received on March 31, 2014; accepted on April 2, 2014.
Vaccination (3 doses of DNA prime vaccine followed by recombinant adenovirus-5 vaccine; n = 14). Neither strategy achieved the goal of reducing HIV-1 DNA levels by at least 0.5 log_{10} copies/mL at 1 year postrandomization in at least 2 participants. Only 1 participant in the intensification alone group achieved this goal. Similarly, no participant in the intensification alone in at least 2 participants. Only 1 participant in the intensification alone group achieved this goal. Similarly, no participant in the intensification alone group achieved this goal.

**Predictors of Residual Viremia**

Residual viremia (ie, viremia detected using a plasma HIV RNA assay with a sensitivity of <1 copy/mL) has been proposed as a measure of the HIV-1 latent reservoir. Riddler et al. investigated predictors of residual viremia in patients with long-term suppression on antiretroviral therapy (Abstract 425LB). They examined 334 patients who maintained virologic suppression for 4 years after initiating antiretroviral therapy. They analyzed 2 plasma samples obtained approximately 4 years after antiretroviral therapy initiation using a single copy assay. Consistent with prior studies, residual viremia (plasma HIV RNA level ≥1 copy/mL) was predicted by higher pretreatment plasma HIV-1 RNA level. They also found that higher on-treatment CD8+ cell counts and lower on-treatment CD4+/CD8+ cell count ratios were predictive of detectable residual viremia, even when controlling for pretreatment plasma HIV-1 RNA levels.

**Vorinostat**

Prior single-dose studies of vorinostat suggested that this histone deacetylase inhibitor reactivates latent HIV-1 in vivo. Margolis and colleagues examined 5 participants who received vorinostat for 4 cycles (where 1 cycle is defined as 3 daily doses followed by 4 days off), followed by 4 weeks to 8 weeks off therapy, followed by another 4 cycles. They found that in contrast to single-dose studies of vorinostat, repeated doses did not appreciably increase histone deacetylase inhibition from baseline and expression of cellular HIV-1 RNA was not increased. These results do not support further studies of vorinostat for HIV-1 cure strategies.

### Investigational Antiretroviral Therapy Agents

#### Entry Inhibitors

Kattenhorn and colleagues presented preclinical data on eCD4-Ig, an enhanced CD4-immunoglobulin (lg) fusion protein consisting of the first 2 N-terminal domains of the CD4 molecule and the Cc region of human IgG1 coupled with a small C-C chemokine receptor type 5 (CCR5)-mimetic sulfopeptide (Abstract 528). This compound neutralized a wide array of viral isolates that were resistant to broadly neutralizing monoclonal antibodies. The investigators noted that this compound is a promising candidate for both the treatment and prevention of HIV-1 infection.

#### Inhibitors of Vif-APOBEC3 Interactions

Two abstracts presented data on targeting the interaction between APOBEC3G (apoB mRNA editing enzyme, catalytic polypeptide-like 3G; also known as A3G), a cellular cytidine deaminase that restricts HIV replication by inducing G-to-A hypermutation in viral DNA, and Vif (viral infectivity factor), a protein produced by HIV that binds A3G and targets it for proteasomal degradation. Pery and colleagues conducted a high-throughput screen to identify a lead compound that inhibits HIV regulation by increasing A3G activity and freeing it from control by Vif. Bennett and colleagues targeted Vif dimerization, which is a necessary step prior to binding A3G (Abstract 552). They have identified a compound that blocks Vif dimerization and inhibits infection of PBMCs against a broad range of viral isolates.

### Clinical Trials of Initial Antiretroviral Therapy

#### Comparison of Non–Efavirenz-Containing Antiretroviral Regimens

Landovitz and colleagues presented data from AIDS Clinical Trials Group (ACTG) A5257, an open-label clinical trial of 3 non–efavirenz-based antiretroviral regimens (raltegravir, ritonavir-boosted [r] atazanavir, or darunavir/r, each given with tenofovir/emtricitabine) for initial treatment of HIV-1 infection (Abstract 85). Participants (n = 1809) were randomized 1:1:1 to these 3 arms and began assigned therapy. Using a definition of +1–10%, these 3 regimens were equivalent in terms of virologic efficacy (time to confirmed plasma HIV-1 RNA level >200 copies/mL). The regimens were not equivalent with regard to the second primary end point of time to change in randomized treatment. Participants randomized to atazanavir/r changed therapy more often than did those randomized to raltegravir or darunavir/r, which were found to be equivalent to each other (16% vs 1% and 5%, respectively). Atazanavir/r discontinuations were due to hyperbilirubinemia (as would be expected) but also to higher rates of gastrointestinal toxicities.

When looking at a preplanned comparison of time to a composite of either primary end point, raltegravir appeared superior to darunavir/r, which was in turn superior to atazanavir/r. Among 295 virologic failures across the study arms, 9 (1.5%), 18 (3%), and 4 (<1%) participants in the atazanavir, raltegravir, and darunavir arms had treatment-emergent resistance detected during follow-up. Similar to prior studies, no protease resistance was detected at failure. For the raltegravir arm, 17 of 18 had nucleoside analogue reverse transcriptase inhibitor (nRTI) resistance and 11 of 18 had integrase strand transfer inhibitor (INSTI) resistance.

#### nRTI-Sparing Antiretroviral Therapy

Raffi and colleagues presented data on NEAT 001/ANRS 143 (European AIDS Treatment Network 001/French National Agency for Research on AIDS and Viral Hepatitis 143), a randomized, open-label clinical trial comparing darunavir/r given with tenofovir/emtricitabine or raltegravir for initial treatment of HIV-1 infection (Abstract 84LB). They enrolled 805 participants (88% male). The primary end point was time to virologic...
failure or clinical failure (death, or new AIDS or serious non-AIDS event). Raltegravir was found to be noninferior to tenofovir/emtricitabine (17.4% vs 13.7% experienced the primary end point, respectively; difference 3.7%; 95% CI, -1.1%-8.6%). A greater decrease in creatinine clearance was found in the tenofovir/emtricitabine arm, and more treatment-emergent resistance was seen with raltegravir. The investigators concluded that darunavir/r plus raltegravir represents a reasonable, nRTI-sparing choice for first-line antiretroviral therapy.

**744 and Rilpivirine**

Margolis and colleagues presented data from the LATTE (Long-Acting Antiretroviral Therapy Treatment Enabling) study, a phase II, dose-finding clinical trial of investigational HIV INSTI GSK1265744 (also known as 744) plus 2 nRTIs versus efavirenz plus 2 nRTIs for initial treatment of HIV-1 infection (Abstract 91LB). Participants were randomized to 1 of 3 blinded doses of oral 744 (10 mg, 30 mg, or 60 mg daily) or open-label efavirenz. If their plasma HIV RNA levels were undetectable just before week 24, participants in the 744-containing arms discontinued nRTIs and initiated rilpivirine (25 mg daily). Further data on the efficacy of maintenance therapy with 744 plus rilpivirine are needed to support future clinical trials of injectable, long-acting formulations of these compounds. This trial randomized 243 participants to the 4 arms: 96% were male, 38% nonwhite.

At week 48, 82% of participants receiving 744 had undetectable HIV RNA levels by the US Federal Drug Administration (FDA) snapshot analysis versus 71% of participants receiving efavirenz. The higher failure rate in the efavirenz-containing arms was driven by higher rates of treatment discontinuation due to adverse events. A second analysis limited to those who entered the maintenance phase found similar rates of continued virologic suppression among the 4 arms. 744 appeared safe and well tolerated, although more participants in the 744-containing arms experienced headache. Drug resistance emerged in 1 participant receiving 744 and 1 participant receiving efavirenz. These data are supportive of future trials to evaluate combination injectable formulations of 744 and rilpivirine for initial treatment of HIV-1 infection.

**Doravirine**

Morales-Ramirez and colleagues presented data from a phase II, dose-finding clinical trial of doravirine (MK-1439), an investigational HIV nonnucleoside analogue reverse transcriptase inhibitor (NNRTI; Abstract 92LB). Participants (n = 208) were randomized to blinded treatment with doravirine (25 mg, 50 mg, 100 mg, or 200 mg once daily) or efavirenz, each given with tenofovir/emtricitabine. The primary end point was achieving plasma HIV-1 RNA levels less than 40 copies/mL at week 24. This ranged from 71% to 80% of participants in the 4 doravirine arms (76% for the 4 arms combined), with no dose-response relationship noted, and 64% in the efavirenz arm. A plasma HIV-1 RNA level less than 200 copies/mL was achieved in 88.5% of participants in the doravirine arms versus 81% in the efavirenz arm. No statistical testing was performed for these comparisons. Doravirine appeared safe and tolerable, and a lower rate of dizziness was observed in the doravirine arms than in the efavirenz arm. The investigators concluded that further studies of doravirine are warranted, and they selected a dose of 100 mg for future studies.

**Clinical Trials of Antiretroviral Therapy During Acute HIV-1 Infection**

Schuetz and colleagues presented data on the relationship between timing of antiretroviral therapy initiation during acute HIV-1 infection and maintenance of the mucosal barrier (Th17 cells on rectal biopsies) and T-cell activation (CD8+/CD38+/HLA-DR+ [human leukocyte antigen-D–related]; Abstract 77). They enrolled 38 participants who initiated antiretroviral therapy during acute HIV-1 infection and had rectal biopsies and blood sampling before and 6 and 12 months after initiating antiretroviral therapy. They enrolled 5 participants who initiated antiretroviral therapy during chronic HIV-1 infection and 10 HIV-uninfected controls who were sampled at 1 time point.

They found that participants who initiated antiretroviral therapy during Fiebig stage I or II (ie, prior to detectable HIV-1 antibody by enzyme-linked immunosorbent assay [ELISA]) maintained levels of Th17 cells similar to those of HIV-uninfected controls. Participants who initiated antiretroviral therapy during chronic HIV-1 infection had depleted Th17 cells, and participants who initiated therapy during Fiebig stage III (ie, detectable HIV-1 antibody by ELISA, but not by Western blot) had levels in between these groups. Fiebig III participants maintained levels of T-cell activation similar to those of HIV-uninfected controls at all time points. Fiebig III participants had increased T-cell activation before therapy compared with Fiebig III participants and HIV-uninfected controls, and similar levels at 6 months and 12 months after therapy initiation. This suggests that early initiation of antiretroviral therapy during acute HIV-1 infection prevents disruption of the mucosal barrier and associated T-cell activation.

Chéret and colleagues investigated an intensive 5-drug regimen for antiretroviral therapy during acute HIV-1 infection (Abstract 549LB). They enrolled 90 participants who initiated treatment during acute HIV-1 infection and were randomized to receive darunavir/r plus tenofovir/emtricitabine with or without maraviroc/raltegravir. They found similar decreases in the HIV-1 reservoir as measured by HIV-1 DNA for 2 years in both groups. The rates of virologic suppression were similar at 2 years. Treatment was interrupted after 2 years. One participant in each group maintained virologic suppression after treatment interruption. The investigators concluded that there was no evidence to support intensive antiretroviral regimens for treatment of acute HIV-1 infection.
Maintenance and Switch Strategies

Once-Daily Lopinavir/r Dosing in Children and Adolescents

Lyall presented data on behalf of the KONCERT team (Abstract 74LB). This clinical trial enrolled 175 children (<18 years of age and ≥15 kg in weight) who were receiving twice-daily lopinavir/r and randomized them to continue twice-daily or change to once-daily dosing. Although all children were required to have plasma HIV-1 RNA levels less than 50 copies/mL at screening, 14% of those randomized to once-daily and 5% of those randomized to twice-daily dosing had detectable plasma HIV-1 RNA at trial entry. Once-daily dosing did not achieve noninferiority with regard to virologic suppression 48 weeks after randomization (difference -6%; 90% CI, -2% to 14%). Pharmacokinetic analyses showed a lower lopinavir exposure in the once-daily arm. There were no safety concerns or appreciable differences in the emergence of viral resistance. The investigators concluded that once-daily dosing of lopinavir/r in children could not be recommended based on these data.

Ritonavir-Boosted Protease Inhibitor Therapy Alone

Paton and colleagues reported on a large study of simplification to a ritonavir-boosted protease inhibitor (PI/r) alone as maintenance therapy (Abstract 550LB). They randomized 587 participants (77% male, 68% white) who had plasma HIV-1 RNA levels less than 50 copies/mL for at least 6 months and no prior virologic failure to continue current antiretroviral therapy or to change to PI/r alone. Participants were monitored for plasma HIV-1 RNA levels every 3 months. Resistance testing was obtained for participants with confirmed plasma HIV-1 RNA levels of 50 copies/mL or higher. Two nRTIs were added for participants in the PI/r arm if there were confirmed plasma HIV-1 RNA levels at this threshold. The primary end point was loss of future drug options based on resistance testing. As expected, confirmed plasma HIV-1 RNA was more common in the PI/r arm than the continuation arm (35% vs 3%, respectively; P < .001); 58% of the PI/r arm remained on PI/r alone through the end of the trial. Resistance was rare in both arms. Loss of future drug options was observed in 6 participants from the PI/r arm and 4 from the continuation arm (P > .5). Antiretroviral drug costs were substantially lower in the PI/r arm. The investigators concluded that PI/r alone was a safe and tolerable long-term management strategy for antiretroviral treatment.

Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Maintenance

Two clinical trials examined the efficacy of changing suppressive antiretroviral therapy to fixed-dose elvitegravir/cobicistat/emtricitabine/tenofovir (EVG/COBI/FTC/TDF). Arribas and colleagues presented data on switching from a PI-based regimen to EVG/COBI/FTC/TDF. They randomized 443 participants (86% male, 18% nonwhite) without prior virologic failure or resistance to tenofovir or emtricitabine to continue current antiretroviral therapy or switch to EVG/COBI/FTC/TDF (Abstract 551LB). At 48 weeks postrandomization, 94% of participants in the EVG/COBI/FTC/TDF arm maintained plasma HIV-1 RNA levels less than 50 copies/mL versus 87% in the PI-based arm (difference 6.7%; 95% CI, 0.4% to 13.7%; P = .025). EVG/COBI/FTC/TDF achieved the primary end point of noninferiority to PI-based regimens and was found to be superior in a secondary analysis. No viral resistance emerged and no safety concerns were found in either group.

Pozniak and colleagues found similar results when enrolling patients receiving an NNRTI-based regimen (Abstract 553LB). They randomized 434 participants (93% male, 22% nonwhite) without prior virologic failure or resistance to tenofovir or emtricitabine to continue current NNRTI plus tenofovir/emtricitabine or switch to EVG/COBI/FTC/TDF. At 48 weeks postrandomization, 93% of participants in the EVG/COBI/FTC/TDF arm maintained plasma HIV-1 RNA levels less than 50 copies/mL versus 88% in the NNRTI-based arm (difference 5.3%; 95% CI, 0.5% to 12%). And EVG/COBI/FTC/TDF was found to be noninferior to NNRTI-based regimens. No viral resistance emerged and no safety concerns were found in either group. Based on these 2 studies, changing suppressive antiretroviral therapy to EVG/COBI/FTC/TDF appears to be safe and efficacious in this selected population without prior virologic failure or nRTI resistance.

Clinical Trials in Treatment-Experienced Patients

BMS-663068

BMS-663068, a prodrug of BMS-656529, is an investigational HIV-1 attachment inhibitor that binds envelope glycoprotein gp120 and prevents the binding of HIV to a CD4+ T cell. Lalazari and colleagues presented data on the antiviral efficacy and dose response for this compound versus atazanavir/r in treatment-experienced adults (Abstract 86). This trial randomized 254 adults to 1 of 4 doses of BMS-663068 (400 mg or 800 mg twice daily, 600 mg or 1200 mg daily) or atazanavir/r. Participants randomized to BMS-663068 received monotherapy for 7 days followed by the addition of tenofovir and raltegravir. Monotherapy led to a reduction in plasma HIV-1 RNA levels from 0.7 log10 copies/mL to 1.5 log10 copies/mL. Participants randomized to atazanavir/r initiated combination therapy with tenofovir and raltegravir. Participants in all arms had good virologic suppression at week 24: 69% to 80% achieved plasma HIV-1 RNA levels less than 50 copies/mL, and there were no safety concerns. The investigators concluded that further studies of this compound are warranted.

Clinical Trials to Reduce Immune Activation

Prednisolone

Kasang and colleagues investigated low-dose prednisolone for treatment of
immune activation and prevention of disease progression in untreated HIV-infected adults (Abstract 336). They randomized 336 HIV-infected adults with a CD4+ cell count higher than 300/µL to prednisolone 5 mg daily or placebo, with a 2-year follow-up period for the occurrence of an AIDS-defining event or CD4+ cell count below 200/µL. There was no difference between arms in this end point, but time to a new AIDS-defining condition was longer in the prednisolone arm. They found that prednisolone decreased soluble (s) CD14 levels and increased CD4+ cell counts and CD4+/CD8+ cell count ratios but increased plasma HIV-1 RNA levels. The investigators suggested that this therapy merited further study.

**Mesalamine**

Samsouk and colleagues investigated the use of mesalamine, a mucosally active antiinflammatory agent, to reduce systemic immune activation by reducing mucosal inflammation and bacterial translocation (Abstract 341). They conducted a randomized, placebo-controlled crossover trial of a once-daily, extended-release formulation of mesalamine. They enrolled 33 (100%) participants with incomplete immune restoration (approximate median CD4+ cell count = 245/µL). They found no effect of mesalamine on systemic or mucosal immune activation as measured by CD8+/CD38+/HLA-DR+ cells in the peripheral blood or on rectal biopsies. Mesalamine did not lead to a reduction in bacterial translocation as measured by sCD14 or in soluble markers of immune activation. The investigators concluded that other strategies are needed to reduce bacterial translocation and systemic immune activation.

**Rifaximin**

Tenorio and colleagues reported on a randomized, open-label clinical trial of rifaximin, an oral, nonabsorbable antibiotic that reduces plasma lipopolysaccharide (LPS; a marker of bacterial translocation) levels in patients with cirrhosis (Abstract 339). They randomized HIV-infected adults with suboptimal immune reconstitution (CD4+ cell count < 550/µL) despite sustained virologic suppression to receive 4 weeks of open-label rifaximin (n = 49) or no treatment (n = 24). A separate control group of HIV-uninfected adults (n = 20) provided a reference for observed results in the randomized population. They found that the rifaximin group had lower levels of immune activation than the no treatment group at week 4 (end of rifaximin treatment) but not at week 2 (2 weeks into rifaximin treatment) or week 8 (4 weeks after rifaximin treatment). Inconsistent responses were observed with the microbial translocation markers: changes in LPS and sCD14 levels were statistically significantly lower for rifaximin at week 2; no changes were observed at week 4; and changes in sCD14 levels were lower for rifaximin at week 8. Rifaximin was associated with a statistically significant, but minimal, decrease in IL-6 and C-reactive protein (CRP) levels 4 weeks after completion of rifaximin treatment. These data suggest that immune activation may be modifiable through reductions of bacterial translocation. However, the magnitude and durability of this effect were minimal, suggesting that further study of alternative treatments is warranted.

**Sevelamer**

Sandler and colleagues investigated the use of sevelamer to reduce microbial translocation and immune activation in HIV-infected adults (Abstract 357). Sevelamer is a nonabsorbable polymer that binds phosphate and reduces LPS by 78% in dialysis patients. The investigators enrolled 30 HIV-infected adults who received sevelamer for 8 weeks. They found that LPS and sCD14 levels were not reduced by sevelamer. Levels of low-density lipo-protein (LDL), oxidized LDL, and tissue factor were statistically significantly reduced with sevelamer, but D-dimer levels showed a small, statistically significant increase. Sevelamer did not decrease microbial translocation as hypothesized and whether its effects on LDL and oxidized LDL merit further study is unclear.

**Probiotics**

Stiksrud and colleagues used a different approach to reduce immune activation (Abstract 342). They attempted to alter the gut microbiota through probiotics to reduce markers of inflammation, coagulation, and microbial translocation that have been associated with all-cause mortality in other studies. The probiotic consisted of fermented skim milk supplemented with *Lactobacillus rhamnosus*, *Bifidobacterium animalis* subsp. *lactis*, and *L. acidophilus*. They enrolled 30 participants and randomized them to the probiotic (n = 14), a placebo of fermented skim milk (n = 8), or a second control of no treatment (n = 8) for 8 weeks. Levels of D-dimer, CRP, and IL-6 declined in the probiotic group but did not change appreciably in the nonprobiotic group (a combination of the placebo and no treatment groups). No change was noted in LPS or sCD14 levels. Further data on gut microbiota and immune activation by flow cytometry are pending. This pilot trial should be followed by larger studies with longer durations of follow-up.

**Pharmacokinetic Considerations**

**Impact of HIV Infection on Intestinal Epithelial Transporters**

Bendayan and colleagues investigated the intestinal mucosal expression of drug transport enzymes in HIV-infected adults not on antiretroviral therapy, HIV-infected adults with well-controlled HIV infection, and a matched control group of HIV-uninfected adults (Abstract 103). They found that the transporters studied were expressed at lower levels in HIV-infected adults than in uninfected controls. These levels were partially restored by antiretroviral therapy. These findings were confirmed by decreased gene expression for these transporters in the HIV-infected groups. This suggests that HIV infection itself may influence drug metabolism.
Rilpivirine and Darunavir/r

Jackson and colleagues presented data on 25 HIV-infected participants initiating a once-daily combination of rilpivirine (25 mg) and darunavir/r (800 mg/100 mg; Abstract 507). They found that rilpivirine concentrations were somewhat higher in this study than in prior phase III studies of rilpivirine given with 2 nRTIs. Darunavir and ritonavir concentrations were not affected. The investigators concluded that this drug combination should be investigated in future studies. Jackson and colleagues found differing results when studying HIV-infected young adults and adolescents (Abstract 508). They found that rilpivirine concentrations were similar to those observed in older adults when dosed without darunavir/r, whereas rilpivirine concentrations were three-fold higher when coadministered with darunavir/r. The investigators could not conclude whether the higher rilpivirine concentrations observed with darunavir/r coadministration would impact safety and tolerability.

Lopinavir/r and Depot Medroxyprogesterone Acetate

Luque and colleagues presented data on behalf of AIDS Clinical Trials Group protocol A5283 that investigated the effect of lopinavir/r on the pharmacokinetics of depot medroxyprogesterone acetate (MPA; Abstract 514LB). They found that lopinavir/r concentrations were not affected by depot MPA. The MPA concentrations were 46% higher than in historic HIV-uninfected controls from a prior study. Depot MPA appeared safe and well tolerated. There was no evidence of ovulation in the study participants.

Antiretroviral Therapy in Pregnancy

Colber and colleagues investigated changes in darunavir/r pharmacokinetics associated with pregnancy (Abstract 887). They reported on darunavir and ritonavir concentrations observed in 15 HIV-infected pregnant women during the third trimester and at least 2 weeks postpartum. They found that darunavir trough concentrations were 64% lower in the third trimester than postpartum. The investigators noted that twice-daily dosing should be used for treatment-experienced patients during pregnancy.

Lê and colleagues reported data on 103 HIV-infected pregnant women receiving atazanavir/r (Abstract 889). They found that atazanavir concentrations were not substantially altered during pregnancy; drug concentrations were assessed during each trimester, at delivery, and postpartum. The trough concentrations were approximately 30% lower during pregnancy than postpartum, which was not thought to be clinically significant by the investigators. The virologic outcomes were excellent: 97% had plasma HIV RNA levels less than 50 copies/mL at the time of delivery, and no cases of mother-to-child transmission (MTCT) were observed. Atazanavir/r appeared safe in this population. Similar reductions of atazanavir trough concentrations during pregnancy were observed in a separate study of HIV-infected women, and these concentrations were not affected by concomitant use of tenofovir (Abstract 892).

Blank and colleagues investigated the pharmacokinetics of raltegravir during pregnancy (Abstract 890). They found that trough concentrations were reduced by 50% during the third trimester but thought this reduction unlikely to be clinically significant. They found that raltegravir efficiently crossed the placenta into the fetal circulation.

Examining the HIV Care Cascade in Resource-Limited and Other Settings

The cascade of care for HIV, prominent at CROI 2013, was again popular this year as a metric for examining the effectiveness of HIV treatment programs. Many investigators presented data on the cascade, or alternative constructions of the cascade itself, yet a few common themes emerged. In studies that examine the complete cascade from diagnosis to successful virologic suppression, substantial barriers to diagnosis and linkage to care remain, even in high-prevalence countries with active testing programs. Population mobility is a key challenge because it leads to loss to follow-up at all stages of the cascade and simultaneously contributes to overestimation of loss to follow-up when care transfers are not accounted for. As Bangsberg pointed out while leading the themed discussion Treatment Cascade and Loss to Follow-Up, without direct ascertainment of vital status for those considered lost to follow-up, mortality and transfers of care are vastly underestimated at all steps of the cascade. Despite these issues, the continued focus on the care cascade at CROI 2014 demonstrates the utility of the construct, and some of the key cascade-related findings are reviewed below.

Population-Based Surveillance of the HIV Care Cascade

Maina and colleagues presented data from KAIS (Kenya AIDS Indicator Survey), a countrywide, 2-stage stratified cluster sampling survey of household residents 18 months to 64 years of age from October 2012 and February 2013 (Abstract 149). KAIS offered home-based HIV testing and CD4+ cell count measurement and linkage to care for those diagnosed with HIV infection. Although the percentage of individuals ever tested for HIV infection increased from 54% in 2007 to 70% in 2012, awareness of HIV serostatus among HIV-infected individuals remained low, 47% in 2012. Prevalence in children (0.9%) was lower than that of adults (5.6%), but only 16% of children had ever been tested for HIV infection.

By Kenyan eligibility guidelines for antiretroviral therapy, 58.8% of individuals with HIV infection were eligible for treatment, but only 60.5% of those eligible were receiving treatment. Encouragingly, 75% of those receiving antiretroviral therapy were virologically suppressed to an HIV-1 plasma RNA level less than 1000 copies/mL. These country-level results highlight the fact that even in the setting of dramatic scale-up of testing and treatment, many individuals, particularly...
children, are unaware of their HIV serostatus, and the drop-off in the care cascade between eligibility and antiretroviral therapy coverage seen in many other settings was also observed here.

Huerga and colleagues conducted a similar cross-sectional population-based study in KwaZulu Natal, South Africa, a population highly impacted by the HIV epidemic, with an overall HIV prevalence of 25% and women (31%) much more impacted than men (16%; Abstract 152LB). Examining the overall cascade, the investigators found that 75% of HIV-infected participants were aware of their HIV serostatus, 65% were linked to care, 57% had initiated antiretroviral therapy, 52% remained on treatment, and 49% were virologically suppressed. Of those with plasma HIV-1 RNA levels greater than 1000 copies/ml, 72% had antiretroviral drug resistance. Statistically significant sex disparities were seen in incidence, awareness of diagnosis, and antiretroviral therapy coverage, and all of these disparities were higher in women. Thus, in both Kenya and KwaZulu Natal, population-based surveys revealed challenges in diagnosis and linkage to care but good virologic response once antiretroviral therapy was initiated, demonstrating the utility of population-based surveys in directing national public health efforts.

**Evaluations of Specific Steps in the HIV Care Cascade and Interventions to Improve Selected Components**

Several groups presented data that shed light on specific steps in the HIV care cascade or interventions to improve specific components. Mehta and colleagues (Abstract 1063) examined the HIV care cascade for men who have sex with men (MSM; n = 12,022) and IDUs (n = 14,481) across 26 treatment sites in India. They found that few HIV-seropositive MSM (30%) and IDUs (41%) were aware of their diagnosis, which represents the most substantial barrier to engagement in care along the cascade for these vulnerable populations. Awareness of HIV serostatus was associated with receipt of and linking HIV testing to other services, such as treatment for tuberculosis, STIs, and opioid dependence.

Barnabas and colleagues (Abstract 148) addressed similar barriers of diagnosis and engagement in care with an intervention package in South Africa and Uganda that included community sensitization, household consent for home-based HIV testing, point-of-care CD4+ cell count measurement, referral to care or prevention services for individuals with negative HIV test results, and follow-up visits. They tested 96% of individuals residing in the target communities and achieved excellent results for clinic engagement (96% at 6 months after study visit), for both newly and previously diagnosed individuals with HIV infection. The intervention package appeared to be highly successful, with 65% of HIV-seropositive individuals achieving virologic suppression (up from 50% pre-intervention).

**Limitations of the Current HIV Care Cascade and Its Paradigms**

McNairy and colleagues (Abstract 151) pointed out limitations of the HIV cascade of care concept: each step is contingent on the prior step; outcomes of people prior to antiretroviral therapy initiation are excluded; there are many reasons for loss between cascade steps; and the time frame for movement between steps is not considered. They proposed a parallel cascade approach to follow up all patients over time and divide them into 3 outcome categories: optimal, retained or transferred to other facilities; suboptimal, retained but without optimal care or missing data; or poor, lost to follow-up or death. They used routinely collected data from 390,603 adults across 217 facilities in sub-Saharan Africa and calculated the proportion of patients in each of the 3 categories at 3, 6, and 12 months after enrollment in care, but considering the lack of data on virologic control, they adapted cascade steps. They found that 56% of patients had an optimal outcome of care at 12 months: retained in care pre-antiretroviral treatment, on treatment, or transferred. Application of the traditional cascade to the same cohort showed only 23% of patients retained on antiretroviral treatment at 12 months. They proposed that the use of both cascades is inclusive of all patients, before and on antiretroviral therapy, and identifies those at high risk for poor outcomes over time.

Three other groups incorporated similar concepts to examine limitations to the traditional HIV care cascade. Reidy and colleagues (Abstract 1061) ascertained vital status for a subgroup of patients in care in Kenya before and after initiation of antiretroviral therapy and found that including the additional vital status information decreased percent lost to follow-up pre–antiretroviral therapy from 38% to 12%; increased those labeled in care from 52% to 75%; owing mostly to clinic transfers; and increased mortality from 10% to 19%. Less dramatic changes after vital status ascertainment were seen for those on antiretroviral therapy, highlighting the limitations of using routinely collected data to assess retention in the care cascade, particularly for pre–antiretroviral therapy patients.

Ahonkhai and colleagues (Abstract 1064) examined unplanned interruptions and return to care along the cascade and found that 37% of patients at a single site in Nigeria had an unplanned care interruption but returned to care at some point during the 3 years of observation. These interruptions were most common in the first year on antiretroviral therapy and at higher baseline CD4+ cell counts. Holmes and colleagues (Abstract 1065) also examined the impact of return to care on the cascade across 18 sites in Zambia. Similar to the results from Nigeria, they found that 35% of the patients classified as lost to follow-up returned to care. They observed negative consequences of these temporary interruptions, including statistically significant decreases in body mass index and CD4+ cell counts and increased rates of active tuberculosis, World Health Organization (WHO) stage III and IV HIV disease, and pregnancy upon return to care.
Data presented at CROI 2014 on the value of the HIV care cascade in other settings support the findings from resource-limited settings. Using data from the US Center for AIDS Research Network of Integrated Clinical Systems (CNICS) sites, Mugavero and colleagues found that incorporating rates of missed clinic visits improved standard prediction models for all-cause mortality that employ a retention-in-care metric of 2 visits per year (Abstract 983). Espinoza and colleagues from the US Centers for Disease Control and Prevention (CDC) found high rates of migration to a different state after diagnosis of HIV infection (11% ever migrated and 2.5% migrated within 1 year of diagnosis), implying that population mobility also impacts the HIV care cascade in non-resource-limited settings.

**Antiretroviral Therapy Scale-Up in Resource-Limited Settings**

**Intersection Between Research, Antiretroviral Therapy Scale-Up, and Policy**

Three sessions at this year’s conference focused on the translation of research into capacity building, successful scale-up of antiretroviral therapy, and development of policy in resource-limited settings. Mboup (Abstract 18) began the dialogue with the 2014 N’Galy-Mann Lecture. He highlighted the success of the Senegalese HIV prevention and treatment program, which began sentinel surveillance in 1989 and initiated antiretroviral treatment in 1997, well ahead of most other countries in sub-Saharan Africa. He proposed several factors responsible for their early success, including fully engaged political leadership; national programs for control of STIs, such as registration and care for commercial sex workers; a strong strategic information system with early sentinel surveillance programs followed by expanded and ongoing behavioral surveys; and a commitment to research, leading to technology transfer and capacity strengthening through international collaboration.

The specific contributions of research to the Senegalese success story include the early development of a longitudinal cohort of commercial sex workers, established in 1985, which provided a comprehensive platform from which to examine the interaction of the simultaneous HIV-1 and HIV-2 epidemics. This foundation allowed the launch of the Senegalese Antiretroviral Access Initiative (ISAARV) in December 1997. This antiretroviral therapy treatment program was expanded to create a decentralized national system with outstanding results, including high levels of adherence, immune response to antiretroviral therapy, and virologic suppression. ISAARV continues and is now pioneering the use of dried blood spot technology for HIV-1 plasma RNA level assessment and HIV genotype testing. Mboup cited international research collaborations as being instrumental in the expansion of a small virology laboratory into an international reference and research laboratory. These collaborations are ongoing and formalized in programs such as the regional West African Platform for HIV Intervention Research (WAPHIR). Their new and ambitious goal is to establish a center of excellence in Senegal for health research. Mboup presents Senegal as a model for the benefits that early political and academic leadership and successful international partnerships can bring to scale-up efforts.

Okello’s presentation (Abstract 118) further supported the need for collaboration between research and scale-up efforts by describing the translation of evidence to policy in Swaziland. Using the WHO framework for evidence-informed policy, she described how specific research findings were translated into policy, tested for impact, and adopted at a national scale. For example, a 2007 nationally representative household survey examined HIV prevalence, convincing many politicians that the high HIV prevalence seen previously in antenatal surveys was real, and a severe and generalized epidemic was present in Swaziland. Evidence from SHIMS (Swaziland HIV Incidence Measurement Survey) in 2012 revealed that 25% of 18- to 49-year-olds with CD4+ cell counts less than 350µL were not receiving antiretroviral therapy.

After meetings with policy makers and stakeholders, a comprehensive electronic database was deployed to track HIV-infected individuals before starting antiretroviral therapy and increased funding was provided for linkage and retention in care services. This has led to reductions in loss to follow-up, particularly before initiation of antiretroviral therapy. Okello concluded with a strong recommendation that research questions be developed in partnership between researchers and policy makers to better reflect the true needs of the community, rather than the preferences of academic institutions, and balance societal priorities with economic reality.

Finally, Bertozzi (Abstract 120) offered an excellent global perspective on the impact of scale-up on the 10-year anniversary of the President’s Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, Tuberculosis and Malaria. He discussed the need for better metrics of success, pointing out the essential flaw in using antiretroviral therapy coverage over time as a measure of success of either of these programs, because the numerator, the number of people living with antiretroviral therapy, accumulates and the denominator includes those without antiretroviral therapy, who are at high risk for death. More appropriate metrics include decreases in HIV incidence in high-prevalence countries, which have occurred across PEPFAR focus and nonfocus countries, and decreases in the number of AIDS-related deaths, which correlate with PEPFAR funding status. Bertozzi cited work by Bendavid and colleagues, presented first at CROI 2012, which demonstrated statistically significant reductions in overall age-adjusted mortality for adults in PEPFAR focus countries versus nonfocus countries.2

Bertozzi made a compelling argument that to truly examine the impact of funding for scale-up of antiretroviral therapy requires facility-level data on relevant outcomes, such as the percentage of patients starting antiretroviral...
therapy at CD4+ cell counts higher than 200/µL, retained at 12 months, and virologically suppressed. Further, he demonstrated that clinic performance data on costs per patient treated can be highly misleading because receiving treatment without achieving virologic suppression is highly cost-inefficient and instead proposed that clinics be examined by the cost per year per patient retained in care and virologically suppressed. Similar arguments apply to the way performance is assessed for HIV testing and counseling programs. Bertozzi's take home points were that performance must be measured at the clinic or facility level for effective intervention and that metrics must be outcome-focused, rather than coverage-focused, to be relevant to the health of the patient.

The utility of this approach was later highlighted by Geng and colleagues (Abstract 1060), who examined the comparative effectiveness of antiretroviral therapy in HIV care programs in East Africa. Using program-based estimates of mortality derived from an approach to sampling that sought definitive outcomes for a subsample of patients lost to follow-up, they found dramatic differences in mortality by program, 22.5% in Tanzania to 4.9% in Uganda. There is a need for deeper understanding of health care organizations, patients, and communities to ensure the effectiveness of all HIV care programs. These are important insights at a time when international funding streams for HIV prevention and treatment programs are diminishing and thoughts increasingly turn to returns on investment.

**Adult Antiretroviral Therapy Outcomes in Resource-Limited Settings**

Bärnighausen and colleagues (Abstract 150) presented data regarding the impact of antiretroviral therapy scale-up on life expectancy in a full population cohort of 90,000 individuals in Kwazulu-Natal, a region of South Africa with an HIV prevalence of 30%. Concurrent increases in antiretroviral therapy coverage and adult life expectancy (from 50 years in 2004 to 61 years in 2012) of the entire cohort have been observed, whereas life expectancy for those without HIV infection has remained stable. This implies that life expectancy gains are due to the scale-up of antiretroviral therapy and that a focus on scale-up has not had a negative impact on the health of the HIV-uninfected population. Further examination of these data demonstrates that adult life expectancy increased much more rapidly in women (from 52 years in 2005 to 65 years in 2012) than men (from 48 years to 55 years over the same time frame). Women access antiretroviral therapy at higher rates in Kwazulu-Natal, a difference not fully explained by enrollments in programs for the prevention of mother-to-child transmission (PMTCT). Lower proportions of engagement in care by men appear to be driving the difference in HIV-related deaths, and studies are under way to understand the sex disparity.

A multinational collaboration in Latin America, the Caribbean, Central and South America Network for HIV Epidemiology (CCASAnet), examined predictors of virologic failure of first-line antiretroviral therapy and major regimen change within their network (Abstract 563). Cumulative incidence of virologic failure and major regimen change 5 years after the start of treatment were 27% and 14%, respectively. Younger age (20 years vs 40 years), prior AIDS, initiation of antiretroviral therapy in earlier calendar years, and treatment initiation with PI-based regimen were all associated with virologic failure. Investigators speculated that the lack of a major regimen change in patients with virologic failure might reflect scarcity of second-line antiretroviral therapy options.

Boender and colleagues (Abstract 570) presented data on long-term outcomes of second-line antiretroviral therapy in the setting of antiretroviral resistance from 13 sites in sub-Saharan Africa participating in the prospective, observational PASER (Pan-African Studies to Evaluate Resistance) study. They found that 54% of the 243 patients starting second-line therapy with a boosted PI had a partially active second-line regimen, defined as a genotypic sensitivity score less than 3, but that this was not statistically significantly associated with failure of the second-line regimen at 12 months or 24 months or the subsequent emergence of PI resistance on second-line therapy. At 24 months, only 15% of patients retained in care experienced virologic failure on second-line antiretroviral therapy. Thus, failure rates for both first- and second-line antiretroviral therapy appear to be lower in resource-limited than in non-resource-limited settings or comparable between the two, and many of the predictors of failure (male sex, young age) are similar between the two, implying that strategies should be adapted in both settings to address these higher-risk groups up front.

**Strategies for Antiretroviral Therapy in Infants and Children in Resource-Limited Settings**

Coovadia and colleagues (Abstract 72) presented data from the NEVEREST (Nevirapine Resistance) 3 study, which enrolled infants exposed to nevirapine for PMTCT, initiated antiretroviral therapy with a lopinavir/r-based regimen until virologic suppression was achieved, and then randomized them to switch to an efavirenz-based regimen or stay on the lopinavir/r-based regimen. They found that overall rates of virologic failure after 48 weeks of follow-up—defined as any measurement of plasma HIV-1 RNA level greater than 50 copies/mL or 2 measurements greater than 1000 copies/mL—were low and did not differ between the 2 arms. The study was designed as a noninferiority trial with a 10% bound, but the efavirenz group had a superior outcome for the greater than 50 copies/mL definition of virologic failure. For children exposed to nevirapine-based PMTCT, transition to efavirenz after successful virologic suppression with a PI appears to be a safe option, and this strategy could be considered in resource-limited settings as it is less costly, is more palatable, and preserves other antiretroviral regimen options.
Three studies examined the impact of antiretroviral therapy initiation in infants. Teijikem and colleagues (Abstract 923) presented data from an ongoing cohort of 210 HIV-infected children in Cameroon who were diagnosed with plasma HIV-1 RNA and DNA at less than 7 months of age, and 91% of whom started antiretroviral therapy at a median age of 4.1 months. At a median age of 19.1 months, 18% had no detectable HIV antibody by ELISA, demonstrating a high rate of seroreversion in these infants. Of the persistently HIV-seronegative infants (n = 9), they found variable levels of HIV-1 RNA and DNA, indicating variability in the HIV reservoir in these children. Failure to interpret these results correctly could lead to misdiagnosis or discontinuation of treatment in these children, and further studies are needed to determine whether these early-treated infants have the potential for HIV control.

In a relevant study in a non-resource-limited setting, Persaud and colleagues examined the impact of virologic control by 1 year of age on HIV-1 reservoir size in children (Abstract 72). Eligible study participants included those patients from PHACS AMP (Pediatric HIV/AIDS Cohort Study Adolescent Master Protocol) who maintained virologic suppression throughout the study period, defined as no 2 consecutive plasma HIV-1 RNA levels of 400 copies/mL or greater. Children who achieved virologic suppression before 1 year of age had a statistically significantly lower median proviral load (4.2 copies per million PBMCs) than those achieving suppression between 1 year and 5 years of age (19.4 copies per million PBMCs) and at greater than 5 years of age (70.7 copies per million PBMCs). Despite this, levels of immune activation, measured by sCD14, TNF-α, GMCSF, IL-β, and IL-8, remained elevated in all 3 groups and were statistically significantly higher than the same parameters in perinatally HIV-exposed, uninfected youth. Those achieving virologic control earlier than 1 year of age had high rates of seronegativity (86%) correlating with decreased proviral reservoirs. Early virologic suppression is therefore associated with decreased proviral load and seronegativity but does not reverse the chronic immune activation associated with HIV infection.

Shiau and colleagues combined data from 3 clinical trials: FInHDER (Finding Infants with HIV Disease), NEVEREST 2, and NEVEREST 3 (Abstract 924). They compared viral dynamics after initiation of antiretroviral therapy between those subjects starting treatment at less than 6 months of age and those starting between 6 months and 24 months of age. Using FInHDER data, they found that age at treatment initiation of less than 6 months was statistically significantly associated with improved virologic suppression at 6 months on antiretroviral therapy (55% vs 33% in those starting treatment at <6 months and at 6 months to 24 months of age, respectively). In the NEVEREST 2 and 3 trials, those initiating antiretroviral therapy at less than 6 months were also more likely than those initiating between 6 months and 24 months of age to have suppressed plasma HIV-1 RNA levels at 52 weeks postrandomization, regardless of whether the trial dictated a switch to a nevirapine-based regimen or they remained on lopinavir/r. These studies demonstrate that antiretroviral therapy initiation at less than 6 months was statistically significantly associated with improved virologic suppression and may contribute to increased seroreversion and reduction of the HIV reservoir in infants.

**Efficacy of PMTCT**

**Prevention of PMTCT**

**Implementation of PMTCT Programs**

New data on the efficacy, implementation, and scale-up of PMTCT programs in resource-limited settings were presented at this year’s conference. Two oral presentations provided data on the implementation of Option B+ for PMTCT in Africa (Abstracts 158, 159). The WHO has promoted a set of strategies for PMTCT: Option A provides antiretroviral therapy guided by CD4+ cell count or prophylactic antiretroviral therapy during pregnancy and extended infant prophylaxis with nevirapine; Option B+ provides lifelong antiretroviral therapy to pregnant and lactating women, irrespective of maternal CD4+ cell count, and shortens the duration of infant antiretroviral therapy prophylaxis. In Session S8, Option B+ was described as substantially simplifying PMTCT implementation and allowing for broad scale-up. Overviews of the benefits and challenges of Option B+ implementation in Malawi (Abstract 158) and Uganda (Abstract 159) show gains in access to antiretroviral therapy for pregnant women, with early surveillance data suggesting a trend toward reduced perinatal HIV-1 transmission. Further information on Option B+ implementation was presented in poster format (Abstracts 882, 883).
Postpartum, no statistically significant differences in virologic suppression were seen between study arms at weeks 24 and 48. CD4+ cell count recovery was greater in the lopinavir/r arm, both at delivery and 24 weeks postpartum. There were substantially more grade 1 or 2 gastrointestinal adverse effects such as nausea and diarrhea in the lopinavir/r arm but no differences in terms of grade 3 or 4 adverse events. There was no clear explanation for the differences seen in virologic suppression at time of delivery.

Additional data from this study was presented in poster format (Abstract 867). Overall HIV-1 transmission rate was 0.5%; the 2 transmission events occurred in the lopinavir/r arm. However, HIV-free survival at end of study did not differ between study arms. These data support the current WHO guidelines, which recommend treatment with efavirenz for pregnant and breast-feeding women.

The ANRS 12174 study team presented data on postnatal prevention of HIV-1 infection (Abstract 70). Describing the breast-feeding period as the Achilles heel of PMTCT, the study randomized HIV-exposed but -uninfected infants to 2 preventive strategies: infant lopinavir/r versus lamivudine for the duration of breast-feeding. The study was conducted in 4 countries in sub-Saharan Africa. Inclusion criteria included maternal CD4+ cell count greater than 350/µL (thus ineligible for maternal antiretroviral therapy under local guidelines), history of maternal receipt of PMTCT treatment, and infant HIV PCR assay negative at day 7. Infants (n = 1273) received prophylaxis between 7 days and 50 weeks of age and were tested for infection quarterly. Women were counseled to exclusively breast-feed for 6 months, followed by partial breast-feeding up to week 50. The primary end point was HIV infection by week 50. The primary end point was infection at 36 weeks of age in infants confirmed to be HIV-uninfected at 5 weeks of age (n = 1477). Adherence greater than 90% on pill or bottle weight count was associated with a 56% relative risk reduction in postpartum HIV transmission (95% CI, 12%-78%).

**Toxicity of PMTCT**

New data on infant toxicity of antiretroviral therapy–based PMTCT was presented at the conference. Data from the US-based SMARTT (Surveillance Monitoring for Antiretroviral Therapy Toxicity) study within PHACS showed an association between in utero tenofovir exposure and loss of bone mineral density (Abstract 71). HIV-infected pregnant women and their -uninfected infants were enrolled beginning in 2011. The investigators included infants with a gestational age greater than 36 weeks at delivery and compared infants that were not exposed to tenofovir (n = 69) with infants exposed to more than 8 weeks of tenofovir in the third trimester (n = 74).

The primary outcome was assessed using whole body bone mineral content at 2 weeks of age by dual-energy x-ray absorptiometry (DEXA) scanning. Baseline characteristics differed substantially between the exposed and unexposed groups: nonexposure to tenofovir was strongly associated with younger maternal age, being an unmarried mother, substance abuse in the mother, lower use of a PI/r-based regimen, and female sex of infant. A surprisingly high (21%) proportion of women in the non-tenofovir arm received triple-nucleoside regimens during pregnancy. Results of DEXA scanning showed a mean whole bone mineral content of 63.8 g versus 56.0 g in the non-tenofovir versus tenofovir groups, respectively (12.2% lower in the tenofovir group; difference of 6.4 g compared to tenofovir (n = 69) with infants exposed to more than 8 weeks of tenofovir (n = 74).

Toxicity of PMTCT

New data on infant toxicity of antiretroviral therapy–based PMTCT was presented at the conference. Data from the US-based SMARTT (Surveillance Monitoring for Antiretroviral Therapy Toxicity) study within PHACS showed an association between in utero tenofovir exposure and loss of bone mineral density (Abstract 71). HIV-infected pregnant women and their -uninfected infants were enrolled beginning in 2011. The investigators included infants with a gestational age greater than 36 weeks at delivery and compared infants that were not exposed to tenofovir (n = 69) with infants exposed to more than 8 weeks of tenofovir in the third trimester (n = 74).

The primary outcome was assessed using whole body bone mineral content at 2 weeks of age by dual-energy x-ray absorptiometry (DEXA) scanning. Baseline characteristics differed substantially between the exposed and unexposed groups: nonexposure to tenofovir was strongly associated with younger maternal age, being an unmarried mother, substance abuse in the mother, lower use of a PI/r-based regimen, and female sex of infant. A surprisingly high (21%) proportion of women in the non-tenofovir arm received triple-nucleoside regimens during pregnancy. Results of DEXA scanning showed a mean whole bone mineral content of 63.8 g versus 56.0 g in the non-tenofovir versus tenofovir groups, respectively (12.2% lower in the tenofovir group; difference of 6.4 g after multivariate analysis). There was no association between maternal CD4+ cell count or viral load and infant bone mineral content. No fractures were observed in any of the infants.

The clinical ramifications of these findings are as of yet unclear, and more follow-up of exposed infants is planned.
A number of abstracts reported on toxicities associated with PMTCT. In an analysis of ANRS observational and randomized studies (Abstract 862), further evidence of the association between in utero zidovudine exposure and cardiac abnormalities was presented. Zidovudine exposure in the first trimester was associated with an adjusted odds ratio (aOR) of 2.2 (CI, 1.3-2.7) for the development of congenital heart disease, mostly ventricular septal defects. In a randomized study nested within the larger observational cohort, zidovudine exposure in the third trimester of pregnancy was associated with ventricular length shortening in girls but not in boys.

Additional data from the SMARTT PHACS surveillance study (Abstract 863LB) showed an overall congenital anomaly rate of 6.7% in antiretroviral therapy–exposed, HIV-uninfected children between 2007 and 2011 (n = 2580). Most anomalies were cardiac or musculoskeletal. In adjusted models, only atazanavir and the rarely used combination of stavudine and didanosine were associated with an increased risk of congenital anomalies.

A comprehensive review (Abstract 160) of the challenges of accurate tracking of antiretroviral therapy toxicities in HIV-exposed, -uninfected infants was presented in a themed discussion session. The presentation summarized existing data on known associations between in utero antiretroviral therapy exposure and the development of birth defects, birth outcomes, growth, and neurodevelopment.

**Antiretroviral Therapy Pharmacokinetics During Breast-Feeding**

Two poster abstracts determined the concentration of NNRTIs in breast milk. Etravirine was found in high concentrations in breast milk in a study conducted in 9 HIV-1–infected pregnant women on suppressive antiretroviral therapy (Abstract 891). Etravirine was added to the suppressive regimen and pharmacokinetic data were obtained in the immediate postpartum period. Etravirine concentrations in breast milk exceeded plasma concentrations. Despite plasma viral suppression in all women, 2 women had detectable HIV-1 RNA in breast milk. In a Nigerian study of 51 HIV-1–seropositive, breast-feeding mothers, the relationship of efavirenz concentration in breast milk and in infants was found to be associated with polymorphisms in the CYP2B6 (rs3745274) gene (Abstract 888).

**Characteristics and Clinical Outcomes in Pregnant Women**

Researchers from South Africa presented data on maternal mortality in different PMTCT eras (Abstract 67). They performed a retrospective review of maternal deaths occurring between 1997 and 2012 at a single referral hospital in Soweto, South Africa. On average, 22,000 deliveries are performed annually at the site, and HIV prevalence in pregnant women was 23.6% in 2012. Four time periods were defined: 1997 to 2002, during which no PMTCT treatment was available; 2003 to 2008, when single-dose nevirapine was introduced; 2009 to 2011, when zidovudine prophylaxis was introduced; and 2011 to 2012, when pregnant women began to be treated with antiretroviral therapy.

There were a total of 589 deaths during the 15-year study period. Of the women who died and had been tested for HIV infection prior to death, 70.7% were HIV-infected. Even during the most recent time period, only 22.9% of HIV-infected women eligible for antiretroviral therapy received treatment at the time of death. Median age at death for HIV-1–infected women was 29.3 years; 75.8% had accessed prenatal care at least once during their pregnancy; and median baseline CD4+ cell count was 71/μL. Eighty percent of deaths occurred postpartum and most of these occurred within 1 week postpartum. The leading causes of death in HIV-infected women were non–pregnancy-related infections, seen in 64.2% of deaths, followed by various obstetric and medical disorders and obstetric hemorrhage. Non–pregnancy-related infections were predominantly respiratory, including community-acquired pneumonia and tuberculosis. HIV-related infections remain the leading cause of maternal deaths in South Africa. These findings were attributed to late presentation, delays in starting antiretroviral therapy, and lack of adherence support.

A high incidence of acute HIV infection during pregnancy was observed in a prospective study conducted in Kenya (Abstract 68). The study enrolled HIV-seronegative women (n = 1304) presenting for antenatal care in a high-prevalence setting (26% HIV seroprevalence among women presenting for antenatal care). Pooled nucleic acid amplification testing was performed at enrollment and every 1 month to 3 months. Subjects were also screened for other STIs. Median age of subjects was 22 years; 78% were married; 7% reported a history of STIs; and only 1% reported having an HIV-1–infected partner. The investigators identified 24 new infections: 10 were detected at enrollment and 14 were seen at follow-up. The overall incidence rate was 2.34 (CI, 0.54-4.34). In the multivariate analysis, a diagnosis of incident HIV infection was most strongly associated with a diagnosis of syphilis (odds ratio [OR], 10.0; 95% CI, 2.46) and bacterial vaginosis (OR, 2.6; 95% CI, 1.2-5.8). The high incidence rates during pregnancy speak to the need for increased prevention efforts, surveillance of seroconversion, and STI screening and treatment in high-risk, high-prevalence populations.

Data from the iDEA (International Epidemiologic Databases to Evaluate AIDS) collaboration was reviewed to determine the incidence of pregnancy among women receiving antiretroviral therapy (Abstract 868). Included in the analysis were 75,403 woman-years of follow-up. The crude pregnancy rate was 1.3 pregnancies per 100 woman-years. Pregnancy incidence was noted to be highest in the first year of starting antiretroviral therapy. Further analysis of this cohort (Abstract 869) evaluated the effect of pregnancy on retention within antiretroviral therapy programs. Of 12,861 women included in the analysis, 6.7% became pregnant during...
48 months of follow-up. Pregnancy was associated with a decreased risk of AIDS or death and of loss to follow-up. The investigators acknowledged that some ascertainment bias and underreporting of pregnancy may have altered the results.

The efficacy of preconception antiretroviral therapy on virologic suppression was evaluated in a study conducted in Cape Town, South Africa (Abstract 874). The investigators enrolled women who were receiving antiretroviral therapy prior to conception (n = 210). Median duration of treatment was 2.7 years and 70% of women received NNRTI-based therapy. The investigators found that 24% of subjects had plasma HIV RNA levels greater than 50 copies/mL, and 13% had plasma HIV RNA levels greater than 1000 copies/mL at presentation to antenatal care. The investigators raised concern that availability of antiretroviral therapy prior to conception may not guarantee effective suppression and optimal PMTCT.

Transmitted Drug Resistance

Surveillance data from the United States show a high prevalence of transmitted drug resistance (TDR; Abstract 87). The investigators compared commercially available gene sequencing with the more sensitive mutation-specific PCR assay to detect drug resistance mutations (DRMs). The analysis focused on 5 mutations thought to represent sentinel markers of TDR, namely, M41L, K103N, Y181C, M184V, and K65R. The data analyzed was part of the CDC VAHRS (Variant, Atypical, and Resistant HIV Surveillance) program. The population included antiretroviral-naive, newly diagnosed subjects who underwent genotype testing within 3 months of diagnosis between 2002 and 2012 with HIV-1 infection (n = 10,894). Prevalence of TDR was compared between age at infection, recent infection, and prevalence of TDR. In the 13- to 19-year-old age group, 59% of infections were determined to be recent (within 6 months) and the prevalence of TDR was 23.1%. Among the older age groups (40- to 59-year-olds), approximately 25% of infections were considered recent and prevalence of TDR was 17%. However, there were no differences in rates of TDR between recently and non–recently infected subjects within age groups. The investigators believe that this observation suggests that decay of transmitted mutations does not explain the high prevalence of TDRs observed in the younger age groups. Minority variants were more prevalent in older subjects. The clinical implications of low-frequency variants, particularly in recent infections, remain unclear. The investigators did not have access to treatment response data in this surveillance study.

Additional surveillance data on TDR in the United States were presented in poster format (Abstract 579). Sequences from newly diagnosed persons during 2008 to 2011 were analyzed and prevalence of TDR was compared between the overall sample (n = 16,985) and those reporting MSM as transmission risk category (n = 10,894). Prevalence of any TDR was 16.7% overall and 17.4% in MSM. There were no differences observed by ethnicity, but higher rates of TDR were seen in young MSM than older MSM (18.6% vs 15.9%, respectively; CI, 1.05-1.32).

Data from the ANRS show stable rates of TDR in France (Abstract 582). Newly infected subjects diagnosed between 2010 and 2012 (n = 796) underwent bulk genotypic sequencing. The overall prevalence of TDR was 10.7%; drug class–specific TDR was detected as follows: nRTIs 5.2%, NNRTIs 7.3%, and PIIs 2.0%. Of note, prevalence of TDR for the second-generation NNRTIs rilpivirine and etravirine was 3.3% and for INSTIs 1.5%. Resistance was more common in subtype B virus and in MSM. The investigators noted that the overall prevalence of TDR in France has not changed since 1996 and that more than 95% of sequenced viruses are susceptible to WHO first-line antiretroviral regimens. Additional data on low-frequency drug-resistant variants in the ANRS database were presented (Abstract 605).

An analysis of data from the Dutch ATHENA (AIDS Therapy Evaluation in the Netherlands) cohort suggests that a single transmitted thymidine analogue–associated mutation (TAM) does not compromise the efficacy of first-line antiretroviral therapy (Abstract 577). The investigators used data from treatment-naive MSM diagnosed between 2002 and 2012 with HIV-1 infection (n = 2314). Subjects were classified into 3 groups based on pretreatment genotype: presence of 1 TAM; presence of a single non-TAM DRM or more than 2 DRMs; or no DRMs. Only 4% of the cohort had a single TAM. No differences were seen in time to virologic failure between the single TAM and wild type groups (hazard ratio [HR], 1.04; CI, 0.58-1.86).

A Spanish study retrospectively analyzed the prevalence of low-frequency DRMs in patients with advanced HIV disease initiating first-line antiretroviral therapy (Abstract 602). 454-pyrosequencing was performed on stored samples from subjects with pretreatment CD4+ cell counts lower than 100/µL and wild type virus on commercial sequencing (n = 145). DRMs were detected in 41% of subjects in pretreatment stored specimens using the sensitive assay. The presence of DRMs was associated with a marginal overall increase in risk of virologic failure.
(HR, 2.0; CI, 1.0-4.3); no increased risk was seen in subjects treated with PI-based regimens.

Cross-sectional data from the European SPREAD (Strategy to Control SPREAD of HIV Drug Resistance) surveillance program showed no circulating signature mutations conferring INSTI resistance prior to the clinical introduction of this class of antiretroviral drugs (Abstract 580) in a random sample of sequences from newly diagnosed subjects in 2006 and 2007 (n = 300). Despite the absence of any identified major INSTI DRMs, polymorphisms known to contribute to the emergence of INSTI resistance were detected in 4% of specimens using commercial sequencing and in 12.5% of specimens using 454-pyrosequencing. The investigators suggested that transmitted INSTI resistance will increase with the expanded use of these agents.

An industry database confirms an increasing prevalence of NNRTI resistance but low levels of other drug class resistance (Abstract 578). Sequences from treatment-naive individuals enrolled in phase III studies between 2000 and 2013 were included in the analysis (n = 2516). Over this time period, NNRTI mutations increased in prevalence from 1.9% to 7.8%. TAMs were detected at a frequency higher than 15% in the transmitter, they were also observed at a correspondingly high frequency in the recipient, both in plasma and PBMCs. In this context, there was 100% overlap between mutations identified in the transmitter and the recipient. Of note, none of the subjects with high-frequency mutations reported antiretroviral therapy use.

Investigators from Kenya found high rates of resistance among patients prescribed second-line regimens containing lopinavir/r (Abstract 584). All patients (n = 401) had failed a previous first-line antiretroviral regimen and had been on a lopinavir/r-based regimen for at least 6 months. Twenty-four percent of subjects had plasma HIV RNA levels greater than 1000 copies/mL. The following DRMs were detected at failure: K103N (22.4%), M184V (20.4%), M41I (20.4%), M46I (19.4%), and I54V (15.3%). Thirty-two percent of patients had no WHO treatment options at failure. However, complete loss of all treatment options occurred in only 1 patient. Nine sequences contained no mutations at failure.

An analysis from China evaluated the risk of acquired drug resistance and mortality in patients receiving nevirapine-based antiretroviral therapy between 2003 and 2005 (Abstract 589). Patients received nevirapine in combination with either zidovudine and didanosine or stavudine and didanosine (n = 517). At a median follow-up of 58 months, 78% of patients had experienced treatment failure, and of those 56% had DRMs. Fifteen percent mortality was observed. No information was provided on adherence to these regimens, which are not recommended first-line regimens by current guidelines.

Acquired Drug Resistance

Failure of First- and Second-Line Antiretroviral Therapy

Investigators from Kenya found high rates of resistance among patients prescribed second-line regimens containing lopinavir/r (Abstract 584). All patients (n = 401) had failed a previous first-line antiretroviral regimen and had been on a lopinavir/r-based regimen for at least 6 months. Twenty-four percent of subjects had plasma HIV RNA levels greater than 1000 copies/mL at a median of 1.9 years on second-line therapy. In these subjects, 182 genotypes were available for analysis, including both plasma and PBMC sequences. In plasma specimens, rates of viral resistance were 78% for any resistance, 67% for nRTI resistance, 73% for NNRTI resistance, and 8% for PI resistance. Archived resistance mutations were seen in 84% of available sequencing from subjects with detectable plasma HIV RNA levels less than 1000 copies/mL.

A study from Nigeria estimated that second-line treatment failure cannot be successfully managed within current WHO guidelines (Abstract 585). Genotype susceptibility scores were calculated for participants failing either lopinavir/r- or atazanavir-based second-line therapy; a score of less than 2 was defined as a lack of further treatment options. Of patients receiving second-line antiretroviral therapy (n = 936), 6% had evidence of viral failure with a plasma HIV-1 RNA level greater than 1000 copies/mL (n = 56). Mean viral load at failure was 5.1 log10 copies/mL. The following DRMs were detected at failure: K103N (22.4%), M184V (20.4%), M41I (20.4%), M46I (19.4%), and I54V (15.3%). Thirty-two percent of patients had no WHO treatment options at failure. However, complete loss of all treatment options occurred in only 1 patient. Nine sequences contained no mutations at failure.

In an oral presentation, investigators described a novel silent mutation that allows HIV-1 subtype B to overcome the fitness cost associated with TAMs (Abstract 89). Silent, or synonymous, mutations alter the genetic code at a specific codon without altering the resulting amino acid sequence. Synonymous
mutations associated with the presence of TAMs were identified at positions K65R and K70R. The investigators hypothesized that the TAMs D67N and K70R cause a viral fitness defect via the insertion of a homopolymeric nucleotide sequence upstream from the mutation and showed that by inserting a synonymous mutation, the virus is able to mitigate this fitness defect.

**NNRTI Resistance**

In the ANRS EASIER trial, investigators determined the prevalence of second-generation NNRTI resistance in subjects with a history of first-generation NNRTI failure who achieved virologic suppression on a subsequent regimen (n = 169; Abstract 591). Sequencing was performed on HIV-1 DNA extracted from whole blood specimens. Amplification was successful in 76% of patients, and 95% of sequences were HIV-1 subtype B. Rilpivirine DRMs were detected in 51% of patients. The most frequent mutations were at the 181, 101, and 138 positions of reverse transcriptase. Etravirine mutations were detected in 4% of subjects. Emtricitabine and tenofovir mutations were found in 56% and 9% of patients, respectively. The investigators noted that resistance to any component of the fixed-dose combination rilpivirine/emtricitabine/tenofovir was seen in 69% of patients. They recommended that pretreated patients with a history of failure on first-generation NNRTIs not be treated with rilpivirine-based therapy.

High rates of NNRTI resistance were detected in patients interrupting suppressive NNRTI-based therapy (Abstract 593). In a retrospective analysis from the UK HIV Drug Resistance Database, subjects were included if they were on a suppressive first-generation NNRTI regimen; had evidence of consistent suppression to plasma HIV RNA levels less than 200 copies/mL after 6 months of therapy; had no evidence of NNRTI resistance on prior genotypes; and underwent treatment interruption. Of the subjects with a genotype determined after treatment interruption (n = 208), 12% had 1 or more NNRTI DRMs at a median of 12 months following treatment interruption. The DRM at K103N was found in 64% and at G190A in 12% of patients. There were no differences observed between those receiving a “nucleoside tail” and those who did not, but the numbers in the nucleoside tail group were small. Only 15% of patients with treatment interruption underwent genotype testing, suggesting that the population studied may have had a higher pretest probability of resistance.

Resistance to second-generation NNRTIs was observed with moderate frequency in patients failing first-generation NNRTI–based therapy in PEPFAR programs in sub-Saharan Africa (Abstract 592). Subjects with available sequences had subtype A or D HIV-1 infection (n = 215). DRMs at position 138 of reverse transcriptase were detected in 13.8% of subjects. The investigators suggested that first-generation NNRTIs may induce mutations associated with second-generation NNRTIs in patients with non-B subtypes.

Investigators analyzed the rate of decay of the DRM at K103N in subjects previously failing efavirenz-based therapy (Abstract 604). At the time of analysis, subjects were virologically suppressed on a PI-based regimen with plasma HIV RNA levels less than 50 copies/mL (n = 28). Proviral DNA was isolated from PBMCs and sequenced. Duration of suppression was not associated with decay of K103N, which was detected in approximately 50% of subjects at all time points, for up to 11 years of follow-up. Log10 viral load at efavirenz failure was associated with an OR of 2.6 (CI, 1.0-6.4) for detection of K103N per log10 copy/mL increase.

**Integrase Resistance**

Integrase resistance was rare in treatment-naive subjects enrolled in an industry trial of Efavirenz/Combivir/FTC/TDF (Abstract 587). Week 144 data shows that INSTI DRMs emerged in 2.6% of the subjects enrolled (n = 701). The most frequent DRMs were E92Q (n = 9), N155H (n = 5), Q148R (n = 3), T66I (n = 2), and T97A (n = 1). Emergent nRTI resistance mutations observed included M184VI (n = 17) and K65R (n = 5).

Using clinical specimens and site-directed mutagenesis, investigators determined the mechanism of resistance conferred by mutations at position 148 of HIV integrase (Abstract 595). Patient-derived viruses (n = 210) containing the raltegravir and elvitegravir DRMs Q148H/K/R displayed reduced susceptibility to dolutegravir (IC50 fold change of 4.6). The largest reductions in dolutegravir susceptibility were observed with the Q148K substitution. All patient viruses contained additional mutations to those seen at the 148 position. By site-directed mutagenesis, substitutions at the 148 position alone did not reduce dolutegravir susceptibility. The addition of mutations at position 140 were associated with reduced susceptibility to dolutegravir, as were mutations at positions 74, 92, 97, and 138.

**Maraviroc Resistance and Tropism**

Proviral DNA from aviremic subjects was used to guide a switch to maraviroc-based therapy (Abstract 607). In this study, HIV-1–infected adults on suppressive antiretroviral therapy (plasma HIV-1 RNA levels <50 copies/mL) for longer than 6 months who required a change of regimen because of drug toxicity were included in the analysis (n = 154). Of these, 88 (85%) had R5 tropic virus; 74 switched to a regimen of maraviroc plus 2 nRTIs; and 61 reached the 24-week analysis time point. At 24 weeks, 51 subjects (84%) remained virologically suppressed. Four of the 10 subjects who did not achieve virologic suppression at week 24 had evidence of viral resistance, 2 with X4 tropic virus.

**Resistance During Tenofovir/Emtricitabine PrEP**

Data on HIV resistance among participants in the VOICE (Vaginal and Oral Interventions to Control the Epidemic) PrEP trial were presented, confirming a high risk of resistance when PrEP is used during acute infection (Abstract 594). A total of 368 women were diagnosed with HIV-1 infection during the trial. Of these, 212 seroconverters were exposed to tenofovir. There was no
evidence of tenofovir resistance in any of the women exposed to tenofovir-containing PrEP. In 1 subject randomized to tenofovir/emtricitabine, the M184V DRM emerged after 309 days on product. Twenty-two subjects were retroactively found to be infected at enrollment, 9 of whom were in the tenofovir/emtricitabine arm. In 2 (22%) of these subjects, the M184V DRM emerged within 1 month of product use. Overall adherence in the VOICE trial was low, suggesting that the true incidence of resistance with PrEP may be underestimated. Increased surveillance of acute or recent infection is essential to assure the safety of PrEP.

Financial affiliations in the past 12 months:
Dr Taylor has grants under review to be awarded to the University of Texas Health Science Center at San Antonio from the Doris Duke Charitable Foundation and the American Heart Association as of publication. Dr Shalev has no relevant financial affiliations to disclose. Dr Wilkin has received research support awarded to Weill Cornell Medical College from Gilead Sciences, Inc, and GlaxoSmithKline/ViiV Healthcare.

A list of all cited abstracts appears on pages 632-638 of this issue. Abstracts are published in Top Antivir Med. 2014;22(e-1):1-570, a special online issue available at www.iasusa.org/pub.

Additional References

Weekly. Helen E. R eynolds, Deir dre Egan, L aura 


retrovirals in P atients With HIV/HC V Coinfection. Darunavir/r in Adolescents and Young Adults. Marc Yali Zhu, Susanne L angley, Patricia Jumes, Stephen P. 

Protease Inhibitor MK-5172 and Tenofovir or Ralte- 

Moore, MC Puert as, Carlos Alonso, Anna Pr ats- 

Garner, Bill Guyer. Domingo, Pierr e-Marie Gir ard, K eith Henry, Will 

ment. Nicholas P aton, W olfgang St ohr, Alejandr o 

Laurence Meyer, Christine Rouzioux. Isabelle Ravaux, Jacques R eynes, Patrick Miailhes, line Melar d, Camille L ecuroux, Car oline L ascoux, 

Moreno, MC Puert as, Carlos Alonso, Anna Pr ats- 

593. Detection of NNRTI Resistance Mutations Af- 

635.
Aza Rakhmanova, Igor Kargov, Massimo Galli, Pere Domingo, Ole Kirk, Jens D. Lundgren, Amanda Mrocz


663. The Effect of Protease Inhibitor Use On Kaposi Sarcoma Incidence in a cART-Experienced Cohort. Elizabeth Chiao, Mark Nowakowski.


734. Myocardial Infarction at Various Lipid Levels. Adeel A. Butt, Matthew S. Freiberg, the VACS Project Team.

735. MACE Incidence Among HIV- and Non-HIV-Infected Patients in a Clinical Care Cohort. Virginia A. Talian, Susan Reigan, Seven Groupup.


738. MACE Incidence Among HIV- and Non-HIV-Infected Patients in a Clinical Care Cohort. Virginia A. Talian, Susan Reigan, Seven Groupup.


740. Long-Term Effects of Nitrite Inhalants On Cardiovascular and Renal Outcomes in the MACS Cohort. Alex Holman, Anupriya Dutta, Dana Gabuzda.


751LB. After 52 Weeks, Pitavastatin Is Superior To Pravastatin for LDL-C Lowering in Patients With HIV. Craig A. Spoonsiker, Judith Aberg, INTRIPTID Team.

753. Impact of CD4 Count and HIV Persistence On Endothelial Function in Patients With Low Plasma RNA. Armanda Schnell Heringer, Hiroyu Hatano, Peter W. Hunt, Yuanaer Wu, Yifei Ma, Rebecca Scherer, Jeffery N. Bantin, Peter Ganz, Steven Deeks, Priscilla Y. Hse.


756. Association of HIV Infection and Immune Activation With Lipid Changes in Longitudinal Cohort. Kevin Martin, Robert Murphy, James Stein, Grace McComsey.


762. Glycemic Control and Its Role in the Onset of Non-AIDS-Related Events. Andra A. Marin, Robert Murphy, James Stein, Grace McComsey.

763. Bone Density Changes After Antiretroviral Therapy With Protease Inhibitors or Raltegravir. Todd Brown, Carlene Moser, Judith Currier, Heather Ribaudo, Jennifer Rothenberg, Michael Dube, Robert Murphy, James Stein, Grace McComsey.


768. Extrapolation From Extrinsic Pathway Coagulation Factors Are Associated With Mortality During Treated HIV Disease. Patricia Ndumbi, Julian Falutz, Jason Bakker, Kathleen Brummel-Ziedins, Jacqueline Neuhaus, James D. Neaton, Russell P. Tracy, INSIGHT SMART and ESPRIT Study Groups.

769. Bone Density Changes After Antiretroviral Therapy With Protease Inhibitors or Raltegravir. Todd Brown, Carlene Moser, Judith Currier, Heather Ribaudo, Jennifer Rothenberg, Michael Dube, Robert Murphy, James Stein, Grace McComsey.


784. Predictions of Progression, Stabilisation, or Improvement of eGFR After Chronic Renal Impairment. Lena Ryom, Amanda Morlott, Ole Kirk, Morlat, Colette Smith, Christoph A. Fux, Jens D. Herrero, PRIMEVA.


802. Low Pre-ART CD4 + T Cells, Female Sex, and Atazanavir Use Increase Obesity Risk After Starting ART. Benjamin Atkinson, Supriya Krishnan, Ann C. Litt, John B. Walsh.


814. Early Infection Among Ugandan HIV-Exposed Infants Whose Mothers Received Option B+ vs Option A: Julie N. Mugensya, Zikahub Nakwuluya, Adeodata Keshitilina, Albert Maganda, Rachael Ayanga, Ayobu Kakande, Joyce Matovu, Josephine Byamugisha, Godfrey Esim, Mary G. Fowler.


816. Darunavir(DRV)/r-Based PEP Versus Standard of Care (SOC) - the Randomized PEP4ar Study. Gerd Falkenheuer, Norma Jung, Heiko Jessen, Albrecht Storl, Darius Navas-Acuña, John C. Souser, Christophe Stephan, Christopher D. Spinner, Olaf Degern, Brita Ranneberg.

820. High Inprent of PreP and ART in a Demonstration Project Among African HIV-Discordant Couples. Renee Heffron, Connie Colum, Nelly Mug, Elly Katabira, Elizabeth Bukusi, Elidora Tumwesigye, Jessica Haberer, Jared Baeten, for the Partners Demonstration Project Team.


961. Contingency Management Facilitates PEP Completion Among Stirnalt-Using MSM. Raphael J. Landovitz, Jesse B. Fletcher, Steve Shoptaw, Cathy J. Reback.


971. Incorrect Identification of Recent HIV Infection Using a Lg-Avidity Assay in Adults in the US. Andrew F. Longosz, Ron Brookmeyer, Shrutti Mehta, Omar D. Kus, Joseph B. Margolick, Joelle Brown, Thomas C. Quinn, Susan H. Eshleman, Oliver Laeyendecker.


1031. Baseline Predictors of HIV-1 Acquisition Among Women Participating in MTN-003 (VOCES). Gonsagrie Nair, Jennifer E. Balkus, Jeanne M. Silver, Jesica M. Sanz, Jessica M. Sanz, Jennifer E. Balkus, Jeanne M. Silver, Jesica M. Sanz.


1038. Erectile Dysfunction Medication Use Associ-at-ed With Unprotected Intercourse in HIV-Infected MSM. Xia Lin, Christine L. Mattson, Mark S. Freedman, Jacek Skarbinski.


1043. HTC Campaign in Households Reached the Majority of Women But Only 50% of Men in Botswana Community. Vlad Novitsky, Hermann Bussmann, Sikhulile Moyo, Erik van Widenfelt, Mompaiti Mmalane, Quanhorn Leig, Joseph Makhema, Shahin Lockman, Victor DeGruntalo, Max Essex.


1046. Comparative Effectiveness of HIV Care and Treatment Programs in East Africa. Elvin Geng, Thomas Odery, Rita Lymamu, Alice Nkowwga-Muwanga, Mwesbesa Bwaij, Paula Braitstein, Andrew Kambugue, Elizabeth Bukusi, Geoffrey Somi, Lameck Diero, Jeffrey Martin.


Guidelines for Authors and Contributors

The IAS–USA publishes Topics in Antiviral Medicine™ as a resource for physicians and other health care practitioners who are actively involved in the care of patients with HIV or other viral infections. The journal is indexed in Index Medicus/MEDLINE and is distributed to approximately 13,000 national and international subscribers.

The following guidelines describe the types of articles and contributions published in the journal, outline its policies, and provide instructions for authors. For further information, contact Topics in Antiviral Medicine™ at journal“at”iasusa.org.

Categories of Articles

Perspectives. Perspective articles are summaries of selected talks given at IAS–USA continuing medical education courses. An IAS–USA medical writer prepares a summary manuscript from a transcript of the talk. The manuscript is reviewed and edited by the presenter and the journal’s appointed peer reviewer(s).

Reviews. Topics in Antiviral Medicine™ welcomes original review articles on current issues related to infection with HIV or other viruses. Topics in Antiviral Medicine™ does not publish original research. Manuscripts should be 3000 to 6000 words (excluding references, tables, and figures) and should include numbered references and a brief introductory abstract of approximately 100 to 200 words. Original, adapted, or reprinted figures and tables may be included and should be cited in the text and accompanied by a brief title. Adapted and reprinted work requires proof of permission obtained from the original publishers and authors. Authors interested in submitting unsolicited manuscripts are encouraged to submit an outline or abstract of the proposed manuscript first; please contact the editor for further information.

Editorials. Topics in Antiviral Medicine™ invites submission of editorials. Editorials should be approximately 500 to 1500 words (excluding references) and should include numbered references, and seek to teach an important lesson for HIV or viral hepatitis care practitioners.

Stories. Stories for the Telling Stories column share the experiences of those involved in the care of people infected with HIV or other viruses. Stories may be approximately 800 to 3500 words; submissions are welcome for consideration.

Commentaries. Discussion on a current issue in the management of viral diseases is welcome as a Commentary. Commentaries should be 500 to 1500 words and include numbered references as appropriate. Commentaries may be invited by the editors, unsolicited submissions are also welcome for consideration.

Letters to the Editor. Letters to the editor are welcome and should be sent to the address listed below. Please limit letters to 300 words.

Special Issues. Topics in Antiviral Medicine™ publishes 1 or 2 issues each year with a special focus, for example, summaries of IAS–USA continuing medical education courses and reports from scientific meetings. For example, the special issues on the Conference on Retroviruses and Opportunistic Infections (CROI), held annually, include one issue that summarizes coverage of major topics relating to HIV, HCV, and other viral infections and another that publishes all of the abstracts presented at the conference.

Online Articles. Occasionally articles are online only. They are distinguished from printed articles by pagination beginning with “e.”

Reprints. Reprints of articles by expert panels convened by the IAS–USA are included periodically in Topics in Antiviral Medicine™.

Submission of Manuscripts

Manuscripts should be submitted via mail or e-mail to the address below. Each author should complete an Authorship Form, which is available online at www.iasusa.org/pub or may be obtained by contacting the editor at the address below. Outlines or abstracts of proposed manuscripts are welcome and may be sent via mail or e-mail.

Editor, Topics in Antiviral Medicine™
IAS–USA
425 California Street, Suite 1450
San Francisco, CA 94104-2120
E-mail: journal“at”iasusa.org

Receipt of submitted manuscripts will be acknowledged by editorial staff, and submissions will be reviewed by peer reviewers. Acceptance for publication is based on the quality and relevance of the work.

Copyright

Copyright to all manuscripts and graphics published in Topics in Antiviral Medicine™ is owned by the IAS–USA unless noted otherwise. All authors and contributors of manuscripts accepted for publication, with the exception of US federal government employees, must sign a copyright transfer form as a condition of publication.

Authorship Requirements

Topics in Antiviral Medicine™ uses the definition of authorship formulated by the International Committee of Medical Journal Editors and published in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals.1 This definition states: “Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3…. Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship.” Topics in Antiviral Medicine™ will not consider ghostwritten articles for publication.

Financial Disclosure

It is the policy of the IAS–USA to ensure balance, independence, objectivity, and scientific rigor in all of its educational programs. To that end, all authors and contributors of articles published in Topics in Antiviral Medicine™ are required to disclose to readers any significant financial interest or other relationship with any organization having financial interest in the content of the manuscript. Financial interests include employment, consultancy, honorarium, grant/research support, major stock ownership, or membership in a speakers bureau and directly paid lectures or other contribution. The complete financial disclosure statements for all authors and contributors are published with the articles.

IAS–USA 2014 Upcoming Courses and Events

- Improving the Management of HIV Disease® Continuing Medical Education (CME) Courses
  - Chicago, Illinois—May 19, 2014
  - Washington, DC, area—June 17, 2014

- Evolving Strategies in Hepatitis C Virus Management CME Workshops
  - Chicago, Illinois—May 20, 2014
  - Washington, DC, area—June 16, 2014

- Conference on Retroviruses and Opportunistic Infections (CROI)—February 23 to 26, 2015