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Topics in Antiviral Medicine™

A publication of the IAS–USA

Highlights of the 20th Conference on Retroviruses and Opportunistic Infections

Topics in Antiviral Medicine™

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Topics in Antiviral Medicine™

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This CME activity is offered from May 7, 2013 to May 7, 2014. 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 *AMA PRA Category 1 Credits*™
- Release date: May 7, 2013
- Expiration date: May 7, 2014

This enduring material provides a review of the 20th 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 or, for paper copies, via fax or mail.

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 20th CROI and the potential clinical implications for patients in the areas of:

- Pathogenesis of HIV disease
- Epidemiology of HIV and prevention efforts
- Antiretroviral therapy
- Complications of HIV disease and its treatments
- HIV-related coinfection

Intended Audience

This enduring material is designed for physicians who are actively involved in the medical care of people with HIV infection, specifically those who:

- Have a solid, working knowledge of HIV disease management
- Provide comprehensive or specialty care for patients with HIV infection
- Are currently active in HIV research

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

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1. Which of the following statements about preexposure prophylaxis (PrEP) for HIV prevention is true?
- ❑ **A.** PrEP is less efficacious in populations with higher HIV incidence
- ❑ **B.** PrEP can delay HIV seroconversion in individuals who become infected while taking PrEP
- ❑ **C.** Recent PrEP studies not showing efficacy can be explained by increased rates of tenofovir-associated toxicity in women
- ❑ **D.** Tenofovir-based PrEP may prevent acquisition of herpes simplex virus 2 and hepatitis B virus infection
- ❑ **E.** Long-acting PrEP agents failed to protect macaques after repeated mucosal simian HIV challenges

2. The rapid HIV self-test that was approved for use by the US Food and Drug Administration in 2012:
- ❑ **A.** Uses a fourth-generation antigen-antibody test
- ❑ **B.** Has equivalent sensitivity for detecting HIV infection compared with testing in clinical settings
- ❑ **C.** Cannot be used to test sex partners
- ❑ **D.** May require proactive strategies to link individuals testing seropositive for HIV into care

3. Which of the following statements best explains the disproportionately high rate of new HIV infections among young black men who have sex with men (MSM) in the United States?
- ❑ **A.** More substance abuse
- ❑ **B.** Lower rates of viral suppression
- ❑ **C.** Higher rates of unprotected anal sex
- ❑ **D.** Less frequent HIV testing
- ❑ **E.** Greater number of sex partners

4. The US South bears a disproportionately high number of new HIV infections. Which of the following statements is true?
- ❑ **A.** In 2010, more than 90% of all HIV-infected persons on wait lists for antiretroviral drug assistance programs (ADAP) lived in the South
- ❑ **B.** Higher HIV infection rates in the South occur only in rural areas; urban HIV infection rates in the South are lower than in other regions
- ❑ **C.** Disproportionate rates of new HIV infections in the South are occurring in women but not in men
- ❑ **D.** Racial disparities are lower in the South than in other regions
- ❑ **E.** After adjusting for race, there are no differences in AIDS-associated fatality rates between the South and other regions

5. Which of the following statements about contraceptives is true?
- ❑ **A.** Most observational studies find that oral contraceptives increase the risk of HIV acquisition
- ❑ **B.** Systematic reviews of observational studies have found no difference in the risk of HIV acquisition by type of hormonal contraceptive used
- ❑ **C.** Underreporting of condom use is the most likely explanation for increased rates of HIV infection in hormonal contraceptive users
- ❑ **D.** Eliminating hormonal contraceptive use would decrease the number of deaths among women worldwide
- ❑ **E.** Hormonal contraceptives do not interfere with the efficacy of PrEP in nonhuman primate models

6. Investigators believe a perinatally HIV-infected infant to be functionally cured because:
- ❑ **A.** The infant's plasma HIV-1 RNA levels were undetectable after delivery
- ❑ **B.** The infant's CD4+ cell count remained elevated despite detectable plasma HIV-1 RNA levels
- ❑ **C.** The infant's plasma HIV-1 RNA levels were undetectable after nearly 8 months without antiretroviral therapy
- ❑ **D.** The infant's mother had an undetectable plasma HIV-1 RNA level at the time of delivery

7. Histone deacetylase inhibitors, such as vorinostat, disrupt:
- ❑ **A.** HIV-1 replication
- ❑ **B.** HIV-1 latency
- ❑ **C.** CD4+ cell senescence
- ❑ **D.** HIV-1 reverse transcriptase

8. Which of the following is 1 of the 5 stages in the process of achieving virologic suppression referred to as the cascade of care:
- ❑ **A.** Knowledge of CD4+ cell count
- ❑ **B.** Prevention with seropositives
- ❑ **C.** Time to virologic failure
- ❑ **D.** Retention in care

9. Investigators studying home-based HIV testing in Malawi found that those who received the option of home assessment of HIV serostatus and initiation of antiretroviral therapy if HIV infected and eligible for antiretroviral therapy initiation had increased odds of:
- ❑ **A.** Initiating antiretroviral therapy
- ❑ **B.** Unintentional disclosure of their HIV serostatus
- ❑ **C.** Testing seronegative for HIV
- ❑ **D.** Accepting their HIV diagnosis

10. In the French Perinatal Cohort Study, receipt of efavirenz during the first trimester of pregnancy was associated with:
- ❑ **A.** Neural tube defects
- ❑ **B.** No harmful effects on the fetus
- ❑ **C.** Agenesis of the corpus callosum
- ❑ **D.** Ocular malformations

11. SAMHD1 (Sterile alpha motif [SAM] domain and HD domain–containing protein 1) restricts viral infection by:
- ❑ **A.** Blocking expression of CD4 on the cell surface
- ❑ **B.** Causing retention of virions on the cell surface
- ❑ **C.** Inhibiting reverse transcription by depleting cellular deoxynucleoside triphosphates (dNTPs)

12. Strategies to eliminate the latent HIV reservoir are based on the rationale that reactivating latency will lead to removal of the cell by cytopathicity and immune-mediated clearance. Which of the following drugs may potentially reactivate latency?
- ❑ **A.** Vorinostat only
- ❑ **B.** Vorinostat and prostratin
- ❑ **C.** Vorinostat, prostratin, and valproic acid
- ❑ **D.** Prostratin and valproic acid

13. Cells susceptible to HIV-1 harbor a protein that blocks detachment of virions from the cell surface and prevents spread of the virus to adjacent cells. This protein is known as:
- ❑ **A.** APOBEC 3 (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like)
- ❑ **B.** Cyclin T
- ❑ **C.** TRIM 5 (tripartite motif-containing protein 5)
- ❑ **D.** Tetherin

14. Based on recent data from a randomized controlled trial, in the setting of cryptococcal meningitis, when should antiretroviral therapy be initiated?
- ❑ **A.** At the same time as amphotericin B
- ❑ **B.** Within 2 weeks of starting treatment for cryptococcal meningitis
- ❑ **C.** Antiretroviral therapy should be delayed until 4 weeks after initiation of treatment for cryptococcal meningitis

15. All of the following have been associated with renal impairment in HIV disease except:
- ❑ **A.** Ritonavir-boosted protease inhibitor use with tenofovir
- ❑ **B.** Nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) use
- ❑ **C.** Low body mass index (BMI)
- ❑ **D.** Older age

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❒ Other (please specify):_____

Evaluation

Please rate this activity in terms of meeting each of its stated objectives.

	Excellent	Very Good	Good	Fair	Poor
Pathogenesis of HIV disease	❍	❍	❍	❍	❍
Epidemiology of HIV and prevention efforts	❍	❍	❍	❍	❍
Antiretroviral therapy	❍	❍	❍	❍	❍
Complications of HIV disease and its treatments	❍	❍	❍	❍	❍
HIV-related coinfection	❍	❍	❍	❍	❍

How challenging was this activity? ❒ Highly challenging ❒ Sufficiently challenging ❒ Insufficiently challenging

Please rate this activity based on:

	Excellent	Very Good	Good	Fair	Poor
Quality of this activity overall	❍	❍	❍	❍	❍
Overall value of this activity to your practice or responsibility	❍	❍	❍	❍	❍
The extent to which the information presented was supported by the evidence	❍	❍	❍	❍	❍
Freedom from commercial bias	❍	❍	❍	❍	❍

Do you expect to make changes in your clinical practice based on the information presented in this activity? ❒ Yes ❒ No

If so, please list 3 measurable changes you expect to make:

1. _____
2. _____
3. _____

Other comments (please feel free to comment on any aspect of this enduring material or *Topics in Antiviral Medicine*™):

_____

_____

How many HIV-infected patients do you personally manage?
❒ None ❒ 1–4 ❒ 5–10 ❒ 11–15 ❒ 16–50 ❒ 51–100 ❒ 101–200 ❒ More than 200

How many HIV-infected patients are in your clinic overall?
❒ None ❒ 1–4 ❒ 5–10 ❒ 11–15 ❒ 16–50 ❒ 51–100 ❒ 101–200 ❒ More than 200

Please rate your expertise in treating HIV infection: ❒ 1 (novice) ❒ 2 ❒ 3 ❒ 4 ❒ 5 (expert)

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Improving the Management of HIV Disease®

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
Friday, May 3, 2013
New York Marriott Marquis
Cochairs: Gerald H. Friedland, MD, Paul A. Volberding, MD

Chicago, Illinois
Monday, May 20, 2013
Chicago Marriott Downtown Magnificent Mile
Cochairs: John P. Phair, MD, Paul A. Volberding, MD

Washington, DC, area
Tuesday, June 18, 2013
Hyatt Regency Crystal City
Cochairs: Henry Masur, MD, Michael S. Saag, MD

Management of Hepatitis C Virus in the New Era: Small Molecules Bring Big Changes

The full-day advanced CME course is 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–infected patients, in what has become an exciting new era in hepatitis C virus care.

South San Francisco, California
Tuesday, June 4, 2013
South San Francisco Conference Center
Cochairs: Marion G. Peters, MD, David L. Wyles, MD

New York, New York
Tuesday, June 25, 2013
New York Marriott Marquis
Cochairs: Robert T. Schooley, MD David L. Thomas, MD, MPH

Evolving Strategies in Hepatitis C Virus Management

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.

Chicago, Illinois
Tuesday, May 21, 2013
Chicago Marriott Downtown Magnificent Mile

Washington, DC, area
Monday, June 17, 2013
Hyatt Regency Crystal City

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CROI 2013: Basic Science Review

Mario Stevenson, PhD

The 20th Conference on Retroviruses and Opportunistic Infections was held in Atlanta, Georgia, and featured strong coverage in several basic science categories. Presentations on viral reservoir and cure research covered a variety of topics, including approaches to gauge viral reservoir size in patients on suppressive antiretroviral therapy, approaches to reactivate latently infected cells, and the role of residual replication in viral persistence under antiretroviral therapy. Research on viral restriction factors remains a strong feature of the conference, and presentations on the impact of viral restrictions on the establishment of viral reservoirs, as well as strategies that harness the antiviral potential of cellular restrictions, generated a lot of interest. Several studies on the nature of proviral latency left us with the sobering message that elimination of the latent viral pool is going to be an even greater challenge than previously suspected.

Keywords: *HIV, pathogenesis, reservoirs, cellular restrictions, eradication*

Research on Viral Reservoirs

A population of memory CD4+ T cells harboring latent proviruses is considered the single biggest obstacle to the eradication of HIV-1 from infected individuals. In virologic terms, latency is defined as the phase in which an infected cell is not manufacturing infectious virus but has the capacity to do so under appropriate conditions. The mechanism through which HIV-1 is held in latency is not fully understood. Studies derived predominately from experimental in vitro models of viral latency indicate that latency is dictated at the transcriptional level, and latent proviruses integrated within highly condensed regions of chromatin are relatively inaccessible to cellular transcription factors that promote proviral gene expression. Furthermore, in the quiescent host cell, low levels of host transcription factors create suboptimal conditions for viral gene expression.

Through in vitro studies, latency can be reactivated with agents (eg, valproic acid, vorinostat) that relax chromatin or agents (eg, prostratin, phorbol esters) that activate the nuclear factor (NF)-κB pathway. Although agents that activate the NF-κB pathway have the most profound impact on viral gene expression, they are unlikely to have utility in reactivation of latency, because of the global impact on cellular gene expression. Therefore, researchers have focused their attention on agents that modify chromatin with the rationale that viral reactivation would lead to elimination of the infected cell either due to the cytopathic effects of the virus on the host cell or to elimination of the reactivated cell by immune clearance mechanisms of the host.

Approximately 1 in every 1 million resting CD4+ T cells obtained from HIV-1–infected individuals on suppressive antiretroviral therapy is believed to harbor latent HIV. This number is based primarily on in vitro end-point dilution experiments. However, the number of CD4+ T cells harboring viral DNA exceeds this number by 100- to 1000-fold. It has generally been believed that the vast majority of proviruses is defective, and indeed, the majority of proviruses sequenced directly from clinical specimens harbors mutations and inactivating mutations that cripple the provirus or show extensive APOBEC (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like)-mediated hypermutations. The fact that the vast majority of proviruses is defective was highlighted in Abstract 371.

Resting CD4+ T cells from patients on suppressive antiretroviral therapy were evaluated for the number of cells harboring provirus and the number that produced RNA following stimulation with CD3/CD28 antibodies or the histone deacetylase (HDAC) inhibitor vorinostat. The study determined that 3% of the proviruses could be induced to produce virions after CD3/CD28 stimulation and less than 1% could be induced following stimulation with vorinostat. Therefore, the vast majority of proviruses is defective rather than latent. These defective proviruses are commonly referred to as graveyard sequences. Although they have no role in the maintenance of infection, they complicate the interpretation of studies that use viral DNA surrogates to gauge the dynamics of the viral reservoirs.

Several presentations provided evidence that a number of silent proviruses are functional yet refractory to reactivation. This suggests that the size of the latent reservoir is considerably larger than estimates based on end-point dilution calculations. In the plenary presentation given by Siliciano (Abstract 16) and further expanded on in Abstract 43, patients' CD4+ T cells were subjected to limiting dilution culture and activated with phytohemagglutinin (PHA). Full-length proviruses were reconstituted from wells that were p24 positive and p24 negative. Approximately 10% of proviruses obtained from p24 negative wells were found to harbor intact open reading frames, and the majority was replication competent in culture. Therefore, functionally intact noninducible

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proviruses exceed inducible proviruses by an order of magnitude. It is possible that some integration sites are refractory to even the most potent stimuli that reactivate viral latency. Abstract 375 looked at the nature of integration sites for latent and expressed proviruses. Inactive proviruses were found to be more commonly located in regions of DNA that had a low density of cellular genes and in regions of low transcriptional activity. Latent proviruses were most commonly associated with regions of cellular DNA devoid of recognized histone-effector modules.

In addition to the challenges involved in reactivation of latent proviruses, it is as yet unclear whether the level to which proviruses can be reactivated is sufficient to ultimately result in the clearance of the reactivated cell. Elimination would require viral reactivation to the extent that the cell succumbs to viral cytopathic effect or that expression of viral proteins and presentation of antigen on the infected cell surface leads to killing of infected cells by cyotoxic effector cells such as cytotoxic T lymphocytes (CTLs). Unfortunately, agents being used in "shock and kill" trials to eliminate the latent reservoir, such as vorinostat, exert a rather modest effect on viral gene expression in vitro and in vivo, raising the concern that this modest induction may not translate into sufficient priming of the host cell for CTL recognition.

Abstract 383 evaluated the ability of HIV-specific CTL clones established from an elite controller to recognize latently infected CD4+ T cells after stimulation with vorinostat in vitro. Treatment of infected cells with vorinostat alone did not lead to reductions in p24, whereas addition of cytokines such as interleukin (IL)-2 and IL-15 resulted in recognition of infected target cells by HIV-specific CTLs. Therefore, strategies employing cytokine augmentation of CTL function may be more effective in clearing latently infected cells following their reactivation.

The 19th Conference on Retroviruses and Opportunistic Infections (CROI 2012) featured presentations documenting the first use of vorinostat in patients aimed at reducing the size of the latent reservoir.[1] Progress of a similarly designed study (Abstract 50LB) was presented at CROI 2013. The aims of the study were to determine the safety and tolerability of numerous doses of vorinostat in HIV-1–infected individuals on suppressive antiretroviral therapy. Patients received vorinostat once daily for 14 days. Numerous doses of vorinostat were well tolerated. Grade 1 or 2 adverse events such as nausea, diarrhea, and fatigue were observed in 90% of patients. Unspliced viral RNA and viral DNA levels were determined in CD4+ T cells from blood and rectal tissue. There was an approximately 3-fold increase in cell-associated RNA during the vorinostat dosing that remained elevated when vorinostat was discontinued. There were no substantial changes in viral DNA levels. Thus, although vorinostat appears to be well tolerated, no discernible impact on the viral reservoir was observed, at least based on measures of total viral DNA. However, the study cannot rule out effects of vorinostat on a subpopulation of latently infected cells. The investigators' analysis focused on total viral DNA, which would measure both functional and defective proviruses. However, the majority of proviruses determined by total DNA measures is defective and insensitive to agents that reactivate viral latency. As such, an impact on a subpopulation of latently infected cells would go unnoticed.

It is likely that efficient purging of latently infected cells will require treatment with agents that would potently activate viral gene expression. Efforts to identify small molecules that can reactivate viral latency were highlighted by Hazuda during her delivery of the 18th Bernard Fields lecture. Importantly, these screening efforts are being validated with primary cell models of HIV-1 latency. As such, agents that emerge from these screens will be more likely to induce viral reactivation in latently infected CD4+ T cells in vivo.

Although antiretroviral therapy can sustain suppression of plasma viremia to below detectable levels, treatment interruption leads to rapid viral recrudescence. The persistent nature of HIV-1 infection is believed predominantly to be a consequence of the intrinsic stability of latently infected CD4+ T cells. However, several lines of experimental evidence support the view that antiretroviral therapy is not fully suppressive, and as a result, there is a low degree of residual replication in some patients on suppressive antiretroviral therapy. It is also possible that this residual replication can contribute to maintenance of viral reservoirs through replenishment. Treatment intensification studies have attempted to broach the issue of residual infection under antiretroviral therapy. If there were residual replication in patients on suppressive antiretroviral therapy, increasing the level of suppression would be predicted to perturb some viral parameter. Unfortunately, the majority of treatment intensification studies has employed different agents, different study designs (eg, treatment intensification interval), and different surrogates with which to gauge the impact of intensification on the viral reservoir. As a result, no clear picture has emerged from treatment intensification studies as to whether there is residual replication or whether intensification further impacts the viral reservoir.

Hatano and colleagues (Abstract 42) examined the impact of raltegravir intensification in patients on suppressive antiretroviral therapy. The study was similar in design to a study previously published by Buzon and colleagues.[2] Both studies examined the impact of raltegravir intensification on the frequency of 2-long terminal repeat (2-LTR) circles. During infection of the cell, a linear viral cDNA is generated by reverse transcription. The linear genome then integrates within chromatin to form the provirus. In the presence of raltegravir, integration and formation of the provirus is blocked. As a result, the linear precursor to the integrated provirus is converted to circular forms of viral cDNA harboring either 1 or 2 copies of the LTR. Therefore, if raltegravir is applied in cells that are supporting de novo infection, there is a specific increase in the abundance of 2-LTR forms. These forms can then be quantitated using

polymerase chain reaction (PCR) and primers that span the unique circle junction created when the LTRs ligate end to end.

Abstract 42 presented results obtained with 31 subjects on suppressive antiretroviral therapy who were aviremic for at least 1 year. 2-LTR circles were analyzed at weeks 0, 1, 2, and 8 by droplet digital PCR (ddPCR). In contrast to real-time PCR, ddPCR does not require comparison with copy number standards. This facilitates quantitation of target molecules in samples obtained at different intervals and also facilitates comparison of data obtained from different laboratories. The impact of raltegravir intensification on 2-LTR circle dynamics was remarkably similar between the 2 studies. There was a rapid and transient increase in 2-LTR circle frequency by 2 weeks postintensification and a subsequent decline to baseline. The Buzon study[2] observed an increase in 2-LTR circles in 30% of raltegravir-intensified patients, whereas the Hatano study (Abstract 42) reported an increase in 2-LTR circles in over half of the subjects undergoing raltegravir intensification.

Two conditions must be satisfied in order for raltegravir to induce increases in frequency of 2-LTR circles. First, there must be infectious virions in order to initiate an infection event. Second, there must be active reverse transcription in order to generate the linear cDNA that is the substrate for 2-LTR circles. Therefore, an increase in 2-LTR circle formation following raltegravir intensification can only occur if there is de novo infection. This demonstrates that even in the presence of antiretroviral regimens comprising inhibitors of protease and reverse transcription, de novo infection persisted in a substantial fraction of individuals on suppressive antiretroviral therapy. It is tempting to speculate that residual infection is occurring at tissue locations that are inefficiently accessed by certain classes of antiretroviral drugs and that raltegravir more readily accesses those sites to impact residual infection.

Although the raltegravir intensification studies provide direct evidence for de novo infection in patients on suppressive antiretroviral therapy, they fall short of being able to prove that there is ongoing replication in these patients. In the virologic definition of ongoing replication, productively infected cells release virions that go on to initiate productive infection of neighboring cells. Ongoing replication would be expected to result in sequence evolution. However, there is little evidence for viral sequence evolution in patients on suppressive antiretroviral therapy. It is important to point out that because of sampling limitations, low levels of sequence evolution could go unnoticed. With the information at hand, the best way to reconcile these results is to invoke a model in which de novo infection under suppressive antiretroviral therapy is a result of limited rounds of infection that is perhaps driven by a chronic virus source. In this scenario, the chronically infected cell releases virions that infect neighboring cells, but those cells do not infect other cells.

Abstract 173LB presented intriguing evidence for a chronic viral source in patients on suppressive antiretroviral therapy. In the study, gut-associated lymphoid tissue (GALT) was obtained from patients on suppressive antiretroviral therapy who interrupted their therapy. GALT was analyzed by in situ hybridization to identify the source of viral recrudescence when treatment is interrupted. In 3 subjects, foci of viral RNA–positive cells emerged simultaneously at numerous anatomic sites and shortly after treatment was interrupted. This simultaneous and focal appearance of viral RNA–expressing cells following treatment interruption was unexpected, as current models indicate that HIV-1 recrudescence originates from a clonal viral source that fuels exponential viral growth. Although it is possible that the emergence of viral RNA–expressing cells was the result of latent cell reactivation, it is difficult to envision simultaneous reactivation of latently infected cells at numerous anatomic sites. Alternatively, viral recrudescence may originate from cells that are productively infected yet are held in check by suppressive antiretroviral therapy.

Although additional studies are required to determine whether residual infection in antiretroviral therapy–suppressed patients is a result of ongoing replication or limited rounds of infection, the Buzon[2] and Hatano (Abstract 42) studies provide some indication that de novo infection under antiretroviral therapy may be clinically significant. The SMART (Strategies for Management of Antiretroviral Therapy) study[3] demonstrated that D-dimer levels were associated with increased risk of cardiovascular disease and mortality in HIV-1–infected individuals and that increased D-dimer was independently associated with venous thromboembolic events. Data presented by the Hatano group (Abstract 42) indicated that raltegravir intensification resulted in a substantial decrease in D-dimer levels. Although the Buzon study[2] did not evaluate the impact of raltegravir intensification on markers of cardiovascular comorbidities, raltegravir intensification led to a reduction in the frequency of activated CD8+ T cells by 24 weeks postintensification. A number of studies indicate that high levels of CD8+ T cell activation in HIV-1 infection are associated with poorer prognosis and that higher CD8+ T cell activation is associated with lower treatment-mediated CD4+ T cell gains.[4] Going forward, it will be important to determine whether raltegravir intensification over the long term has an impact on the size of the persistent viral reservoirs. This will determine whether residual infection sustains the reservoirs that persist in the face of antiretroviral therapy.

HIV-1 Molecular Virology and Immunopathogenesis

Primate lentiviruses encode a set of accessory proteins whose functions are to oppose the antiviral activities of cellular restrictions. The viral infectivity factor (Vif) protein counteracts the APOBEC 3 cytidine deaminases; the viral protein unique (Vpu) protein of HIV-1 and negative regulatory factor (Nef) proteins of HIV-2/simian immunodeficiency virus (SIV) counteract tetherin; and the viral protein X (Vpx)

proteins of HIV-2/SIV counteract the antiviral activities of SAMHD1 (sterile alpha motif [SAM] domain and HD domain–containing protein 1), which is the most recently identified cellular restriction. SAMHD1 is a deoxynucleoside triphosphate triphosphohydrolase that regulates the level of the deoxynucleotides in the cell. By reducing cellular deoxynucleotides, SAMHD1 creates conditions that are inefficient for reverse transcription of viral cDNA. Primate lentiviruses have therefore evolved vpx to antagonize the activity of SAMHD1. The Vpx protein promotes proteosomal degradation of SAMHD1, thereby raising cellular deoxynucleotide levels, which in turn allows efficient reverse transcription of viral cDNA following infection of the cell. Since the discovery of SAMHD1, it has generally been believed that this protein is a myeloid cell–specific restriction that regulates infection of macrophage and dendritic cells.

Abstract 109 presented evidence that SAMHD1 can restrict HIV-1 infection of resting CD4+ T cells. To counteract SAMHD1, the Vpx protein must be packaged with virus particles. When Vpx was packaged within HIV-1, or if intracellular nucleotide levels were elevated by addition of exogenous deoxynucleotides, HIV-1 efficiently infected resting CD4+ T cells. Furthermore, individuals with Aicardi-Goutières syndrome contain an inactivating mutation in SAMHD1; resting cells from these individuals were permissive to HIV-1 infection. Although neutralization of SAMHD1 improved conditions for resting cell infection, it did not remove a block to virion production, indicating the existence of additional barriers to productive infection in resting T cells. Several predictions extend from this line of investigation. HIV-2 and SIV encode Vpx and are thus able to neutralize SAMHD1. Therefore, one would predict that the bottleneck to resting cell infection imposed upon HIV-1 is absent in HIV-2 and SIV. And, therefore, one would expect a much larger resting cell and myeloid cell reservoir in HIV-2–infected humans and SIV-infected monkeys. The overarching question as to why HIV-1 has not evolved the ability to neutralize SAMHD1 remains unaddressed.

Tetherin (also known as BST2/CD317) is a host cell restriction that manifests its antiviral activity by inhibiting the release of virus particles from the surface of the infected cell. The Vpu and Nef proteins of primate lentiviruses neutralize the antiviral activities of tetherin, to promote the release of virions from the cell surface. There is some evidence that the antiviral effect of tetherin is minimal during cell-to-cell transfer of viral particles at the virologic synapse. Abstract 110 presented evidence that tetherin exhibits antiviral activities that extend beyond the physical retention of viral particles at the cell surface. Evidence was presented that human tetherin has the capacity to recruit and signal through a complex that includes TRAF 6 (tumor necrosis factor [TNF] receptor–associated factor 6) and TAK1 (transforming growth factor-β [TGF-β]–activated kinase 1) and that induces NF-κB activation. This activation appears to occur in concert with virion retention. HIV-1 Vpu mutants that were unable to counteract tetherin induced an inflammatory cytokine response in primary CD4+ T cells. This has implications for antiviral strategies aimed at counteracting Vpu, as inhibition of Vpu would lead to tethering of viral particles to the cell surface and activation of an inflammatory cytokine cascade that could be deleterious to the host.

Dendritic cells internalize HIV-1 particles through a nonfusogenic mechanism and transmit virions to bystander CD4+ T cells by a process known as *trans*-infection. Early studies identified a C-type lectin known as DC-SIGN (dendritic cell–specific intercellular adhesion molecule 3–grabbing nonintegrin) as the capture receptor for viral particles on dendritic cells. Abstract 134 presented evidence that HIV-1 capture and transmission to T cells is mediated by a sialic acid–binding lectin called SIGLEC-1 (sialic acid–binding immunoglobulin-like lectin 1; also known as CD169). SIGLEC-1 was upregulated in lipopolysaccharide-matured dendritic cells that are highly capable of mediating *trans*-infection. SIGLEC-1 captured HIV-1 particles through interaction with sialyllactose-containing gangliosides. *Trans*-infection could be blocked with antibodies to SIGLEC-1, and silencing of SIGLEC-1 by RNA interference blocked viral capture and *trans*-infection. Therefore, SIGLEC-1 appears to be a key myeloid cell receptor that mediates HIV-1 *trans*-infection by dendritic cells.[5] The identification of SIGLEC-1 as the primary receptor for HIV-1 *trans*-infection by dendritic cells was reinforced by data presented in Abstract 107. These studies have substantial implications for the design of agents that prevent dendritic cell–mediated transmission at mucosal surfaces and in lymphoid tissue.

Pathogenic HIV and SIV infection are associated with increased permeability of the gastrointestinal (GI) tract. Increased GI tract permeability permits translocation of microbial products that drive inflammation of lymphoid tissue and exacerbate conditions for viral replication. Morbidity and mortality in HIV-1–infected individuals on suppressive antiretroviral therapy is associated with elevated levels of microbial translocation and immune activation. Although antiretroviral therapy improves integrity of the GI tract, it does not completely restore it. Investigators have begun to turn their attention to the composition of the enteric microbiome. Research has revealed a synergistic relationship between the gut microbiota and mucosal responses to viral pathogens. Abstract 53 examined microbial translocation and GI tract immunology in SIV-infected macaques undergoing antiretroviral therapy with and without probiotics and prebiotics. Symbiotic treatment in conjunction with antiretroviral therapy enhanced CD4+T cell reconstitution and reduced fibrosis of lymphoid follicles. Abstract 54 examined the enteric virome in pathogenic SIV infection. Thirty-two previously undescribed enteric viruses were identified in macaques undergoing pathogenic SIV infection that were not observed in nonpathogenic SIV infection. Therefore, undiagnosed

enteric viral infections may contribute to mucosal damage and impaired immune response to viral antigens during pathogenic infection. A highly tractable model with which to examine the interplay of the gut microbiota and GI immune function was described in Abstract 52. The study utilized an intestinal loop model that allows examination of early mucosal responses to probiotic and pathogenic bacteria in the GI tract. This model will direct the design of strategies aimed at establishing a healthy microbiome and that restore the integrity and immune function of the GI tract.

Financial Affiliations: Dr Stevenson has served as a consultant for Merck.

A list of all cited abstracts appears on pages 90-95 and is available online at www.iasusa.com.

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Top Antivir Med. 2013;21(2): 42-46

Correction

There was an error in the figures accompanying the article "Update of the Drug Resistance Mutations in HIV-1: March 2013" published in Volume 21, Issue 1, of *Topics in Antiviral Medicine*. On page 9, one of the elvitegravir-associated resistance mutations at position 92 was listed incorrectly. The correct designation is E92Q/G not E92Q/C.

The figures and downloadable slides posted on our website (www.iasusa.org) show the correct designation, but the error remains in the printed journal copies and in the folded pocket cards inserted with the issue. Corrected pocket cards are available on request through our website, where updates are posted as they become available. We regret any inconvenience this error has caused.

CROI 2013: New Tools to Understand Transmission Dynamics and Prevent HIV Infections

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

New tools to track HIV incidence and identify transmission networks are providing insights about the leading edge of new HIV infections globally. Phylogenetic analyses point to the continued global nature of HIV transmission patterns and the challenges to reducing HIV infections through targeted antiretroviral programs alone. New methods for measuring acute infection and HIV incidence using cross-sectional surveys are proving useful in tracking the impact of prevention programs at the population level. Globally, men who have sex with men, and young men and women continue to be at highest risk of HIV acquisition; the US South also bears a disparate burden of new HIV infections and poor HIV-related outcomes. The use of injectable hormonal contraception may increase HIV acquisition risk; new, effective contraceptive methods and contraceptive counseling are needed, as simply removing this strategy could lead to a net increase in deaths due to unintended pregnancies. Another preexposure prophylaxis efficacy trial failed to show protection, likely because of poor adherence by women in the trial. Fortunately, new strategies are being developed that could substantially reduce new infections globally, such as methods to increase adherence and the use of long-acting antiretroviral agents.

Keywords: *HIV, epidemiology, prevention, transmission*

New Strategies to Track the HIV Epidemic

This year's Conference on Retroviruses and Opportunistic Infections (CROI) highlighted a number of new tools being used to track transmission patterns, improve HIV diagnosis for individuals, and follow incidence trends within populations, including the impact of interventions at a population level.

Using Phylogenetic Analysis to Probe Transmission Dynamics

Several posters explored the ability of phylogenetic analysis to identify transmission patterns, pointing to the strengths and limitations of particular types of prevention strategies. Wertheim presented data in a themed discussion on the global diversity of HIV, by pooling data from more than 85,000 sequences in public databases (Abstract 488). In the 3.5 billion pairwise comparisons, he and his colleagues were able to demonstrate a number of clusters that highlight the ongoing global nature of HIV transmission. For example, he described 2 global transmission clusters, one of 333 (mainly) heterosexuals and injection drug users (IDUs) in 17 countries, and another of 674 (mainly) men who have sex with men (MSM) and IDUs in 18 countries. Grabowski reported on 189 incident cases from 46 communities in the Rakai district of Uganda (Abstract 489). She noted that 39% of the new transmissions appear to have occurred within stable household partnerships. However, of those occurring outside of such partnerships, 62% occurred from outside of the community, suggesting that test-and-treat strategies within communities may not be sufficient to substantially reduce new infections. Paraskevis and colleagues presented data on a recent outbreak of HIV infections among IDUs in the metropolitan area of Athens, Greece (Abstract 502). They detected a 10-fold increase in new diagnoses among IDUs from 2011 to 2012, compared with 2010. Evaluation of viral sequences from these newly infected persons identified numerous subtypes, suggesting numerous introductions from diverse geographic regions dating from 2008 to 2010, and pointing to the ability of HIV to spread rapidly within IDU populations. Lai and colleagues analyzed 3786 sequences from patients with clade B infection enrolled in the Italian ARCA (Antiretroviral Resistance Cohort Analysis) cohort from 1996 to 2012 from 42 clinical centers (Abstract 494). They identified 157 epidemiological clusters of 3 to 106 patients, accounting for more than a quarter of all sequences. Cluster dating suggests that the number of new infections grew until 1990 and has remained constant since that time, demonstrating that these types of analyses can also be used to identify general trends in HIV infections within a population.

Chan and colleagues presented data on sequencing of approximately three-quarters of the HIV-infected patients in Rhode Island from 2004 to 2011 (Abstract 497). In their analysis of 1277 unique sequences, 45% formed 151 clusters, with a mean of 3.5 persons per cluster (range, 2-23). They estimated that only 16% of infections occurred within 6 months of another infection in that cluster, suggesting that the majority of infections are occurring from chronically infected persons. Parry and colleagues presented data from sequencing of 51 seroconverters

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and more than 500 randomly selected HIV seropositive men and women in 5 fishing communities on the shores of Lake Victoria, Kenya (Abstract 97). Although they also found that a minority of infections were likely due to acute infections (15%-43%), they noted that these infections may not be prevented by test-and-treat strategies, which can miss acute infections. Dennis and colleagues sequenced virus from 177 Latino subjects and 1496 non-Latino subjects enrolled in the University of North Carolina HIV Clinical Cohort from 1997 to 2011 (Abstract 495). In their study, immigrant- and US-born Latino participants were equally likely to be in clusters, but immigrants were more likely to be in clusters with another Latino (78% vs 25%; $P = .006$), pointing to the potential for prevention interventions targeted to this group to spread beyond those directly participating in the intervention. In sum, these presentations point to the power of phylogenetic analyses to provide insight into ongoing transmission dynamics and point to opportunities to have a substantial impact on ongoing HIV transmission within sexual and drug-using networks.

Advances in Monitoring the HIV Epidemic

Laeyendecker and colleagues provided an update on cross-sectional HIV incidence testing (Abstract 164). Advantages of accurate cross-sectional incidence testing include lower cost, ability to estimate incidence on a larger scale (eg, countrywide surveillance of incidence), shorter time required to obtain estimates, and ability to include hard-to-reach individuals. Laeyendecker described a multiassay algorithm (MAA) his group developed that includes CD4+ cell count, 2 serologic assays (BED–capture enzyme immunoassay [CEIA], and avidity assay), and HIV RNA level. This algorithm has a window period of approximately 5 months in a clade B setting. Incidence estimates generated by the MAA were nearly identical to observed HIV incidence in 3 large longitudinal cohorts. CD4+ cell testing, which is costly, can be replaced by a high-resolution melting (HRM) diversity assay that does not compromise the mean window period. Laeyendecker and colleagues also optimized an MAA for use in clade A and clade C epidemics that was used as the primary end-point for Project Accept, described below.

In the same session, Hall presented on the use of viral load measures to guide interventions, evaluate research and treatment program outcomes, assess HIV disparities among populations, and estimate trends in relation to HIV incidence (Abstract 165). Viral load data can be obtained through HIV surveillance systems, care practitioner reports, population surveys, and large cohort studies. Hall pointed out that viral load data can be used to identify individuals who are not in care and intervene to facilitate linkage and reengagement in care. On the aggregate level, community viral load measures can be used to evaluate differences in viral burden by geography, demographics, and risk behaviors, as well as among patients in care at a clinic or facility. These measures can also be used to monitor progress toward achieving the goals of the US National HIV/AIDS Strategy.

Justman and colleagues described the first national population viral load estimate in Swaziland to assess the effectiveness and transmission-lowering potential of antiretroviral therapy programs (Abstract 96). Justman pointed out that community viral load measures do not account for those individuals unaware of their diagnosis and proposed more precise terminology to describe such measures (Figure 1): treatment viral load among HIV seropositive individuals on antiretroviral therapy; diagnosed viral load among individuals who have been diagnosed with HIV infection and may or may not be on antiretroviral therapy; and population viral load among the entire HIV seropositive population, including individuals who are unaware of their HIV serostatus. In a nationally representative household sample of 18,154 men and women in the SHIMS (Swaziland HIV Incidence Measurement Survey) study, 5802 (32%) were HIV seropositive; 63% were aware of their serostatus; and among those, 48% reported antiretroviral therapy use. Population viral load was high overall (94,644 HIV RNA copies/mL), with a higher mean viral load among those unaware of their serostatus than those aware of their serostatus (129,307 and 74,319 copies/mL, respectively) and among those not on antiretroviral therapy than among those on antiretroviral therapy (129,260 and 22,979 copies/mL, respectively). Overall, approximately one-third had a high viral load (more than 50,000 copies/mL). Having a high viral load was associated with being unaware of HIV serostatus (adjusted odds ratio [aOR], 14.6; $P < .0001$), being aware of HIV serostatus but not on antiretroviral therapy (aOR, 13.2; $P < .0001$), and being male (aOR, 1.96; $P < .0001$). Viral load data also provided evidence of an effective antiretroviral therapy program, with 85% of those who reported current antiretroviral therapy use having a viral load less than 1000 copies/mL. However, transmission potential remains high in Swaziland, with 65% of HIV-seropositive adults not virally suppressed.

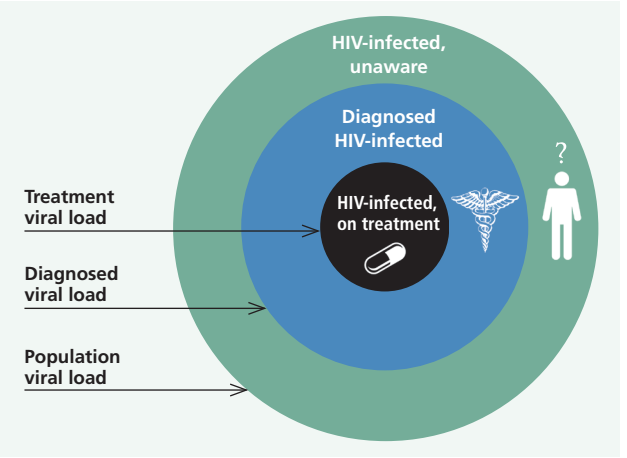

Figure 1. Viral load terminology proposed by Justman and colleagues (Abstract 96). Adapted with the permission of the authors.

Improving HIV Diagnosis, Including Acute HIV Infection

Several poster presentations evaluated fourth-generation antigen-antibody (Ag/Ab) tests for early detection of HIV infection. Manak and colleagues presented performance characteristics of a combination Ag/Ab enzyme immunoassay (EIA) in the ECHO (Early Capture HIV Cohort) Study conducted in Tanzania, Uganda, Kenya, and Thailand (Abstract 630). This fourth-generation EIA detected acute HIV infection on average 8.8 days earlier than the third-generation EIA and 15.5 days earlier than HIV-1 Western blot. Peters and colleagues presented results from the STOP (Seek and Treat for Optimal HIV/AIDS) study, an ongoing prospective study comparing a combination Ag/Ab test with pooled nucleic acid amplification testing (pNAAT) (Abstract 632). Out of 43 cases of acute HIV infection, the combination Ag/Ab test detected 38 (88%) acute infections, and pNAAT detected 42 (98%) acute infections. The combination Ag/Ab test also detected 100% of established HIV infections. Chang and colleagues also demonstrated high sensitivity and specificity of 3 fourth-generation Ag/Ab combination assays in Taiwan (Abstract 633). In contrast, Duong and colleagues described poor performance of an HIV-1/2 Ag/Ab combination test in detecting early infections in the SHIMS study (Abstract 631), with a 0% sensitivity and positive predictive value for detecting acute infections in this cohort (12/12 individuals who had NAAT positive samples and seroconverted 6 months later were nonreactive on an HIV 1/2 Ag/Ab combination test). These studies point to the progress being made to narrow the window between infection and diagnosis, and to how performance characteristics for different tests vary among populations.

Guanira and colleagues presented data from the iPrEx (Chemoprophylaxis for HIV Prevention in Men) trial to help streamline HIV testing during preexposure prophylaxis (PrEP) use (Abstract 635). In iPrEx, HIV infection was assessed by 2 rapid HIV tests at monthly visits, with Western blot performed if either test was positive. Simulations were performed for 5 different HIV testing algorithms to help streamline HIV testing during PrEP use. An algorithm using 1 rapid HIV test to screen and a second rapid test to confirm infection, followed by Western blot in only those with discordant results performed well, with a high positive and negative predictive value (100% and 99.9%, respectively). Using such algorithms could substantially reduce the delay arising from performing Western blot assays after a single positive rapid test result.

Methods for Delivery of HIV Testing

Myers presented an overview of opportunities and challenges with HIV self-testing (Abstract 162). She reviewed the history of development and evaluation of the rapid HIV self-test kit, leading up to the approval of the rapid HIV self-test by the US Food and Drug Administration for over-the-counter sale in 2012. She highlighted potential uses for HIV self-tests, including encouraging testing among persons unaware of their HIV infection, more frequent testing of persons at highest risk for new infection, and mutual testing of sex partners. She also described a number of concerns raised about HIV self-testing, including the lower sensitivity (91%) of the self-test than its administration in clinical settings (98%), potential for increased risk taking if individuals test their sex partners and subsequently engage in high-risk sexual activities, the high cost of the test in the United States, and concern that HIV-infected individuals will not link to care.

In Session 8, McNaghten and colleagues reported results from Project STATUS (Strengthening HIV Test Access and Treatment Uptake Study), a study to determine which of 3 different models of practitioner-initiated HIV testing and counseling (HTC) work best in outpatient departments (OPDs) in Africa (Abstract 31). In this study, 36 OPDs in South Africa, Tanzania, and Uganda were randomly assigned to 1 of 3 HTC models: Model A, OPD health care practitioners refer eligible patients to on-site voluntary counseling and testing after the clinical consultation; Model B, OPD practitioners offer and provide HTC during the clinical consultation; or Model C, nurse or lay counselors offer and provide HTC before the clinical consultation. All 3 models resulted in high rates of HIV testing. Models A and C had the highest rates of acceptance of HIV testing, and Model C tested the highest proportion of eligible OPD patients (54% in Model C, 42% in Model A, and 34% in Model B). Models did not differ in the proportion of patients who tested HIV seropositive (10%) or HIV seropositive patients who were referred to care and treatment services (94%). McNaghten suggested that high testing rates in Model C could be attributed to having a designated area for testing (patients approached in the waiting area were informed that they would not lose their place in line to see a clinician), delivering a health-oriented talk including HIV information in the waiting area, and having designated staff tasked to provide HTC.

Several posters presented outcome data on implementation of the Centers for Disease Control and Prevention (CDC) guidelines for routine, opt-out HIV testing in clinical settings issued in 2006. Momplaisir and colleagues presented data on HIV testing trends from the Southeastern Pennsylvania (SEPA) Household Survey before and after the guidelines were released (Abstract 1059). Overall, HIV testing increased by 33% (OR, 1.33; 95% confidence interval [CI], 1.24-1.4) after the 2006 CDC recommendations, with testing rates increasing faster among African Americans than among whites, and faster among patients in general seeking care at a community health center compared with private clinics. Giordano and colleagues described outcomes from a routine screening program implemented in an emergency department (ED) setting in Houston, Texas, from 2009 to 2012 (Abstract 1063). This program performed more than 170,000 HIV tests and identified 594 (0.34%) new HIV infections; linkage to

care has improved (44% in 2009 and 62% in 2011; $P = .002$) with focused efforts. Lyons and colleagues conducted a randomized comparison of universal screening (offering HIV testing to all regardless of risk) versus targeted HIV screening (offering HIV testing to individuals with any potential indication of HIV risk or disease from charts, staff referral, or self-disclosure) in the ED (Abstract 1062). Targeted HIV screening, even using broad risk criteria, did not increase the rate of positive results nor reduce the number of HIV tests performed, and the universal testing approach identified more HIV cases. Finally, Spaulding and colleagues demonstrated that routine rapid HIV testing in a high-volume jail identified undiagnosed cases of HIV infection, with costs comparable with a routine HIV screening program in the ED (Abstract 1061).

Two posters presented innovative approaches to increase HIV testing in Africa. First, Van Rooyen and colleagues presented results of a home-based counseling and testing (HBCT) program to identify heterosexual couples for HIV testing and linkage to care and treatment in South Africa and Uganda (Abstract 1065). HBCT achieved almost universal (>95%) uptake of HIV testing among 1384 individuals who identified being in a couple, with almost all (99%) disclosing the results to each other. Second, Black and colleagues presented outcome data from an integrated youth center program in Cape Town, South Africa (Abstract 1066). This multifaceted program increased HIV testing among adolescents compared with testing in a community-based clinic, particularly among 12- to 14-year-old boys and 15- to 17-year-old girls.

In sum, these presentations provided evidence that broad screening programs that include outreach in homes, outpatient departments, and community centers may increase uptake of HIV testing. Although progress has been made in linking HIV-infected persons to care, more needs to be done to ensure this linkage is successful, particularly for home-based self-testing initiatives.

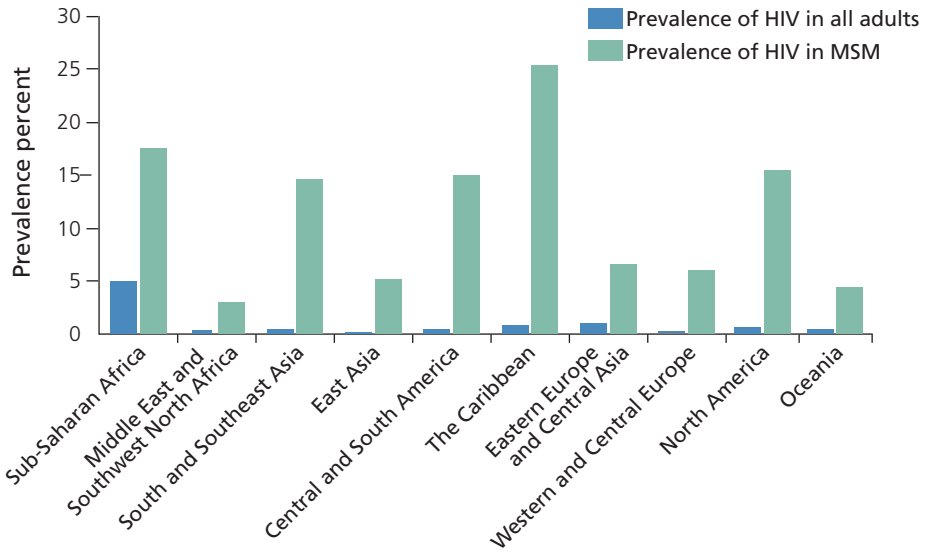

Figure 2. Prevalence of HIV in all adults and men who have sex with men (MSM) worldwide, by region. Adapted from Beyrer C et al. *Lancet*. 2012.

Highly Affected Populations

Men Who Have Sex With Men

This year's CROI demonstrated the considerable work that is being done to understand patterns and factors contributing to the global MSM epidemic. In a plenary session, Beyrer reviewed what is known about the global epidemiology, drivers of risk, and potential for interventions to reduce HIV infections in MSM globally (Session 21). He pointed to the higher HIV prevalence rates among MSM than among other adult populations in all regions of the world (Figure 2), as well as the high and rising rates of new infections in this population globally. He pointed to recent data published by van Griensven and colleagues[1] of a cohort of MSM in Bangkok, Thailand, showing a cumulative HIV incidence of 23% during a 5-year period, with rates as high as 31% among MSM aged 18 years to 21 years. This was seen in Thailand despite widespread antiretroviral treatment, no laws criminalizing homosexuality, and a heterosexual epidemic that has been in marked decline.

Beyrer turned to an exploration of the factors that may be driving the MSM epidemic. The per act risk for receptive anal sex is quite high (1.4%), approximately 18 times higher than with vaginal sex. He also pointed out that because of sexual role versatility (ie, MSM may be both receptive and insertive), there is increased chance for forward spread in this population compared with the heterosexual population. Beyrer also explored the particularly concentrated epidemic among young black MSM in the United States, where networks appear to be both homogeneous and dense. High HIV prevalence rates (eg, approaching 50% in black MSM in Baltimore, Maryland) mean that a relatively low rate of individual risk can spread HIV more rapidly than can higher rates of risky practices in substantially lower-prevalence populations. In fact, a systematic review by Millet demonstrated that after network effects on HIV acquisition rates, the factors most strongly related to increased HIV infection risk for black MSM are biologic and clinical, such as higher rates of sexually transmitted infection (STIs) and undiagnosed HIV infection, fewer HIV-infected men who are virally suppressed, and a greater proportion of HIV-infected partners with low CD4+ cell counts. Many studies have demonstrated fewer individual risk factors for infection among black than with other MSM, including a lower number of sex partners, less methamphetamine use, and a lower proportion of men

reporting having sex while using drugs. Therefore, interventions may more effectively focus on reaching into networks and addressing biologic factors rather than relying on individual risk practices.

Beyrer pointed to both the challenges and the promises of prevention interventions directed toward MSM. Despite great enthusiasm about increasing treatment of HIV-infected persons to reduce HIV transmission, there is biologic plausibility but no direct evidence that antiretroviral treatment reduces the risk of HIV transmission from 1 HIV-infected man to another. The HIV Prevention Trials Network (HPTN) 052 study enrolled only 37 MSM couples, and none had linked transmission during the study. Other factors that could limit the effectiveness of a treatment-as-prevention approach for MSM are the possibility of lower antiretroviral efficacy for transmission during anal sex than during vaginal sex, the potential for a larger proportion of infections to occur from recent (untreated) infection and from younger persons (for whom treatment is less likely), and the possibility of increased risk practices among HIV-infected MSM (as evidenced by increased sexually transmitted infection rates in this population). Beyrer's group has done stochastic modeling that suggests that biomedical and behavioral interventions could have synergistic effects in reducing the HIV epidemic, eg, antiretroviral therapy for HIV seropositive men, a targeted use of PrEP for high-risk HIV seronegative men, and modest reductions in behavioral risk. He ended his presentation with a call to action to address the global MSM epidemic through collection of additional data, dissemination of known effective interventions including provision of condoms and lubricant, and a focus on reducing stigma and increasing access to prevention and treatment services for young, minority, and stigmatized communities.

Session 29 was a themed discussion on HIV prevalence and risk factors among MSM in developing countries. Hakim presented data on 601 MSM recruited using respondent-driven sampling from October 2011 through February 2012 in Abidjan, Cote d'Ivoire (Abstract 1021). Although HIV prevalence in the adult population in this city is 3.5%, HIV prevalence in the recruited sample of MSM was 18%, 86% of whom were unaware that they were HIV seropositive. Only 37% of the cohort had ever received an HIV test. Although approximately one-third of participants reported using condoms consistently with anal sex, only 10% of the total population used both condoms and condom-compatible lubricants, an important adjunct to condom use with anal sex in order to decrease the risk of condom breakage. Independent risk factors for HIV infection included more than 1 male sex partner in the prior 12 months (aOR for 2 partners, 1.8; aOR for 3 or more partners, 3.2), receptive anal sex in the prior 12 months (aOR, 4.9), self-perceived risk of infection (aOR, 4.0), and not having received an HIV test result at last test (aOR, 4.9). Aberle-Grasse presented data from 4 respondent-driven sampling surveys conducted from April through November 2011 in 4 cities in Ghana (Abstract 1022). Although the national HIV prevalence among the general adult population is 1.5%, prevalence in MSM in these 4 sites ranged from 4.7% to 34.3%. Overall, fewer than 10% of men who tested HIV seropositive were aware of their HIV serostatus. In all 4 regions, higher HIV prevalence was associated with increased age, employed status, higher levels of income, a greater number of male sex partners in the previous 12 months, or a lower number of female sex partners during that time period. Corby presented data on male sex workers in Ho Chi Minh City, Vietnam (Abstract 1023). Of the 300 men who were recruited and provided HIV testing, 6.3% were HIV seropositive. HIV positive serostatus was associated with opiate use, an age of 26 years or older, and being a call boy. To evaluate the potential for other syndemics to affect HIV risk, the authors constructed a syndemic scale in which each of the following is assigned 1 point: present symptoms of posttraumatic stress disorder, alcohol use, amphetamine use, suicide risk, low self-esteem, and childhood sexual abuse. The investigators demonstrated a strong dose-response relationship between the number of points scored in the syndemic scale and being HIV seropositive. The studies in Session 29 demonstrate the high prevalence of HIV in developing countries among MSM and low rates of condom use, condom-compatible lubricant use, and HIV testing availability.

Disparities in HIV Infection in the United States

Several presentations focused on MSM in the United States, the group accounting for 63% of all new HIV diagnoses in the nation in 2010. Wejnert and colleagues compared data from the 2008 and 2011 NHBS (National HIV Behavioral Surveillance System) in 20 US cities (Abstract 90). Using venue-based, time-space sampling and limiting this analysis to men aged 18 years or older with at least 1 male sex partner in the previous 12 months and a valid HIV test result, they found the prevalence of HIV infection to be similar (19% in 2008 and 18% in 2011). Prevalence was highest among black participants in both years (eg, 30% in blacks and 14% in whites in 2011). Although awareness of HIV infection among HIV seropositive men improved in all age and race/ethnicity groups between 2008 and 2011 (increasing from 56% to 66% overall), awareness of HIV serostatus was 40% lower among black MSM than among white MSM and remained lower over time. These data demonstrate the substantial improvement in awareness of HIV infection status but highlight the continued racial disparities that may be substantially contributing to the ongoing concentrated epidemic, particularly among black MSM.

Scott explored age and racial disparities in the per contact risk of HIV acquisition among more than 10,000 HIV seronegative MSM participating in 3 cohort studies from 1995 to 2003 (Abstract 91). The risk of HIV acquisition from both unprotected receptive and unprotected insertive anal sex per

episode with a known HIV seropositive partner was highest among men 18 years to 25 years old, and next highest among men 26 years to 30 years old, compared with men older than 30 years, after adjusting for other demographic variables. These estimates also trended toward being higher in black than in white MSM but did not reach statistical significance. Of interest, Latino MSM had statistically significantly higher risk of HIV acquisition for unprotected insertive anal sex with a known seropositive partner than white MSM; one possible explanation for this finding is the lower rate of circumcision among Latino men. By limiting this analysis to contacts with known HIV seropositive partners, these data suggest that higher rates of HIV infection among young MSM and MSM of color may stem from either increased susceptibility in these groups or partner characteristics (eg, higher viral load), rather than individual risk practices, as noted in the Millett meta-analysis cited earlier.

Adimora presented an overview of the epidemiology of HIV in the southern United States and discussed potential ecologic and social factors that may contribute to the disproportionate rates of HIV infections and HIV case fatality in those states (Abstract 55). The South has the highest rates of new diagnoses per 100,000 persons for both men and women, in all types of residential areas (urban, suburban, and rural). New HIV diagnoses among younger men and women (aged 13-29 years) increased substantially more rapidly from 2007 to 2010 in the South than in other US regions. Adimora highlighted the particular disparities in HIV infection rates in African Americans and MSM. Outcomes were also poorer in the South; in 2010, 9 of the 10 states with the highest AIDS case fatality rates were in the South, even after adjusting for race. Time to antiretroviral initiation after acute infection was also substantially longer in the South than in other regions.

In looking for the underlying causes of these disparities in HIV infection and outcomes in the South, Adimora used an ecosocial framework. She noted that the South has higher STI rates, higher all-cause mortality, higher poverty rates, and higher standards to qualify for Medicaid than other regions. In 2010, more than 90% of all persons on wait lists to acquire antiretroviral therapy through the AIDS Drug Assistance Program (ADAP) resided in the South, and 8 southern states are opting out of obtaining federal support to insure residents through the Patient Protection and Affordable Care Act (PPACA). Sex education is not mandated in 7 southern states; in 4 others, the mandate is for abstinence-only education. Eleven southern states still criminalize sodomy, despite the 2003 Supreme Court ruling that such laws are unconstitutional. These challenges to equitable delivery of health care, inadequate funding for infrastructure, and HIV-associated stigma may all contribute to the disparities in HIV infection and outcomes seen in the US South.

Adolescents

Young people are disproportionately affected by the HIV epidemic. At this year's CROI, a symposium on adolescents and HIV explored ethical issues in conducting prevention research in this population and highlighted challenges and opportunities in preventing HIV infections among gay or bisexual male adolescents and other young MSM and young African women (Session 35).

Philpott provided a framework for considering ethical issues in conducting HIV prevention trials in adolescents (Abstract 115). He first made the case that research in this population is justified based on the principle of distributive justice because adolescents, compared with adults, are particularly susceptible to acquiring HIV and other sexually transmitted infections, and physiologic and sociologic differences in adolescents make it difficult to extrapolate safety and efficacy results in adults to this vulnerable population. Philpott described several legal and ethical challenges in obtaining informed consent in adolescents, including poor harmonization of guidelines and laws across countries on the age of consent for research, who qualifies as a legal guardian, and who can consent if a parent or legal guardian is unavailable, which is a common problem in developing countries. Other considerations include whether the risks posed by the study are justified in adolescents, determinations on whether parental consent can be waived for research related to reproductive health, and local reporting requirements (eg, for statutory rape in some jurisdictions in the United States). As adolescents may not have fully developed cognitive and decision-making capacity, the development of age-appropriate materials and training for study staff are necessary to maximize adolescent decision making in research. Philpott recommends involvement of key stakeholders in all stages of the research process, particularly community members and regulators, to minimize risk and maximize the benefits of research conducted in adolescents.

Harper discussed drivers of the epidemic in gay and bisexual male adolescents and other young MSM (Abstract 116). In the United States, young gay and bisexual men had the greatest increase in diagnosed infections from 2005 to 2008, with the greatest increase among young black MSM. Harper presented a socioecologic model for understanding risk and resiliency in young gay and bisexual men and provided examples of factors operating at the intrapersonal, interpersonal, institutional, community, and public policy levels. An important focus is examining resiliency factors identified in gay male youth, including having positive conceptualizations of being gay or bisexual (eg, flexibility, connectedness with the gay and bisexual community) and maintaining resiliency in the face of oppression (eg, self-acceptance and acceptance by others, self-care behaviors, and rejection of stereotypes). Harper commented that a number of these socioecological factors appear to apply to young MSM in Sub-Saharan Africa. As few prevention interventions have been developed for gay and bisexual male youth, greater attention is needed in this area. To be most effective, HIV prevention programs

should be developmentally and culturally appropriate, address numerous socioecological factors, be designed in collaboration with youth and service providers, and engage cultural icons.

Delany-Moretlwe presented on drivers of HIV infection in young African women and opportunities for intervention (Abstract 117). In South Africa, HIV incidence is 10 times higher in young women than in young men and is the highest of any group in the country. Biologic and developmental changes during adolescence increase the susceptibility of young women to acquiring HIV infection. Important risk factors to consider include early sexual debut, having numerous concurrent partners and sex with older partners, alcohol use, violence, structural factors including poverty (particularly in urban settings), income inequality, and limited access to education. Early interventions focusing on behavior change at the individual level have not shown substantial impacts on behavior change or HIV incidence and suggest the need for combination prevention interventions. Delany-Moretlwe presented several examples of interventions addressing contextual and structural factors, including microfinance interventions, trainings on gender and violence, and conditional cash-transfer programs. Given the expansion of social media and mobile technology use among youth in Sub-Saharan Africa, use of mobile phones to deliver interventions, collect data, and change social norms may be a particularly promising approach.

Two posters explored prevention interventions among adolescents in South Africa. Rosenberg and colleagues (Abstract 1084) evaluated the effect of HTC on HIV acquisition in a longitudinal cohort of South African youth. In a weighted analysis adjusting for risk factors and refusal of testing, HTC was associated with lower HIV incidence (weighted hazard ratio [HR], 0.59; 95% CI, 0.45-0.78). Bekker and colleagues presented data on the safety, adherence, and efficacy of PrEP in MSM aged 18 years to 24 years in the iPrEx study, a group that comprised more than half of the study cohort (Abstract 997). Young MSM had a higher incidence of HIV acquisition in both the active and placebo arms than did older MSM. There was a trend toward lower PrEP efficacy in younger MSM, consistent with lower drug detection in this cohort (3.74 times less likely to have drug levels in plasma; $P < .001$). The investigators recommend additional research to understand the best ways to support PrEP adherence in this age group.

Understanding Risk Factors for HIV Transmission and Acquisition

Hormonal Contraception

Symposium 34 at this year's CROI focused on what is known about the relationship of hormonal contraceptives and the risk of HIV acquisition and transmission. Mauck presented an overview of the mucosal and systemic effects of different types of progestins in women (Abstract 111). She explained that medroxyprogesterone (used as depot medroxyprogesterone acetate [DMPA]) is structurally similar to progesterone, whereas norethindrone (found in the injectable contraceptive norethisterone enanthate [NET-EN]) and levonorgestrel (found in implants, intrauterine devices, and cyclic oral contraceptives) are more similar in structure to testosterone. These structural differences result in different biologic effects. For instance, the progesterone-like progestins bind strongly to glucocorticoid receptors, and the testosterone-like progestins do not. In fact, DMPA binds approximately 3 times more strongly than natural progesterone. Mauck noted that although the direct effects of this enhanced binding are not known, corticosteroids can cause an increase in HIV promoter activity, virus replication, and disease progression in HIV-infected persons. She also noted that DMPA is given in relatively high doses to last for 3 months, and that this degree of suppression of the hypothalamic-pituitary-ovarian axis leads to profound suppression of estradiol production, mimicking levels seen in postmenopausal women. These low estradiol levels, in turn, lead to vaginal epithelial thinning, potential loss of integrity of the mucosal barrier, trafficking of leukocytes into the genital tract, and a change in the microbiome leading to a rise in vaginal pH, all of which could increase susceptibility to HIV infection. Less is known about the other progestins; when estrogen is included, as in combination oral contraceptives, these potentially negative effects of the progestins may be somewhat mitigated.

Garcia-Lerma presented data on the effect of progestins in nonhuman primate (NHP) models and how their effects may influence the results of prevention trials (Abstract 112). From the mid-1990s, when Marx published data on the ability of progesterone implants to increase simian immunodeficiency virus (SIV) acquisition in NHP models, primatologists have been using DMPA to increase the likelihood of SIV infection among control animals in vaginal challenge studies. However, the doses (30 mg) of DMPA used in these challenge models are supraphysiologic, compared with the recommended dosing for women. More recently, pigtail macaques have been used, as their menstrual cycle more closely mimics those of women. Garcia-Lerma demonstrated that DMPA 3 mg (ie, doses 10 times lower than previously used) appears to have effects on the vaginal epithelium in pigtail macaques similar to those in human clinical experience, and he recommended using this as the new HIV prevention model. Dosing has to occur more frequently in this model (ie, every 5 weeks) than in women (ie, every 12 weeks) because NHPs metabolize drugs more rapidly than do women. Garcia-Lerma outlined an ambitious and important research agenda for NHP models, including (*a*) evaluating the potential impact of hormonal contraception on prevention efficacy; (*b*) assessing potential interactions between hormonal contraceptive methods and antiretroviral drug absorption and pharmacokinetics; (*c*) using hormonal contraceptives in the NHP model to identify biomarkers of risk; and (*d*) defining the impact of different doses and methods of hormonal

contraception on cell subpopulations in vaginal tissue. He also pointed out that these models may help in risk ranking of different types of hormonal contraceptives for use in populations.

Garcia-Lerma noted that questions about the interaction of hormonal contraceptives and antiretrovirals are increasingly important, as products are being developed to deliver contraception and PrEP simultaneously. His group presented 2 related posters at this year's CROI. Radzio demonstrated that DMPA affects neither the pharmacokinetics nor the efficacy of fixed-dose combination emtricitabine/tenofovir in the pigtail macaque model (Abstract 992). Dobard presented a poster demonstrating that systemic absorption of vaginal emtricitabine/tenofovir gel increases during the luteal phase of the pigtail macaque menstrual cycle and that DMPA creates a luteal-like environment during a 5-week period, effectively increasing drug absorption (Abstract 985). He hypothesized that this increased absorption of vaginal tenofovir may counteract any negative impact of DMPA on increased susceptibility.

Polis reviewed observational data on the relationship between hormonal contraception and HIV acquisition risk (Abstract 113). Data from available studies are mixed, although a systematic review of observational data meeting data quality standards found that DMPA was associated with a 1.5 to 2 times greater risk of HIV acquisition in 3 of 8 studies; the balance showed no statistically significant difference. There was no clear increase in risk for oral contraceptive users in the 7 quality studies assessing oral contraceptive use, and insufficient data on NET-EN in 3. The World Health Organization (WHO) issued the opinion from a meeting of 75 experts in January 2012 that the data were not sufficiently conclusive to change guidance about the type of contraceptive used but that all women at risk for HIV acquisition should be counseled about preventive practices. Since the meeting, 3 additional pieces of data have been published or presented. Heffron conducted sensitivity analyses on her previous meta-analysis and found no evidence that confounding accounted for the substantially increased risk of HIV acquisition among DMPA users. McCoy published a secondary data analysis of the MIRA (Methods for Improving Reproductive Health in Africa) trial that found an increased risk associated with injectable contraceptives when adjusted for study site. After adjusting for other covariates, the point estimate remained essentially unchanged but the CI broadened to include 1. Crook presented a secondary data analysis of an antimicrobial gel for the potential prevention of HIV infection at the meeting of the MDP301 RCT (Microbicides Development Programme Randomised Controlled Trial) that found the gel to have no efficacy in more than 9000 women (Abstract 28). Among the 8663 women included in the analysis, 382 seroconverted, and women using DMPA had a 36% increase in HIV acquisition compared with women not using hormonal contraception. There was no increased risk of HIV acquisition among women using NET-EN or oral contraceptives. The WHO will convene another expert panel in 2014 to review new data and revise recommendations as appropriate. Different opinions were voiced during the question and answer period about the need and appropriateness of a randomized controlled trial (RCT) to better understand the risk associated with different forms of hormonal contraception. Additional systematic reviews were presented that showed no clear association of increase in transmission or disease progression among HIV-infected women.

Smith explored the potential population-level impact of injectable hormonal contraceptives (IHCs) on overall morbidity and mortality (Abstract 114). First, she explored whether differential underreporting of condom use between hormone-users and –nonusers could account for the substantial increased risk of HIV acquisition in observational studies. She demonstrated that even with large differences in reporting of condom use between hormone-users and -nonusers, the result could only be a very modest increase in risk associated with IHCs, which is not compatible with the data found in observational studies (eg, OR, 1.2). For the estimates of the relative hazard generated from meta-analyses (eg, HR, 1.5 or greater), the only way for confounding from condom use reporting to occur would be if nonusers underreported condom use and IHC-users overreported their use, an unlikely scenario. Smith then presented modeling to explore the net population-level impact on morbidity and mortality if IHCs were eliminated and women used other or no contraception, based on background rates of nonhormonal contraception use within that country. Areas with high HIV incidence and high maternal mortality could potentially benefit from eliminating IHCs, if AIDS-related deaths currently outnumber maternal deaths; this applies mostly to South Africa. If the risk associated with IHCs is high enough (approximately a 2-fold increased risk [Abstract 113]), southern and East African countries would benefit. However, without substitution of a highly effective contraceptive for IHCs in much of the rest of the world where HIV incidence is not as high, removal of IHCs could lead to a substantial number of unplanned pregnancies, and a net increase in mortality in women. This is particularly true in Southeast Asia, where maternal mortality rates are high. McGrath presented data from the Africa Centre for Health and Population Studies at the University of KwaZulu-Natal, which has been collecting behavioral and clinical data on a population of 90,000 in the KwaZulu-Natal region of South Africa and performing HIV testing annually since 2003 (Abstract 897). She and her colleagues estimate that only 5.2% of HIV infections would be attributable to IHCs in this population, if the adjusted HR were 1.24, as estimated in some analyses. However, if the risk were as high as 1.98, as estimated in other analyses, they estimate that 18.1% of new infections could be attributed to IHC use.

These data suggest the importance of understanding the degree to which IHCs increase risk, and of increasing contraceptive choices for women. Others at this year's CROI pointed to the need for practitioners to address family

planning with female and male patients, to increase HIV testing among women of reproductive age and their partners, and to help women use contraception more effectively. Matthews presented data on 209 HIV seropositive women and 83 HIV seropositive men with recent births, whose partners were either HIV seronegative or of unknown serostatus (Abstract 895). Among this group, only 11% of women and 5% of men had planned the pregnancy, and only 32% of women and 25% of men had desired the pregnancy. Speaking to the potential role of practitioners in reducing unwanted pregnancies, they reported that only 22% of women and 12% of men had previously spoken with a health care practitioner about fertility.

McCoy presented data from a representative sample of women from 5 provinces in Zimbabwe, recruited from 9 months to 18 months postpartum (Abstract 898). Of the 8659 women in this study, 27% had not intended to get pregnant, and an additional 9% had intended to get pregnant at a future date but not at the time they became pregnant. Slightly more than half of these women were not using contraception at the time of pregnancy, and slightly fewer than half had been using contraception at least some of the time, and could be considered to have had a "contraceptive failure." Among the 12% of the women in this sample who were HIV seropositive, nearly three-quarters were unaware of their HIV infection at the time they became pregnant, and 44% reported that the pregnancy was unintended or mistimed. These data point to the important need for increased family planning discussions that would include HIV testing and selection and adherence to contraceptive method, depending on the individual's and couple's needs.

Sexually Transmitted Infections

Several studies explored the relationship of bacterial STIs and HIV transmission or acquisition risk. Desai and colleagues described the incidence of STIs among men and women attending STI clinics in England from 2008 to 2011 (Abstract 1072). Among this population, the incidence of acute STIs was statistically significantly higher among MSM (13/100 patient-years of observation) than among heterosexual men (1.65/100 patient-years) and among women (1.4/100 patient-years). MSM were also the only population in whom STI incidence rates statistically significantly increased during those years, nearly doubling. In multivariate Cox regression analyses, younger men were statistically significantly more likely than men aged 50 years or older to be diagnosed with an STI, with the increased odds ranging from a 2-fold risk among 35- to 49-year-olds, to a 4-fold risk among 15- to 24-year-olds. Among heterosexuals, the association of younger age with STI diagnosis was even more striking: 15- to 24-year-olds had a 6.6-fold increased likelihood of STI diagnosis compared with men aged 50 years or older, and 25- to 34-year-olds had a 3.7-fold increased risk. Among heterosexuals, the incidence of STIs was statistically significantly higher among white heterosexuals than black heterosexuals or other racial groups. These investigators also assessed HIV incidence among HIV seronegative MSM attending these same clinics over the same period of time and found that gonorrhea or *Chlamydia* spp. infection increased risk for HIV acquisition (adjusted HRs 2.2 and 2.0, respectively) (Abstract 1020). Refugio and colleagues presented data on 99 HIV-infected men in the US military, based in San Diego, California (Abstract 1071). Nearly a quarter of these men had asymptomatic gonorrhea or *Chlamydia* spp. infection in 1 or more locations, pointing to the importance of active STI screening among HIV seropositive persons. Golden and colleagues presented data collected through partner services provided to MSM with bacterial STI diagnoses in King County, Washington, from January 2007 through June 2012 (Abstract 1019). They found that MSM with bacterial STIs and their partners had a high prevalence of undiagnosed HIV infection (9% and 7%, respectively), pointing to the importance of HIV testing for these patients and their partners and perhaps targeting this population for PrEP and other prevention services.

Transmission Behaviors Among HIV-Infected Persons

Landovitz explored unprotected sexual practices among antiretroviral treatment–naive men and –women enrolling in ACTG (AIDS Clinical Trial Group) A5257 (Abstract 1069). Of 704 men and women who had been sexually active in the previous month and with available covariate data, the following variables were independently associated with reporting unprotected sex in the month prior to enrollment: higher number of lifetime sex partners (aOR for 21-50 partners, 1.8; aOR for >50 partners, 2.9), having numerous sex partners in the previous month (aOR, 2.7), and using stimulants in the prior month (aOR, 2.4). Factors associated with a reduced likelihood of unprotected sex in the month prior to enrollment included older age (aOR, 0.4 compared with 18-29-year-olds), Latino ethnicity (aOR, 0.5 compared with non-Hispanic whites), men having sex only with women (aOR, 0.4 compared with MSM), and having had sex only with a nonprimary partner in the past month (aOR, 0.4 compared with having sex only with a primary partner). Despite the limitation of these self-administered surveys, with substantial missing data and lack of information about partner HIV serostatus, this study does identify younger, substance-using MSM having numerous, nonprimary partners as those who may be at greatest risk for forward transmission of HIV. Patel and colleagues evaluated HIV seropositive men prescribed phosphodiesterase type 5 inhibitor drugs (typically used to treat erectile dysfunction) seen at the Albany Medical Center from 2007 to 2010 (Abstract 1073). They noted a modest but statistically significant increased risk of acquiring a sexually transmitted infection among these men compared with other HIV seropositive men, suggesting that these medications may identify men engaging in high-risk sexual practices, who could be targeted for prevention interventions. Freedman

and colleagues presented data from the 2009 national probability sample of HIV-infected adults in medical care in the United States, the Medical Monitoring Project (Abstract 1017). In this first nationally representative study of risk practices of bisexual men, they report that bisexual men reported statistically significantly higher rates of unprotected vaginal or anal sex and a greater number of sex partners than heterosexual men but lower rates of unprotected sex and fewer sex partners than MSM. They suggest that special programs be developed that target bisexual men, as they appear to be different demographically from both heterosexual men and MSM.

Social Determinants of HIV Risk

Two interesting presentations evaluated both individual- and community-level factors associated with HIV transmission or acquisition risk. Haubrich and colleagues presented data from the San Diego Center for AIDS Research Network of Integrated Clinical Systems from 2011 that included geocoding to census block group (Abstract 1076). Their analysis of a number of individual-level demographic (eg, younger age, male sex), risk (eg, substance use), and clinical variables (eg, higher nadir and current CD4+ cell count, no current mental health diagnosis) was associated with high-risk practices. Risk factors were also higher in census block groups with lower income, a greater percentage of men, higher level of education, shorter distance to care, and higher population density. Willis and colleagues presented data on individual- and community-level determinants of HIV infection among blacks in Washington, DC, in 2008 (Abstract 1075). Combining data from the Enhanced HIV Surveillance Reporting System (eHARS) with 2000 Census data and that from municipal Washington, DC, agencies, they found that poverty, lack of home ownership, and a greater number of housing vacancies were associated with higher HIV prevalence among black men and women. These analyses demonstrate the power of using census and geomapping strategies to uncover social and environmental factors associated with HIV risk, pointing to populations with the greatest need for primary and secondary prevention tools.

Prevention Strategies

Medical Male Circumcision

Medical male circumcision (MMC) was the first biomedical intervention definitively shown to reduce the risk of sexually acquired HIV infection, but a scale-up to levels that ensure maximal impact will require approaches to increase both demand and supply. In a themed discussion focused on MMC (Session 14, Abstract 1009), Kong presented data from Rakai, Uganda, the location of two MMC trials from 2004 through 2007 and where MMC has been offered free of charge since 2007. Despite more than 95% of the population understanding the benefits of MMC and knowing where MMC is offered, only 28% of the non-Muslim men aged 15 years to 49 years were circumcised by 2011, with an annual MMC rate of only 4% of eligible men per year. MMC rates were somewhat higher in men with numerous sexual partners but were lower among men who reported never using condoms in the prior year. Kacker suggested that MMC may have an even greater impact at less cost than previously published estimates, as these models generally fail to take into account the impact of MMC on reducing sexually transmitted infections (Abstract 1010). Her model suggests that previous cost estimates may underestimate cost effectiveness by 10% to 50%, and reduction in STIs could account for half of the cost savings from campaigns in the first 5 years of roll out. Hellar found that offering MMC increased screening for STIs in Tanzania (Abstract 1013), further amplifying these benefits.

Several poster presentations focused on strategies to increase demand. Plank presented data on neonatal MMC in Botswana (Abstract 1011). She found that although 93% of the 547 women approached in maternity wards from 2009 through 2010 said they wanted to have their male child circumcised, only 55% brought their child in within 28 days after birth for the procedure. Women who stated they knew that MMC could protect their child from HIV infection, those saying they were one of the decision makers about MMC for their child, and women who said they received no support from their partner were statistically significantly more likely to have their child circumcised. Women who said the father was a decision maker were statistically significantly less likely to have their child circumcised, suggesting that prenatal couples counseling should provide information and opportunity for discussion about wishes for MMC for boys. Mahler and colleagues presented data from the Iringa and Njombe regions of Tanzania from October 2009 through December 2012 (Abstract 1014). They found that outreach campaigns were more likely to bring in younger boys (aged 10-14 years), whereas use of fixed sites with ongoing services was more likely to be taken up by boys 15 years or older.

Other posters focused on strategies to minimize adverse events (AEs) associated with MMC. Chesang presented data from 2008 through 2011 in Kenya, demonstrating substantial decreases in AEs during that time period (20-fold intraoperatively and 4-fold postoperatively), suggesting that experience is an important factor in the safe provision of MMC (Abstract 1008). In that study, AE rates were low in all groups; nurses had particularly low rates, suggesting task shifting can occur safely. Kanyago reported on an RCT of the Shang ring versus forceps-guided adult MMC (Abstract 1007). Shang rings required less operative time and allowed men to return to work more quickly, and men were equally likely to be satisfied with the procedure as with forceps-guided MMC. Infection rates appeared to be substantially higher in the Shang ring group.

Two posters focused on the impact of MMC on the mucosal environment, offering potential explanations for its beneficial effects on HIV acquisition risk. Liu and colleagues presented data on the impact of MMC on the penis

microbiome (Abstract 344). Comparing baseline and 1-year coronal sulcus swabs between men undergoing MMC and those who did not, they noted a substantial decrease in anaerobic bacteria and a decrease in bacterial diversity among the men undergoing MMC. They suggest that these changes may decrease target cell recruitment or proliferation, or both, resulting in a decrease in HIV acquisition rates. Dinh and colleagues reported that in contrast with circumcised men, uncircumcised men have substantial fluctuations in the water content of epithelial cells of the foreskin, correlating with increased entry of HIV virions in an explant model (Abstract 345). These findings may help in the development of topically applied agents.

Impact of HIV Testing on HIV Incidence and Antiretroviral Therapy Uptake

Coates and colleagues presented results from Project Accept (HPTN 043), a community-randomized trial to encourage widespread HIV testing in 48 communities in Africa and Thailand (Abstract 30). Communities were randomized to community-based voluntary counseling and testing (CBVCT), an integrated strategy of community outreach and mobilization, mobile HIV testing, and posttest support services (including stigma reduction and coping-effectiveness training), or to standard clinic-based voluntary counseling and testing (SVCT) normally provided in that community. HIV incidence was evaluated at the community level (including individuals in the community who did not participate in the intervention) and was assessed in a probability sample of more than 54,000 community residents between the ages of 18 years and 32 years using a multiassay testing algorithm described previously. The project performed more than 86,000 HIV tests (69,987 in the CBVCT communities, 7636 in SVCT communities) and increased HIV testing by 45% in men ($P < .0001$) and 15% in women ($P = .01$) in the intervention versus control communities, which were substantial and statistically significant increases. In the postintervention assessment, there was a 14% reduction in HIV incidence ($P = .08$) in the CBVCT communities compared with the SVCT communities, and a 25% reduction in individuals between the ages of 25 years and 32 years. The intervention produced an almost 4-fold increase in detection of undiagnosed HIV cases and also led to a statistically significant reduction in sexual risk, particularly in HIV-infected men. There was no increase in negative effects or social harms observed in the CBVCT communities. These results indicate that a large-scale community-based program to increase HIV testing is feasible and may produce a modest reduction in HIV incidence. Coates pointed out that greater reductions in HIV incidence may be achieved by adding referral and linkage to additional services, including HIV care and early treatment, male circumcision, and PrEP.

MacPherson and colleagues presented results from a cluster-randomized trial evaluating the impact of home-based assessment and initiation of antiretroviral therapy in the context of home-based HIV self-testing in Blantyre, Malawi (Abstract 95LB). In 2012, adult residents in 14 urban neighborhoods were offered HIV self-testing by community counselors, and neighborhoods were randomly assigned to receive facility-based HIV care alone (control arm) or with optional home-based assessment and initiation of HIV care (intervention arm). Overall uptake of HIV self-testing was high (58%), and somewhat higher in the intervention arm (65% vs 53% in control arm; risk ratio [RR], 1.23; 95% CI, 0.96-1.58). The proportion of total adult residents initiating antiretroviral therapy was higher in the intervention arm than in the control arm (2.2% vs 0.7% adult residents; RR, 2.94; 95% CI, 2.10-4.12), as was disclosure of HIV test results to a community counselor (6% vs 3.3%; RR, 1.86; 95% CI, 1.16-2.97). Based on epidemiologic estimates of HIV prevalence in Blantyre, Malawi, the authors estimated that 15% of all HIV-infected adults and 46% of treatment-naive HIV-infected adults with CD4+ cell counts below 350/μL initiated antiretroviral therapy in the intervention arm, compared with 4% and 15% respectively in the control arm. These results suggest the potential for home-based self-testing for increasing HTC but also suggest the need for proactive strategies to link individuals to HIV care.

Katz and colleagues estimated the impact of replacing clinic-based HIV testing with home-based testing on HIV transmission among MSM in Seattle, Washington (Abstract 1064). Using data from a 2003 risk behavior survey, their mathematical model predicted that home-use tests may increase HIV prevalence among Seattle MSM. This increase is driven mainly by the long window period of the currently approved home-based test compared with fourth-generation and NAAT and was not completely reversed by increasing the frequency of testing. Potential delayed linkage to care also increased HIV prevalence and decreased the proportion of HIV-infected MSM on antiretroviral therapy in the model. One limitation is that this model did not account for MSM who supplement (vs replace) clinic-based testing with home-use tests. Additional research to understand how home-use tests influence HIV testing, sexual behaviors, and linkage to care is recommended.

Antiretroviral Treatment to Prevent HIV Transmission

The use of antiretroviral therapy as a strategy to reduce HIV infection rates was highlighted in several presentations at this year's conference. In 2011, the HPTN 052 study demonstrated a 96% reduction in heterosexual HIV transmission within HIV-discordant couples with early initiation of antiretroviral therapy.[2] In a plenary session on the prospect of ending the AIDS epidemic, Dabis reviewed recent data on the use of antiretroviral therapy as prevention and its potential population-level impact on reducing HIV incidence (Abstract 6). He presented data from a recently published systematic review that found the risk of sexual HIV transmission for heterosexual serodiscordant couples to be minimal

when the HIV seropositive partner was fully suppressed on antiretroviral therapy (0.0-0.14 transmissions/100 person-years; upper limit of the 95% CI, 0.31). He also presented data from a cohort study in rural KwaZulu-Natal, South Africa, where antiretroviral therapy initiation was rapidly scaled up to more than 20,000 patients between 2004 and 2011. This analysis demonstrated a substantial and statistically significant reduction in an individual's risk of HIV acquisition with increasing antiretroviral therapy coverage in the surrounding local community. For example, the risk of HIV acquisition was 38% lower for an individual living in an area with 30% to 40% antiretroviral therapy coverage than for one in an area with less than 10% antiretroviral therapy coverage. Dabis also shared data from the HIV Modelling Consortium forecasting HIV incidence in generalized epidemics over the next 20 years. In 7 different models of the South African epidemic, initiating HIV treatment at a higher threshold (CD4+ cell count < 500/μL) or in all HIV-infected individuals led to substantial reductions in HIV incidence (fewer than 5 new infections per 1000 person-years) compared with antiretroviral therapy coverage at the status quo. Several cluster-randomized trials are planned or under way in Africa and the United States to evaluate the feasibility and acceptability of antiretroviral therapy as prevention, and several of these studies will evaluate its population level impact on HIV incidence.

Several presentations highlighted the importance of addressing gaps in the "HIV care continuum" to maximize clinical benefit in HIV seropositive individuals and reduce transmission to HIV-uninfected populations. In a symposium on preventing HIV/AIDS in the United States, Greenberg presented several national and local estimates of the HIV care cascade, from HIV diagnosis, linkage to care, retention in care, initiation of antiretroviral therapy, and viral suppression (Abstract 58). Based on surveillance data from the CDC, it is estimated that only 28% of HIV-infected persons in the United States were fully suppressed in 2011. Other studies on the continuum of care have demonstrated higher viral suppression rates in some US cities (40%-44% in Los Angeles, San Francisco, and New York) and in different health delivery systems (>50% in the Veterans Administration and >60% in Kaiser Permanente). Greenberg pointed out several challenges to using the HIV cascade as a population-based public health metric, including the use of different types of databases that are not directly comparable, and different measures to calculate cascade steps. The calculation of cascade steps is also likely to underestimate the true proportion at each stage, given that there are individuals who are diagnosed but not reported, are linked or retained in care but move to other jurisdictions, or are virally suppressed but do not have viral load data available. Greenberg described modeled data indicating that optimizing viral suppression will require interventions to address gaps at each step of the cascade.

The US National HIV/AIDS Strategy has incorporated a number of cascade steps into its goals, including increasing testing, linkage to care, retention, and viral suppression. Greenberg described a case study of optimizing the HIV care cascade in Washington, DC, where data from 2005 to 2009 indicate that only 29% of HIV seropositive individuals maintained viral suppression. In response, the district launched a number of efforts to address gaps in the care continuum, including (*a*) expanding publicly funded HIV rapid testing, which has resulted in an increase in median CD4+ cell count at diagnosis, (*b*) developing linkage to care programs, including a "Red Carpet Program" in which residents who are newly diagnosed or returning to care are provided a clinic appointment within 1 to 2 business days, (*c*) implementing a "Recapture Blitz" to find and reengage clients who are lost to care, and (*d*) establishing progressive policies and programs, including achieving near universal health insurance coverage through the PPACA. These efforts appear to be improving metrics in several steps of the HIV care cascade in Washington, DC.

In the same session, del Rio made the case that the use of antiretroviral therapy for treatment and prevention adds substantial value for healthcare dollars spent (Abstract 57). He identified HIV testing as a crucial first step in engaging HIV-infected individuals in care and reducing HIV transmission, referring to data that those who are unaware of their HIV infection account for the majority of new HIV infections each year. He made several recommendations on how to optimize allocation of funds to maximize prevention benefits. These include (*a*) targeting MSM populations, who account for the greatest number of new HIV infections (61%) yet receive only 41% of government funding for prevention, and (*b*) focusing preventive efforts on high-prevalence cities. He described the ECHPP (Enhanced Comprehensive HIV Prevention Planning) project, a demonstration project focused on 12 US cities with the highest number of people living with AIDS. ECHPP incorporates a number of interventions to address gaps at various stages of the treatment cascade, including programs to increase HIV testing, linkage and retention in care, and adherence to treatment, as well as partner services and behavioral interventions. del Rio also highlighted several opportunities to maximize our prevention efforts, including the use of generics for antiretroviral therapy, which could save the United States an estimated $1 billion in healthcare costs; linking data management systems and using consistent indicators to monitor provision of services across the continuum of care; and harnessing the PPACA to capture additional funds for HIV prevention activities.

PrEP

New data from several PrEP studies were presented at this year's CROI. PrEP involves HIV-uninfected persons using antiretroviral medications to lower their risk of becoming HIV-infected. Several clinical trials to date have demonstrated the efficacy of daily oral tenofovir or of emtricitabine/tenofovir in reducing HIV acquisition in MSM

and transgender women across 4 continents,[3] and serodiscordant heterosexual couples and young heterosexual men and women in Africa.[4,5] A trial in South African women also showed a protective effect of 1% tenofovir gel when used vaginally before and after sex.[6] In July 2012, the US Food and Drug Administration approved daily oral emtricitabine/tenofovir as PrEP to prevent sexually acquired HIV infection in adults at high risk for HIV infection.

Marrazzo and colleagues presented data on the VOICE (Vaginal and Oral Interventions to Control the Epidemic) trial, a study of 5029 women at risk for HIV acquisition in South Africa, Zimbabwe, and Uganda (Abstract 26LB). Enrolled women were young, mostly unmarried, and the majority used injectable contraception. Participants were randomized to one of 5 arms: (*a*) daily oral emtricitabine/tenofovir, (*b*) daily oral tenofovir, (*c*) daily oral placebo, (*d*) daily vaginal tenofovir, or (*e*) daily vaginal placebo. The daily oral tenofovir and vaginal tenofovir arms were stopped early because the Data and Safety Monitoring Board determined that these products were safe but not effective. Overall, 312 women became HIV-infected postenrollment, resulting in an overall annual HIV incidence of 5.7 per 100 person-years. None of the study products demonstrated efficacy in reducing HIV acquisition; efficacy was -49% for oral tenofovir (HR, 1.49; 95% CI, 0.97-2.3), -4% for emtricitabine/tenofovir (HR, 1.04; 95% CI, 0.7-1.5), and 15% for tenofovir gel (HR, 0.85; 95% CI, 0.6-1.2). The products appeared safe, with serious AEs and laboratory events well balanced between the active and placebo arms. Although product return and self-reported data suggested high product adherence rates, tenofovir was detected in only 25% to 30% of tested plasma samples collected at quarterly visits, and 50% to 58% of women did not have detectable drug at any visit. Thus, actual adherence to study products was low in this trial, particularly among younger, unmarried women. HIV incidence was also highest in these groups. These negative results are consistent with findings from the FEM-PrEP (Preexposure Prophylaxis Trial for HIV Prevention among African Women) study reported in 2012, which showed a lack of efficacy of daily oral emtricitabine/tenofovir in at-risk women in Africa due in part to low adherence,[7] and support the development of long-acting PrEP delivery systems not dependent on daily product use.

New data from the iPrEx study were also presented in this session (Abstract 27). In 2010, the iPrEx trial reported a 44% reduction in HIV acquisition among MSM and transgender women provided emtricitabine/tenofovir compared with placebo, with higher levels of protection among participants who had detectable drug in their blood.[3] At CROI 2013, Grant and colleagues presented data on HIV incidence after stopping PrEP during a gap period between the blind randomized phase of iPrEx that ended in November 2010 and enrollment in the iPrEx OLE (iPrEX Open Label Extension) which occurred between June 2011 and June 2012, depending on the study site. iPrEx OLE enrolled 1529 previously HIV seronegative iPrEx participants, approximately two-thirds of the randomized cohort. Although enrollment in iPrEx OLE did not differ based on prior randomization group, older participants and those who reported higher risk practices or had drug detected in the randomized phase were more likely to enroll in iPrEx OLE. HIV incidence remained high after stopping PrEP, with 78 new HIV infections during the gap phase: 43 among those previously enrolled in the placebo arm (HIV incidence, 4.1/100 patient-years), and 35 among those in the active arm (HIV incidence, 3.3/100 patient-years). These rates were comparable to the HIV incidence rate in the placebo arm of the randomized phase (3.9/100 patient-years). In contrast, HIV incidence in the active arm of the randomized phase was 0.3 per 100 patient-years in those with higher drug levels and 3.1 per 100 patient-years in those with lower drug levels. Thus, there was no evidence of delayed seroconversion or increased HIV risk after stopping oral emtricitabine/tenofovir PrEP. Condomless receptive anal sex, younger age, and herpes simplex virus (HSV) infection were the main risk factors for HIV acquisition during the gap. The effectiveness of open label PrEP and how it affects choice of prevention strategies, adherence, and sexual practices will be evaluated in iPrEx OLE.

As PrEP adherence can be influenced by perception of HIV risk, Curran and colleagues evaluated the relationship between sexual risk practices and adherence through a 2-month, daily short-messaging service survey conducted at the Partners PrEP study site in Thika, Kenya (Abstract 1004). The Partners PrEP study previously demonstrated the efficacy of tenofovir and emtricitabine/tenofovir PrEP in serodiscordant couples in Kenya and Uganda.[4] In multivariable analyses presented in this poster presentation, those who were not having sex were statistically significantly more likely to report missing PrEP doses (aOR, 1.82; 95% CI, 1.31-2.52; $P < .001$). However, although unprotected sex was common, there was no correlation between unprotected sex and PrEP use ($P = .2$). Hosek and colleagues reported on the relationship between sexual behavior and adherence among young MSM enrolled in Project PrEPare (Adolescent Trials Network [ATN] 082), which randomized participants to receive daily emtricitabine/tenofovir, daily placebo, or no pill (Abstract 996). Among participants categorized as high-risk, 26% were nonadherent, 58% intermittently adherent, and 16% consistently adherent based on plasma tenofovir levels, compared with 67% of no-risk participants being nonadherent and none consistently adherent.

Some have hypothesized that PrEP is less efficacious in populations with higher HIV incidence. This hypothesis was evaluated in a subgroup analysis of the Partners PrEP study presented by Murname and colleagues (Abstract 1000). High-risk subgroups included participants who had partners with high plasma HIV viral loads, those in partnerships for less than 2 years, young women, and women with older male partners. PrEP was protective against HIV acquisition in all

subgroups, with efficacy between 52% and 87%. These findings suggest that prioritizing PrEP for individuals at higher risk of HIV-1 will maximize its prevention impact.

In addition to reducing HIV acquisition, tenofovir-based PrEP may also prevent other sexually transmitted viral infections. In the CAPRISA (Centre for the AIDS Programme of Research in South Africa) 004 study, 1% vaginal tenofovir gel reduced HSV-2 acquisition by 51% in South African women.[6] Celum and colleagues reported on a secondary analysis of HSV-2 acquisition among 1522 participants in the Partners PrEP study who were HIV-1 and HSV-2 seronegative at enrollment (Abstract 999). HSV-2 incidence was 6.6 per 100 person-years in the placebo arm and was reduced by 21% (95% CI, -18%-47%; P = .3) in the tenofovir arm, 35% (95% CI, 1-58; P = .05) in the emtricitabine/tenofovir arm, and 28% (95% CI, -2%-49%; P = .06) overall, suggesting that oral tenofovir–based PrEP may modestly reduce the risk of HSV-2 acquisition. Brinkman presented data on behalf of Hueft and colleagues from a retrospective study evaluating the impact of hepatitis B virus (HBV)-active antiretroviral therapy (lamivudine, emtricitabine, tenofovir) on HBV incident infections (Abstract 33). Among 2492 HIV-infected patients attending a large HIV clinic in the Netherlands, 871 were HBV-susceptible at entry, and 35 new HBV infections occurred during follow-up. Although HBV vaccination is recommended for all HBV-susceptible HIV-infected individuals, only 19% had serologic evidence of HBV vaccination during follow-up, possibly reflecting low rates of vaccination or failure to respond to vaccination, which has been reported in 40% to 76% of HIV-infected patients. The risk of acquiring HBV was statistically significantly lower in those who used HBV-active antiretroviral therapy, with tenofovir-based regimens being more protective than regimens containing only lamivudine. These findings suggest that HBV-active antiretroviral therapy may protect individuals against primary HBV infection (and can be considered HBV PrEP); the researchers recommended confirmation of their findings in prospective cohort studies.

Long-Acting Antiretroviral Agents and Delivery Systems

Given the profound relationship between PrEP adherence and efficacy, 2 presentations in Session 8 (Abstracts 24LB, 25LB) focused on evaluating investigational long-acting systems for delivering PrEP agents to help overcome obstacles related to daily product dosing. Andrew and colleagues presented data on GSK744LAP (an investigational long-acting parenteral [LAP]) in a macaque repeated low-dose intrarectal challenge model (Abstract 24LB). The LAP formulation of GSK744, a potent integrase strand-transfer inhibitor, has a half-life of 3 weeks to 7 weeks in humans and supports monthly to quarterly dosing. None of the 8 animals treated with 2 intramuscular injections of GSK744LAP 4 weeks apart (started 1 week prior to first virus exposure) became infected, compared with all 8 placebo-recipient macaques becoming infected. Future studies will determine the minimum protective dose against intrarectal challenge and evaluate this PrEP agent in female macaques. Smith and colleagues reported on a tenofovir disoproxil fumarate intravaginal ring (IVR) containing 120 mg of tenofovir in a repeated low-dose vaginal challenge model in pigtailed macaques (Abstract 25LB). The IVR was replaced every 28 days during a 4-month challenge period (16 weekly virus exposures). All 6 tenofovir IVR-treated animals remained uninfected, and 11 of 12 controls became infected. The tenofovir IVR is expected to enter a phase I clinical testing later this year.

In a themed discussion on new approaches to antiretroviral drug delivery systems, Boffito discussed the potential opportunities and challenges for long-acting agents to optimize antiretroviral delivery for both chronic HIV-infection treatment and PrEP (Abstract 511). A key challenge is that the target drug concentration in plasma or tissue required for protection for PrEP or viral suppression for HIV treatment is currently unknown. She highlighted several important drug characteristics to consider in selecting HIV PrEP agents and implications for long-acting agents. For example, to ensure safety, a lead-in period with an oral formulation that can be quickly discontinued if adverse effects develop may be warranted prior to administration of the long-acting formulation, an initial loading dose may be required to determine optimal dosing, and oral drug intake may also be needed to cover the period of low drug exposure after therapy is stopped (eg, the "pharmacokinetic tail") to minimize the potential for emergence of viral resistance. Other considerations include whether data on drug–drug interactions from studies of the oral formulation apply to long-acting formulations of the drug, given that first pass elimination is bypassed with injectable formulations and given the need for studies to evaluate the acceptability of long-acting formulations globally. She presented data from a recently completed study in the United Kingdom of TMC278LA, an investigational long-acting formulation of the nonnucleoside analogue reverse transcriptase inhibitior rilpivirine. In a pharmacokinetic study of 60 HIV seronegative women, there was evidence of dose proportionality of TMC278LA, with peak concentrations in plasma and cervicovaginal fluid above a proposed target concentration with 600 mg and 1200 mg dosing. In addition, substantial HIV inhibition was observed in an ex vivo model using cervical lavage samples, particularly at the 1200 mg dose. These studies suggest that future strategies to improve adherence to antiretrovirals, both for treatment and prevention, could have a profound impact on reducing new HIV infections and getting us closer to an "AIDS-free generation."

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A list of all cited abstracts appears on pages 90-95 and is available online at www.iasusa.com.

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CROI 2013: Complications of HIV Disease, Viral Hepatitis, and Antiretroviral Therapy

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Studies with direct-acting antivirals (DAAs) for hepatitis C virus (HCV) monoinfection and HIV coinfection were highlighted at the 2013 Conference on Retroviruses and Opportunistic Infections (CROI). In HCV monoinfected patients, several interferon alfa–sparing, all-oral regimens demonstrated cure rates of greater than 90% with 12 weeks of treatment, including for hard-to-treat patients. Cure rates of 75% were attained in HIV/HCV coinfected patients with the addition of the investigational HCV protease inhibitor (PI) simeprevir to peginterferon alfa and ribavirin. Drug-drug interaction data to inform safe coadminstration of antiretroviral therapy with DAA-based HCV treatment were presented. There was continued emphasis on pathogenesis, management, and prevention of the long-term complications of HIV disease and its therapies, including cardiovascular disease, renal disease, alterations in bone metabolism, and vitamin D deficiency, along with a growing focus on biomarkers to predict development of end-organ disease. Understanding the elevated risk for non–AIDS-defining malignancies in the HIV-infected population and optimal management was a focal point of this year's data. Finally, the conference provided important information on tuberculosis coinfection and cryptococcal meningitis.

Keywords: *HIV, coinfections, comorbidities, hepatitis C virus, HCV, cardiovascular, tuberculosis, bone, vitamin D, malignancies, cryptococcosis*

Hepatitis C Virus

Hepatitis C virus (HCV) drug development continues at a breakneck pace, with remarkable data emerging on highly effective interferon alfa–containing and –sparing regimens. Much of the data presented were from phase II studies with small sample sizes; these results must be interpreted with caution. Nonetheless, this year's conference bolstered growing evidence that that 12-week, interferon alfa–free regimens that are highly effective in curing HCV should soon be a reality.

HCV Monoinfection Trials

Impressive HCV cure rates were attained with several investigational interferon alfa–free combinations of the ritonavir-boosted (/r) HCV protease inhibitor (PI) ABT-450 with ribavirin, a nonnucleoside polymerase inhibitor, or an NS5A inhibitor. In 10 of ll (91%) of treatment-naive individuals with HCV genotype 1, 12 weeks of treatment with the HCV PI ABT-450, the nonnucleoside polymerase inhibitor ABT-072, and ribavirin led to a sustained virologic response (SVR) at 24 weeks (HCV undetectable 24 weeks after discontinuation of treatment; SVR24). However, 2 relapses were reported, at weeks 8 and 36, respectively, after discontinuation of treatment. When ABT-072 was substituted with the nonnucleoside polymerase inhibitor ABT-333, SVR24 was attained in 18 of 19 (95%) of subjects who were given a higher dose of ABT-450, with no reports to date of late relapses, out to 48 weeks post treatment discontinuation. In those who previously did not respond to treatment (60% with partial nonresponse and 40% with null response), SVR24 was lower, at 47%, but still above what has historically been seen with peginterferon alfa and ribavirin retreatment in this population (Abstract 38). The late relapse at week 36 after treatment discontinuation (confirmed to be a relapse, not a reinfection) stresses the importance of long-term follow up of participants receiving novel interferon alfa–free regimens to ensure durability.

In updated data from the AVIATOR trial, a triple direct-acting antiviral (DAA) regimen of HCV PI ABT-450/r, the NS5A inhibitor ABT-267, the nonnucleoside polymerase inhibitor ABT-333, and ribavirin administered to treatment-naive patients for 8 weeks led to an SVR 12 weeks after discontinuation of treatment (SVR12) in 88% of patients. The same regimen administered for 12 weeks increased SVR12 to 99%. Notably, patients with prior null response responded equally well, with a 93% SVR12 after 12 weeks of triple DAA treatment. Higher relapse rates were associated with higher baseline HCV RNA and with HCV genotype 1a, but not with IL28b phenotype (Abstract 39).

In the latest results from the ELECTRON trial, the HCV polymerase inhibitor sofosbuvir was combined with the NS5a inhibitor ledipasvir (GS-5885) and ribavirin for 12 weeks of therapy. SVR rates 4 weeks after discontinuation of treatment (SVR4) were attained in 25 of 25 (100%) of treatment-naive patients with HCV genotype 1, and in 9 of 9 (100%) of patients with prior null response (Of note, SVR4 is an early marker of off-treatment response

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but has not been established to indicate HCV cure, as have SVR24 and, increasingly, SVR12.[1,2]) By contrast, in previously presented ELECTRON data, patients with prior null responses who were treated with sofosbuvir and ribavirin alone for 12 weeks experienced near universal relapse (90%) after treatment discontinuation.[3] Although these new results are early and from a small sample size, they suggest that the addition of an NS5A inhibitor to sofosbuvir may offer a highly effective 12-week interferon alfa–free regimen for even the hardest-to-treat patients with prior null response and HCV genotype 1.

DAA Regimens in Hard-to-Treat Populations

The COSMOS (Combination of Simeprevir and Sofosbuvir in HCV Genotype 1 Infected Patients) study evaluated treatment with sofosbuvir in combination with the pangenotypic PI simeprevir (TMC-435), with or without ribavirin, in patients with HCV genotype 1, prior null response, and limited fibrosis (Metavir score of F0-F2) (Abstract 155LB). In an interim analysis, rapid virologic response (RVR; HCV undetectable at 4 weeks on therapy) was 85% in those treated with 12 weeks of simeprevir, sofosbuvir, and ribavirin versus 57% in those treated with 12 weeks of simeprevir and sofosbuvir alone; however, 100% of patients in each of these arms had HCV undetectable by the end of treatment. Two relapses have occurred to date after treatment discontinuation, 1 in each arm of the study. The SVR rate 8 weeks after discontinuation of treatment (SVR8) was 96.3% (26 of 27) in the 12-week ribavirin-containing arm versus 92.9% (13 of 14) in the arm that did not contain ribavirin. There was no difference in response between those with HCV genotype 1a and 1b. Common adverse effects included headache, fatigue, and anemia (anemia limited to the ribavirin-containing arm). Grade 3 and 4 adverse events were uncommon, occurring in only 10% of patients. Although the sample size is small and these results are preliminary, this study demonstrates remarkable potential for 12-week, interferon alfa–sparing, oral therapy with an anticipated high cure rate, in one of the hardest-to-treat patient populations, those with HCV genotype 1 and prior nonresponse. Unlike many interferon-sparing regimens to date, ribavirin may not be needed to attain high cure rates with this HCV PI and NS5A combination; however, further data are needed.

The SPARE study evaluated the use of sofosbuvir and ribavirin in a Washington, DC, population in which factors made HCV-infected patients harder to treat (ie, non-CC IL28b genotype, high baseline HCV RNA level, high body mass index [BMI], black race, advanced liver fibrosis)(Abstract 157LB). Fifty treatment-naive patients with HCV genotype 1 received 24 weeks of sofosbuvir and were randomized to receive either weight-based ribavirin (1000 mg–1200 mg daily) or low-dose ribavirin (600 mg daily). Eighty-two percent of participants were black, 50% were obese (BMI > 30), 84% possessed the unfavorable non-CC IL28B genotype, and 6% had advanced fibrosis (histologic activity index [HAI] score of 3/4). SVR12 was 68% in patients who received weight-based ribavirin and was 48% in those who received low-dose ribavirin (by intention-to-treat analysis). All virologic failures were relapses after treatment discontinuation, and high baseline HCV RNA levels and male sex were associated with virologic failure. The 12-week interferon alfa–sparing regimen, with weight-based ribavirin, performed well in this traditionally hard-to-treat population. It would be interesting to investigate whether higher cure rates might be attained by extending the treatment period to longer than 12 weeks or by the addition of a third agent.

HCV Treatment in HIV Coinfection

Data in HIV/HCV coinfection were generally more preliminary than those presented in HCV monoinfection. However, important early data for several DAA-containing treatment strategies were presented at this year's conference.

In the TMC435-C212 phase III study, simeprevir (TMC-435), an HCV PI with pangenotypic activity, was given in conjunction with peginterferon alfa and 800 mg daily of ribavirin to HIV/HCV-coinfected patients with HCV genotype 1, who were treatment-naive or treatment-experienced (Abstract 154LB). All participants received 12 weeks of simeprevir, peginterferon alfa, and ribavirin followed by peginterferon alfa and ribavirin alone. Treatment-naive patients who did not have cirrhosis and those with prior relapse were eligible for response-guided therapy (24 weeks of total therapy if there is sufficient HCV response at weeks 4 and 12), and patients with cirrhosis and those with null or partial response received 48 weeks of treatment. Permitted antiretroviral therapy included raltegravir, rilpivirine, maraviroc, and nucleoside analogue reverse transcriptase inhibitors (nRTIs); HIV PIs and nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs) were not permitted due to concerns of drug-drug interactions with simprevir.[4,5] In an interim analysis of the data, the overall SVR12 rate was 77%, with 75% in treatment-naive patients and 80% in patients with prior nonresponse (no cirrhosis). Eighty-eight percent of participants eligible for response-guided therapy qualified to receive shortened therapy of 24 weeks total; the SVR12 rate with shortened therapy was 75%. Data from 48 weeks of treatment in patients with prior null response or cirrhosis were not yet available. Adverse events were largely attributed to peginterferon alfa, and increased bilirubin attributed to simeprevir was reported in 5% of patients.

In the STARTVerso 4 study, the HCV PI faldaprevir was given in conjunction with peginterferon alfa and weight-based ribavirin to HIV-infected patients with HCV genotype 1, with a response-guided strategy of 24 weeks to 48 weeks, depending on HCV RNA levels at weeks 4 and 12. Efavirenz, ritonavir-boosted HIV PI- (atazanavir/r and darunavir/r), maraviroc-, and raltegravir-based antiretroviral therapy regimens were permitted in the study. Among HCV treatment-naive patients,

60% had undetectable HCV RNA at week 4 and 82% had undetectable HCV RNA at week 12, using the more stringent below the limit of detection (BLD) cutoff for HCV RNA levels. Patients with prior relapse had similar responses, with 74% with HCV undetectable at week 4 and 91% with HCV undetectable at week 12. Seventy-seven percent of treatment-naive patients and 88% of those with prior relapse qualified for randomization to shortened, 24-week, response-guided therapy versus 48 weeks (Abstract 40LB). By comparison, in HIV-uninfected patients with HCV genotype 1, faldaprevir with peginterferon alfa and ribavirin led to similar week 4 and week 12 response rates and, ultimately, SVR24 in 72% to 84% of treatment-naive patients[6] and 29% to 42% of those with prior nonresponse to peginterferon alfa.[7]

When a combination of the HCV PI telaprevir, peginterferon alfa, and ribavirin was evaluated in 33 HIV/HCV-coinfected patients in an observational cohort, 61% attained SVR12 compared with 43% of 113 HIV-monoinfected patients (Abstract 679). This is consistent with phase II data demonstrating that HIV coinfection cure rates with telaprevir-containing regimens are similar to those seen in patients with HCV monoinfection.[8] Notably, the SVR12 rates for HCV-monoinfected patients are lower in this instance than what is reported in most clinical trials of telaprevir.

Data on DAA-based treatment in acute HCV infection are limited. In a cohort of 20 HIV-infected men who have sex with men (MSM) with acute genotype 1 HCV–infection, a shortened course of 12 weeks of telaprevir, peginterferon alfa, and ribavirin was initiated within 6 months of first alanine aminotransferase (ALT) elevation (Abstract 156LB). SVR4 was attained in 17 of 20 patients (85%) and SVR12 was attained in 14 of 17 (82%). Three failures occurred during therapy and there have been no relapses to date after treatment discontinuation. Notably, the majority of patients had the more favorable IL28B-CC (13 of 20) or -CT (4 of 20) genotypes. These SVR rates compare favorably to published SVR24 rates of 59% to 80% in HIV/HCV-coinfected patients who received 24 weeks of peginterferon alfa and ribavirin alone for treatment of acute HCV infection.[9-11] These results should be interpreted with caution because there are no control or comparison arms in this small cohort. However, these preliminary data suggest that 12 weeks of telaprevir, peginterferon alfa, and ribavirin may be an attractive shortened treatment option for acute HCV infection.

Retreatment of Patients With Prior Nonresponse

Patients with prior nonresponse to peg-interferon alfa and ribavirin are some of the hardest to successfully cure with retreatment for HCV infection. In the ANRS (Agence Nationale de Recherche sur le Sida et les Hépatites Virales) HC26 TelapreVIH study, HIV/HCV-coinfected patients with prior nonresponse to peginterferon alfa and ribavirin (patients with null response and cirrhosis were excluded from the study) were given telaprevir, peginterferon alfa, and ribavirin, with a response-guided strategy, for 32 weeks to 56 weeks; length of treatment was determined by HCV RNA level at week 4 of triple-drug therapy (Abstract 36). Patients received a 4-week lead-in treatment with peginterferon alfa and ribavirin alone, which is not standard practice with this triple-drug regimen. Efavirenz-, atazanavir/r–, and raltegravir-based antiretroviral therapy regimens were permitted. Of patients in the study, 88.4% qualified for shortened triple therapy at week 4 of triple therapy (week 8 of overall HCV treatment) if HCV RNA levels were below 15 IU/mL. Early virologic response (EVR, HCV RNA < 15 IU/mL at week 12) was also reached in 88.4% and did not substantially differ by baseline fibrosis (F1/F2, 88.1% vs F3/F4, 88.9%), type of prior treatment failure, or type of antiretroviral therapy used. Despite a considerable burden of treatment-associated toxicity, with grade 3 or 4 adverse events occurring in 28%, and 61% requiring epoetin alfa for anemia, this study demonstrated a robust early response in a traditionally hard-to-treat population. Data on SVR rates are forthcoming.

In a similar study design, the ANRS HC27 BocepreVIH study examined HIV/HCV-coinfected patients with prior nonresponse (again, those with prior null response and cirrhosis were excluded) with a response-guided regimen of boceprevir, peginterferon alfa, and ribavirin for 48 weeks to 72 weeks. The length of treatment was determined by HCV RNA levels at week 4 of triple therapy (week 8 of overall HCV treatment) (Abstract 37). Raltegravir and atazanavir/r were permitted. RVR occurred in 60% of patients at week 4 of triple therapy and EVR occurred in 63% at week 16 of triple therapy. In contrast with the ANRS HC26 TelapreVIH study, patients' previous responses to peginterferon alfa–based treatment were predictors of EVR; EVR was attained in 90% of those with prior relapse, 60% of those with breakthroughs, 61% of those with previous partial response, and 38% of those with prior null response. Of note, fibrosis score was not associated with EVR. There was a trend toward decreased efficacy with atazanavir-based antiretroviral therapy compared with raltegravir-based therapy (EVR, 56%, or 18 of 32, vs EVR, 70%, or 19 of 27, respectively). Grade 3 or 4 adverse events were common, occurring in 61% of patients. Final SVR rates will be important to clarify boceprevir-based regimens given with atazanavir- versus raltegravir-based antiretroviral therapy and to provide comparative data with telaprevir performance (Abstract 36). A Spanish observational cohort (in which 12%-18% were HIV coinfected) reported increased RVR rates with telaprevir plus peginterferon alfa and ribavirin compared with boceprevir-based treatment (84% vs 60%; $P < .001$) (Abstract 676). However, fibrosis was more advanced in those receiving boceprevir than in those receiving telaprevir (95% and 66%, respectively) and this was not a randomized study. SVR data were not presented.

Antiretroviral Drug Interactions With DAAs

Several studies provided important new information on drug-drug interactions between DAAs and antiretroviral drugs. Faldaprevir, an HCV PI that has shown promising responses when used in combination with interferon alfa and ribavirin, is metabolized by and moderately inhibits CYP3A4. Faldaprevir did not meaningfully impact tenofovir or darunavir/r levels. However, the area under the curve (AUC) of levels of faldaprevir was markedly increased (130%) with darunavir coadministration. To account for this drug interaction, faldaprevir has been given at a lower dose (120 mg daily) with darunavir and atazanavir in an ongoing phase III study (Abstract 40LB). In contrast, faldaprevir concentration was decreased by tenofovir (AUC decreased by 22%) and by efavirenz (AUC decreased by 35%), although it is unclear if these decreased concentrations are clinically significant (Abstract 35).

Boceprevir coadministration with the NNRTI rilpivirine increased rilpivirine exposures slightly but not to a clinically significant degree, and boceprevir exposure was unaffected by rilpivirine (Abstract 537). This adds another antiretroviral drug to those that can be used with boceprevir. The current boceprevir package insert permits raltegravir coadministration but advises against the use of other NNRTIs or HIV PIs.[12] Further evaluation of boceprevir with antiretroviral drugs, including ritonavir-boosted HIV PIs, is currently under way.

Epidemiology of HCV Infection in HIV

Sexual transmission of HCV between MSM has increasingly been seen in the HIV-infected population. Several abstracts highlighted the predominant role of MSM sexual transmission in current HCV epidemics in the United States and Europe (Abstracts 638, 704, 707, and 708). The frequency of HCV reinfection after successful treatment was high in a cohort of MSM, with 31% experiencing reinfection during a follow-up period of 5 years. The majority of patients in the cohort were reinfected with a different genotype of HCV, suggesting partial protective immunity against the initial HCV genotype (Abstract 708). Testing for HCV is recommended at the time of engagement in HIV care, given the high rate of HCV coinfection in HIV-infected individuals in the United States. However, guidance on repeat HCV testing is limited. Analysis from the SUN (Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy) study found that incident HCV infection was associated with elevated liver transaminases 50% of the time and with MSM exposure in 50% of cases, suggesting that repeat testing should not be limited to patients with transaminitis, and reiterating the role of MSM sexual exposure as an important route of HCV transmission (Abstract 704).

Complications of HCV: Fibrosis Progression and Extrahepatic Disease

HIV coinfection in those with HCV infection has generally been associated with faster progression of fibrosis. In a cross-sectional study from Thailand, 66.7% of HIV/HCV-coinfected patients had substantial fibrosis (liver stiffness > 7.5 kPa) compared with 41% of HCV monoinfected patients (Abstract 646). The NEAT (European AIDS Treatment Network) followed up patients with acute HCV, 93% of these infections attributable to MSM sexual contact, for a median of 130 weeks, and found that 14 of 122 (11.5%) developed advanced fibrosis (liver stiffness > 9.0 kPa) (Abstract 637). Progression to fibrosis was associated with persistent viremia and did not appear to be correlated with other risk factors (ie, alcohol use, drug use, diabetes, d-drug [didanosine, d4t] use, etc), although the small number of patients with advanced liver disease limits this evaluation. Using serum markers to detect fibrosis (FIB-4 index), or clinical evidence of cirrhosis, an Italian cohort reported a lower overall fibrosis rate, with 11% progression to cirrhosis from the time of HCV diagnosis, during a period of up to 9 years (Abstract 638). Notably, HCV acquisition decreased in all risk groups except MSM, in whom incidence remained unchanged. The presence of advanced fibrosis is an important risk factor for hepatic decompensation. In one study, 41% of those with stage F4 fibrosis (by liver biopsy) experienced decompensation during a 5-year period. Advanced fibrosis is also a risk factor for decompensation in those with precirrhosis (F3 by biopsy or liver stiffness from 9.5-14.6 kPa), highlighting the importance of prompt HCV therapy (Abstract 727).

The extrahepatic impact of HCV infection has increasingly been recognized. Patients with HIV/HCV coinfection demonstrated elevated pre-treatment nonhepatic markers of cardiovascular disease (CVD; eg, soluble intercellular adhesion molecule 1 [sICAM-1], lipoprotein-associated phospholipase [Lp-PLA2], soluble platelet [sP]-selectin, and interleukin [IL]-6), and curative HCV therapy was associated with a statistically significant decrease in sICAM-1, suggesting that successful HCV treatment may lower systemic inflammation and thus CVD risk (Abstract 715). However, despite a recognized increased risk for CVD with HCV[13] and HIV/HCV coinfection,[14] use of the Framingham Risk Score (FRS) did not identify HCV- and HIV-infected individuals as being at increased risk (Abstract 716), suggesting this risk score may underestimate cardiovascular risk in HCV and HIV infection. Compared with HIV-monoinfected individuals, HIV/HCV-coinfected patients had an increased risk of renal impairment, particularly in those with HCV viremia (Abstract 718). In a Veterans Affairs (VA) analysis, overall mortality was nearly twice as high in patients with HIV/HCV coinfection than in HIV-monoinfected patients (all-cause mortality, 74.1/1000 person-years vs 39.8/1000 person-years, respectively), and SVR was strongly associated with mortality reduction (hazard ratio [HR], 0.35).

HCV Assays

Stopping rules for and duration of therapy with DAAs rely on interpretation of HCV RNA levels during the early months of therapy. Evaluation of 5 commercially available HCV RNA assays indicated that there were substantial discrepancies between test performances in samples with low levels of HCV RNA (Abstract 661). Thus, the same assay should be used throughout HCV treatment to inform clinical decisions and to avoid interassay variability.

Hepatitis B Virus

A Dutch cohort evaluated the effect of the hepatitis B virus [HBV]–active antiretroviral drugs tenofovir, emtricitabine, and lamivudine in the prevention of new HBV infections. In 530 HBV-uninfected individuals who were followed up for a median of 7.8 years, 35 HBV infections occurred, the majority (32) in MSM. As anticipated, tenofovir use (in conjunction with lamivudine and emtricitabine in most cases) reduced the risk of HBV acquisition, with no new HBV cases occurring during tenofovir administration ($P < .001$). Use of emtricitabine and lamivudine without tenofovir also reduced the risk of HBV acquistion; however, 3 HBV infections still occurred during treatment.

Several studies evaluated the efficacy of lamivudine and emtricitabine, with or without tenofovir, in the suppression of HBV. There was a trend toward increased HBV suppression and hepatitis B e antigen (HBeAg) loss with the combination of tenofovir plus lamivudine or emtricitabine compared with lamivudine or emtricitabine alone, in a longitudinal AIDS Clinical Trials Group (ACTG) cohort (Abstract 665). Notably, HBV viral rebound was only reported in patients who received lamivudine or emtricitabine alone. Tenofovir-based therapy is generally very effective in HBV viral suppression, with 92% HBV DNA undetectable after 5 years of treatment (Abstract 666). However, despite effective HBV DNA suppression, HBeAg loss occurred in only 35% (25 of 85) of patients and hepatitis B e antibody (HBeAb) conversion in 10.5% (9 of 85). To investigate strategies to improve HBeAg loss and seroconversion, 2 French studies looked at the addition of peginterferon alfa to tenofovir-containing treatments. In the first study, a median of 7 months of peginterferon alfa was added to the regimens taken by HBeAg-positive patients (4 with detectable HBV DNA) on tenofovir-containing antiretroviral therapy. Peginterferon alfa was associated with more rapid HBeAg loss, but not with an overall increased HBeAg loss, than that which occurred for those on tenofovir-containing antiretroviral therapy alone (46.7% vs 45%, respectively; P = not significant) (Abstract 668). In a single-arm study, ANRS HB01 EMVI-PEG, 1 year of peginterferon alfa was added to the regimens of patients who had at least 6 months of tenofovir plus lamivudine and emtricitabine; the addition of peginterferon alfa was associated with 24% HBeAg loss during treatment but did not result in long-term HBeAg loss, HBeAb conversion, or hepatitis B surface antigen (HBsAg) loss and was associated with substantial peginterferon alfa–related adverse effects (Abstract 669). Thus, the addition of peginterferon alfa does not appear to improve immunologic control of HBV infection in HIV/HCV-coinfected individuals.

Hepatitis E Virus

Hepatitis E virus (HEV) infection is an increasingly recognized cause of acute hepatitis worldwide, particularly in patients who are pregnant or immunocompromised. Although HEV infection is typically enterically transmitted and self-limiting, similar to hepatitis A virus (HAV), a Spanish group reported 2 HIV-infected patients with chronic HEV viremia associated with transaminitis and increasing liver stiffness. The use of ribavirin appeared to temporarily control replication in both patients, but 1 developed subsequent HEV viremia. Chronic HEV may be a consideration in the evaluation of HIV seropositive patients with transaminitis that is not attributable to other etiologies (Abstract 664).

End-Organ Complications of HIV Infection

The constellation of chronic diseases such as cardiovascular, renal, bone, and liver diseases, as well as non–AIDS-defining malignancies, persist as major causes of morbidity and mortality in treated HIV infection. Research in this area is focused on the epidemiology and risk factors for these problems, identification of the contributions of HIV-related immunopathology to specific and collective end-organ diseases, and evaluation of interventions to prevent or reduce the morbidity associated with these conditions. This year's Conference on Retroviruses and Opportunistic Infections (CROI) provided new insights into all of these areas.

Biomarkers to Predict the Risk of End-Organ Disease and Mortality

IL-6, d-dimer. Previous work by investigators in the SMART (Strategies for Management of Antiretroviral Therapy), ESPIRT (Evaluation of Subcutaneous Proleukin in a Randomized International Trial), and SILCAAT (Subcutaneous Recombinant, Human Interleukin-2 in HIV-Infected Patients with Low CD4+ Counts Under Active Antiretroviral Therapy) study groups identified a strong association between biomarkers of inflammation and coagulation and the risk for mortality during treated HIV infection. Now these groups have expanded the analyses to explore the relationship between the combined measurement of IL-6 and d-dimer and the risk for serious non-AIDS (SNA) events and all-cause mortality among treated patients. They modeled the data to evaluate the expected reduction in events associated with lowering levels of either or both of these biomarkers (Abstract 60). The rates of SNA morbidity or all-cause death (SNA/death) were 14% lower among patients with 25% reductions in IL-6, and 9% lower for a 25% reduction in d-dimer. These were not actual reductions in the levels of the markers but, rather, were event rates among those with lower baseline values. Although causality between

these markers and end points remains to be determined, these analyses highlight the potential utility of a combined marker score and help set the stage for planning interventional trials aimed at reducing levels of these specific measures of inflammation and coagulation.

Endothelial activation biomarkers. Endothelial cell activation markers may play an important role in the long-term complications of HIV disease. Vascular cell adhesion molecule 1 (VCAM-1) is an immunoglobulin-like adhesion molecule expressed on activated endothelial cells. Intracellular adhesion molecule 1 (ICAM-1) is present on endothelial cells and leukocytes. Graham and colleagues reported that levels of sICAM-1 and VCAM-1 rose soon after HIV infection (Abstract 264). They also reported that VCAM-1 measured at the time of the HIV viral load set point was independently associated with time to HIV progression or death (after control for HIV-1 RNA and ICAM-1 levels) in a prospective study of Kenyan women who seroconverted. Whether VCAM-1 remains an important predictor of outcome during treated HIV infection remains to be determined.

Myocardial Infarction, End-Stage Renal Disease, and Non-AIDS Cancer

There continues to be some debate as to whether people with HIV infection experience the onset of chronic noncommunicable diseases at an earlier age than the general population. A study by Shiels and colleagues[15] highlighted the importance of controlling for the age distribution of the general population when comparing rates of malignancies in the HIV population and the general population. Althoff and colleagues explored this issue further using the Veterans Affairs Health System database (Abstract 59). They examined rates of myocardial infarction (MI), cancer, and end-stage renal disease (ESRD) in veterans with HIV compared with an age-, sex-, race-, and ethnicity-matched group of HIV-uninfected veterans. The scope of this analysis is therefore limited to the age distribution of US veterans with HIV disease and may not completely reflect that of the US HIV-infected population. Nonetheless, Althoff and colleagues clearly demonstrated that within the large group examined, who had a median age of 55 years, the risk of each of these diseases is more common among those with HIV infection: an 87% increase in the risk of MI, a 37% increase in cancer, and a 55% increase in ESRD. However, they saw no difference in the age at which these conditions occurred (for most conditions, the median age of onset was close to 55 years). Notably, less than 10% of the matched population was under the age of 40 years and few were women. Therefore, the generalizability of these results to the younger HIV-infected population and to HIV-infected women is limited.

CVD

Several studies examined trends in causes of death, prevalence of chronic disease risk factors, and outcomes of cardiovascular events among patients receiving HIV care. In France, the proportion of deaths due to cardiovascular-related disease increased from 8% in 2000 to 10% in 2005, and increased again to 14% in 2010 (Abstract 1048). This trend likely reflects the aging of the HIV-infected population, but it was notable that the proportion of smokers also increased, from 58% to 75%, among those who died. A German cohort study compared cardiovascular risk profiles in men and women with HIV infection compared with a matched HIV-uninfected group. They found that FRSs were comparable between HIV-infected and -uninfected men, and the women with HIV disease had a higher predicted risk, due in part to higher rates of smoking and hypertension in the HIV-infected group (Abstract 774). Among a large cohort of patients in Uganda receiving antiretroviral therapy with a median age of 34 years, the prevalence of hypertension was 28% and stage 2 hypertension (systolic blood pressure [BP] ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg) was 14% overall (Abstract 776).

Not all the news was discouraging, however. Investigators from the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study (Abstract 748) reported improvements in survival during the first month following MI in the period from 2009 to 2011 compared with the period from 1999 to 2002, when more than a quarter of patients died within the first month following an MI. The improved outcomes appeared to be attributable to enhanced patient management following an MI in more recent years. Collectively, these studies confirm the need for integration of primary prevention of CVD into HIV disease management across all settings.

Noncalcified plaque and monocyte activation markers. Noncalcified coronary plaque (NCP) represents an early stage of atherosclerosis and it can be detected by computed tomography (CT) angiography, by which plaque can be characterized as noncalcified, mixed, or calcified. Investigators from the MACS (Multicenter AIDS Cohort Study) and Grinspoon's group at Massachusetts General Hospital have described the prevalence of and examined factors associated with NCP in HIV disease. Post and colleagues working in the MACS reported that older age was associated with increased rates of NCP in those infected with HIV but not in HIV seronegative men (Abstract 62). Zanni and colleagues examined plaque morphology in a matched study of HIV seropositive and HIV seronegative men, all matched for cardiovascular risk factors (Abstract 63). Using standard definitions and blinded readings by cardiologists or radiologists, arterial segments with plaque were graded on the presence of factors associated with vulnerability, including positive remodeling, low attenuation, and spotty calcification. The major finding of this study was that among a well-treated HIV-infected group, with low FRS, they observed a higher prevalence of vulnerability factors in plaque (8% in the HIV-infected group vs 0% in the control group), suggesting a higher risk for future cardiac events.

Activated monocytes and soluble markers of monocyte activation. Baker and colleagues examined factors associated with the progression of coronary artery calcium among 436 HIV-infected adults with a median age of 42 years (Abstract 66 LB). Higher frequencies of activated monocytes were associated with higher rates of progression but not tissue factor expression, T cell activation, or senescence phenotype. Tenorio and colleagues reported the results of a case-control study evaluating the relationship between cellular and soluble markers of inflammation and the risk for SNA events (ie, MI, stroke, non–AIDS-defining malignancy, serious bacterial infections) and nonaccidental death in participants with suppressed HIV-1 RNA enrolled in ACTG treatment studies (Abstract 790). As has been reported from other studies, higher levels of IL-6, soluble tumor necrosis factor receptor (sTNFR), soluble CD14 (sCD14), and d-dimer are associated with the risk of SNA events. Notably, these associations existed pre–antiretroviral therapy and persisted despite antiretroviral therapy, whereas cellular markers of T cell activation did not appear to predict the risk of SNA events.

Walker and colleagues used the simian immunodeficiency virus (SIV)-infected, CD8 T lymphocyte–depleted rhesus macaque model (SIV+/CD8-) to examine the features of CVD and to test the effects of PA300, an antitumor drug that inhibits macrophage activation and trafficking, on the development of CVD (Abstract 64). A substantial increase in CD163+ macrophages (a measure of macrophage activation) was seen in SIV-infected macaques compared with SIV-uninfected macaques. After 28 days of daily doses of PA300, the number of CD163+ macrophages and the degree of cardiac damage, measured histologically, declined. These data add to the growing body of evidence supporting a role for innate immune response and specifically activated monocytes in the pathogenesis of HIV-related CVD and pave the way for interventional studies aimed at reducing macrophage activation.

Heart failure. The prognostic value of the suppression of the tumorigenicity 2 (ST2) gene, 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 assessed in a cohort of HIV-infected patients who underwent echocardiograms and clinical follow-up (Abstract 749). Both markers were found to be higher in the HIV-infected group than in the control group and each was associated with mortality, suggesting that these markers may have the same predictive value in HIV-infected individuals as they do in the general population.

Rates and characteristics of heart failure were examined in HIV-infected and -uninfected veterans in the VACS-VC (Veterans Aging Cohort Study–Virtual Cohort) (Abstract 750). Rates of heart failure (with preserved or reduced ejection fraction) and mortality due to heart failure were higher in the HIV-infected group. These findings highlight the importance of heart failure as a clinical consideration for patients with HIV disease.

Statins. Several studies explored different aspects of statin use in HIV-infected individuals. The prevalence of statin use among patients with HIV infection compared with controls was examined in the MACS. Only 10% of the HIV-infected group who had an indication for a statin were not receiving it, compared with 16% of the HIV-uninfected control group (Abstract 771). With regard to aspirin use in patients with HIV disease, just the opposite was seen. Among patients with 2 or more risk factors for coronary heart disease in a large Boston, Massachusetts, database, only 22% of the HIV-infected group were receiving aspirin compared with twice that in the HIV-uninfected control group (Abstract 65).

A large Danish study examined the outcomes of virologically suppressed patients who were prescribed a statin compared with those who did not take statins and found a nonstatistically significant reduction in deaths among those patients who had been prescribed a statin (Abstract 764). An even larger VA analysis (25,884 patients) suggested a trend toward mortality benefit and a reduction in malignancy rates with the use of high-potency statins (rosuvastatin or atorvastatin). These studies highlighted the issue of confounding by indication that limits these types of analyses.

Drug-drug interactions complicate the use of some statins in patients taking PIs; hence, there is interest in the use of newer drugs that may have fewer interactions. Sponseller and colleagues demonstrated that 4 mg of pitavastatin, a newer statin with a low potential for cytochrome P450 drug interactions, was superior to 40 mg of pravastatin in lowering low-density lipoprotein (LDL) cholesterol, in a 12-week randomized trial of HIV-infected patients. Declines in high-sensitivity C-reactive protein (hs CRP) were modest in this trial, though it was notable that oxidized LDL declined substantially in the pitavastatin group (Abstract 187LB).

The potential for statins to reduce immune activation and inflammation in the setting of treated HIV infection has been a topic of great interest. McComsey and colleagues presented preplanned, interim, 24-week results from a 96-week, double-blind, placebo-controlled trial of rosuvastatin in patients with well-controlled HIV infection. In the group treated with rosuvastatin, the results showed a reduction in monocyte activation markers (sCD14 and circulating $CD14^{dim}CD16^{+}TF^{+}$ monocytes) and in the vascular inflammation marker Lp-PLA2 (Abstract 186LB).

Statins may increase the risk of diabetes in the general population; 2 groups who addressed this potential risk in HIV-infected patients reached different conclusions. Italian researchers found that HIV-seropositive patients who used statins had a reduced risk of diabetes compared with those who did not use statins (Abstract 766), whereas US researchers found statin use to be associated with a higher rate of incident diabetes (Abstract 767). Differences in the distribution of risk

factors for diabetes in different populations may have contributed to these disparate findings.

Renal Disease

The increased prevalence of chronic kidney disease (CKD) among people with HIV disease was once again highlighted at this year's conference. The higher prevalence of CKD, as defined by an estimated glomerular filtration rate (eGFR) of greater than 60 mL/min/1.73 m^2, among people with HIV disease who are in care (estimated at 1 in 13 adults in the United States) (Abstract 809) and the higher rates of ESRD among HIV-infected veterans, as noted above (Abstract 59), are 2 examples of this increased prevalence.

Creatinine clearance. Debate continues about which formula should be used to estimate GFR in clinical practice and research settings. The Cockcroft Gault (CG) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations were compared using a very large dataset from the EuroSIDA study. No gold standard for measuring renal function was included in this analysis; however, the equations were compared for their ability to diagnose moderate to advanced kidney disease and to predict the risk for CKD and mortality. Incidence of moderate CKD was higher when the CG was used, though CG and CKD-EPI performed similarly in predicting the risk of ESRD and all-cause mortality (Abstract 808).

Renal function. Observational studies have suggested that ritonavir-boosted PIs may increase tenofovir levels, increasing the risk of renal toxicity. Several studies, including 2 that focused on women, presented at this year's CROI added further evidence to support this notion. However, an analysis from the D:A:D study identified lower CD4+ cell counts and traditional renal risk factors as being most important for predicting ESRD (Abstract 810). Baxi and colleagues conducted an intensive pharmacokinetic study among 105 women enrolled in the WIHS (Women's Interagency HIV Study) who were receiving tenofovir. They identified ritonavir use, older age, lower BMI, and reduced renal function at the start of tenofovir use as risk factors for higher tenofovir plasma levels (Abstract 522). From the ACTG A5208 OCTANE (Optimal Combination Therapy After Nevirapine) study, Mwafongo and colleagues compared renal events and increases in grade 3 or 4 serum creatinine among 741 African women who were randomly assigned to receive tenofovir and emtricitabine combined with either lopinavir/r or with nevirapine (Abstract 152). Although rates of renal events and grade 3 or 4 creatinine increases were generally low (3% and 5%, respectively), the times to first renal event were shorter and overall event rates were higher among the women randomized to receive lopinavir/r than among those who received nevirapine. In a small study, tenofovir plasma levels did not vary between pre- and postmenopausal women (Abstract 900). However, in another study, tenofovir plasma levels were higher in lower-weight patients and were associated with drug-related renal and bone toxicity (Abstract 523). A detailed analysis of renal events using several different measures of GFR, in the ACTG A5224s trial, similarly found higher rates of decline in eGFR when tenofovir was combined with atazanavir/r as opposed to efavirenz (Abstract 811). These findings suggest that combining tenofovir with NNRTI-based regimens, especially among patients weighing less than 50 kg may be associated with lower rates of renal dysfunction. Weight-based dosing of tenofovir (a reasonable but somewhat impractical strategy) in Thai children appeared to be safe but did not fully mitigate changes in bone mineral density (BMD) (Abstract 972).

Tenofovir alafenamide fumarate (GS-7340), a prodrug of tenofovir, is currently in phase II studies. Unlike tenofovir, this prodrug does not appear to interact with the renal transporters organic anion transporter 1 (OAT1) or OAT3 in vitro and therefore is unlikely to accumulate in renal tubules and lead to toxicity (Abstract 540). The 24-week results of a study comparing GS-7340 with tenofovir combined with elvitegravir, cobicistat, and emtricitabine demonstrated comparable efficacy and statistically significant improvements in bone density and renal function in those receiving GS-7340 versus tenofovir (Abstract 99LB).

Impact on Bone Health

Examination of the risk factors for and pathogenesis of bone loss in HIV disease remains an important area of investigation. Several studies at this year's CROI confirmed and extended prior observations highlighting the importance of this complication.

A large cross-sectional Irish study confirmed that bone density is lower in men and women with HIV disease than in well-matched controls (Abstract 817). Despite similar levels of vitamin D in both groups, the HIV-infected group had higher levels of alkaline phosphatase, and despite adjustment for this, the independent effects of HIV persisted. A detailed study of a small group of adolescents with HIV disease (some infected at birth and others during adolescence) documented lower values of peak bone mass in those with HIV disease than in controls. High-resolution peripheral quantitative CT found markedly abnormal trabecular and cortical bone microarchitecture in both groups of HIV-infected adolescents, suggesting that they will have an increased life-long risk of fractures. Using quantitative morphometry assessments of lateral chest x-rays, an Italian group reported a higher rate of asymptomatic vertebral fractures in a group of HIV-infected patients than in control subjects (Abstract 822). In a pooled analysis of data from 3 ACTG trials, lower CD4+ counts, particularly those below 50 cells/μL, were an independent risk factor for bone loss after the initiation of antiretroviral therapy (Abstract 823).

In vitro studies using bone marrow–derived mesenchymal stem cells (MSC) suggested that exposure to the PI lopinavir/r, more so than atazanavir/r, reduced the proliferative activity of the cells and led to premature cell

senescence, as measured by the presence of farneslyated prelamin A (a marker of cell aging) (Abstract 799). This effect appeared to be blocked by statin treatment of the cell cultures. In addition, exposure of the MSC to the HIV proteins Tat (transactivator of transcription) and Nef (negative regulatory factor) also increased cell senescence. These findings suggest a mechanism for HIV-associated bone loss attributable to HIV proteins and lopinavir/r. The clinical significance of these findings, in particular the effects of statins, remains to be determined.

Switching antiretroviral therapy because of bone loss. It is reasonably clear that untreated HIV infection and antiretroviral therapy may contribute to bone loss; the clinical question remains of how best to manage osteoporosis when detected in HIV disease. Negredo and colleagues conducted the OsteoTDF study to investigate whether switching from tenofovir to abacavir would provide any benefit to patients with virologic suppression and documented osteopenia or osteoporosis, who were on a tenofovir-based regimen (Abstract 824). After 48 weeks of follow-up there was a statistically significant improvement in the abacavir-treated group in femur BMD (+1.98%), with more modest improvements in bone density at the trochanter. How this strategy compares with other interventions for osteoporosis is still to be determined but it is one option for clinicians to consider.

Vitamin D. Low levels of vitamin D are common among HIV-infected patients and several studies have identified a link between low levels of vitamin D and poor clinical outcomes. However, the causal relationship between vitamin D and HIV disease progression remains undefined. In vitro studies by Campbell and Spector suggest that TLR8 ligand activation of macrophages upregulates the expression of the human cathelicidin antimicrobial peptide (CAMP) gene through a vitamin D–dependent mechanism that is required for the autophagic inhibition of HIV (Abstract 285). These data may suggest that the maintenance of adequate vitamin D levels could help to modulate the effects of HIV infection. Results from a 12-week randomized trial comparing supplementation with a daily dose of 4000 IU or 7000 IU of vitamin D_3, conducted across a wide age range of HIV-infected patients in Botswana, demonstrated no detrimental effects overall and improvement in vitamin D status, with some suggestion of greater improvements in CD4+ cell counts among the group receiving the higher dose (Abstract 965).

Several studies have documented a decline in 25-hydroxyvitamin D (25[OH]D) in patients on antiretroviral therapy, in particular with exposure to efavirenz. The body composition substudy of SMART noted an improvement in BMD in the group that was randomized to receive intermittent antiretroviral therapy and updated these results to include information on vitamin D levels and BMD. Levels of 25(OH)D increased during periods when antiretroviral drugs were not being taken. These increases correlated with improvement in BMD, suggesting that some component of bone loss during antiretroviral therapy may be mediated through reductions in vitamin D levels. However, Adeyemi and colleagues measured the levels of 1-25-dihydroxyvitamin D ($1,25[OH]_2D$) among women with low levels of 25(OH)D who were taking efavirenz and found that the levels of $1,25(OH)_2D$ were within the normal range for 84% of these women. This suggests that levels of $1,25(OH)_2D$ remain tightly controlled even when levels of 25(OH)D are low (Abstract 807).

Malignancy

Non–AIDS-defining cancers (NADCs), particularly those caused by infectious etiologies (ie, hepatocellular carcinoma caused by a hepatitis virus, Epstein-Barr virus [EBV]-related Hodgkin lymphoma, and human papillomavirus [HPV]-related genital or head and neck malignancies), are more prevalent among the HIV-infected population and effective antiretroviral therapy does not appear to mitigate this risk. Using data from 8 US clinics, the CNICS (Centers for AIDS Research [CFAR] Network of Integrated Clinical Systems) analyzed cancer incidence following the initiation of antiretroviral therapy in more than 11,000 patients during a 16-year period (1996-2011).

Incident cancers were evenly divided between AIDS-defining cancers (ie, Kaposi sarcoma [KS] and non-Hodgkin lymphoma [NHL]) and NADCs. In the first 6 months after initiation of antiretroviral therapy, KS and lymphomas (Hodgkin lymphoma and NHL) were the most frequent incident cancers. As expected, the majority of cases of KS occurred in individuals with CD4+ cell counts below 200/μL and incidence of KS and lymphoma declined after 6 months of antiretroviral therapy. Low CD4+ cell counts were associated with KS, lymphomas, and virus-related NADCs (such as cervical and anal) but not with cancers unrelated to viral infections (such as lung and colon). Conversely, there was a trend toward increased incidence of NADCs in the years following antiretroviral therapy initiation (Abstract 141). A German multicenter cohort found that although 62% of cases of NHL occurred in patients who had not received antiretroviral therapy, 75% of cases of Hodgkin lymphoma occurred in patients who were taking effective antiretroviral therapy, suggesting that antiretroviral therapy did not provide protection from this EBV-related cancer (Abstract 745).

The VACS reported a 37% increase overall in the risk of NADCs among HIV-infected subjects compared with HIV-uninfected controls, but they also found that NADCs did not occur at younger ages in HIV-infected individuals compared with their HIV-uninfected counterparts (Abstract 59). Lung cancer remains a key cause of NADCs in the HIV-infected population. Observations from the US SEER (Surveillance, Epidemiology, and End Results) registry indicate that HIV seropositive patients with non–small cell lung cancer had a higher risk of lung cancer mortality than HIV seronegative patients (odds ratio [OR], 1.7; 95% confidence

interval [CI], 1.2-2.4) despite effective antiretroviral therapy and adjustment for known risk factors of poor prognosis and competing causes of death. These data suggest that HIV infection plays a role in lung cancer–related mortality (Abstract 740).

Unlike traditional AIDS-defining cancers, HPV-related dysplasia and malignancy incidence does not decline after initiation of antiretroviral therapy. This was demonstrated in various settings, including in the Swiss HIV Cohort Study (Abstract 730), in Botswana (Abstract 731), and in Senegal (Abstract 733). Despite effective antiretroviral therapy, high rates of genital HPV infection (50%-90%), particularly oncogenic strains, were reported in several studies (Abstracts 732, 733, 734, and 735), contributing to the development of HPV-related dysplasia and malignancy. PI use was associated with a higher rate of oncogenic HPV infection (Abstract 735) as well as the development of squamous cell carcinoma of the anus (Abstract 736). Given the observational nature of these 2 studies, this may reflect confounding but merits further exploration.

Random cervical biopsies may improve the detection of high-grade squamous intraepithelial lesions (HSILs),[16,17] although there is substantial debate about the advisability of routine random biopsies during colposcopy.[18] To investigate the yield of random biopsy in the evaluation of anal dysplasia, random biopsies of normal-appearing rectal mucosa were performed during high-resolution anoscopy of 372 men, 70% of whom were referred due to abnormal pap smears and 70% of whom were HIV seropositive. Of the 372, 132 (33.8%) patients were diagnosed with HSL, and of those 132, 13 patients had HSIL that was detected solely via random biopsy. HSIL was detected in 25% of biopsies of abnormal mucosa and 3.7% of random biopsies. Although it appears that random biopsies may slightly improve HSIL detection, the vast majority of HSILs were diagnosed with standard biopsies of abnormal mucosa. As has been the case with random biopsy in colposcopy, questions remain about the advisability of routine random biopsy in light of the additional cost, lower yield, and uncertain benefit this strategy would have on the prevention of HPV–related disease (Abstract 140).

Tuberculosis

The tuberculosis (TB) research presented at CROI continued to pick up steam this year, fueled by new drug developments, treatment strategies, and diagnostics. Presentations on TB science were concentrated on Wednesday, starting with a plenary session by Andreas Diacon from Capetown, South Africa. Diacon reviewed opportunities and challenges facing researchers as they approach using new drugs to develop shorter and more compact TB therapies (Abstract 123). Even with advances in antiretroviral therapy rollout, TB remains a major cause of mortality and requires better diagnostics, treatments, and care delivery systems. In a Kenyan study, autopsies of persons dying while on antiretroviral therapy revealed TB infection in 52% of cases (Abstract 831). In another study from South Africa, it was found that in a third of deaths occurring at home, there was microbiologic evidence of undiagnosed infectious TB (Abstract 837).

Simplifying and shortening TB treatment. The RIFAQUIN (High-Dose Rifapentine and a Quinolone in the Treatment of Pulmonary Tuberculosis) study examined 2 moxifloxacin-containing regimens for the treatment of drug-sensitive TB (Abstract 147LB). This was a randomized noninferiority trial of adults with smear-positive pulmonary TB. The control arm was given a standard 6-month TB treatment regimen of isoniazid, rifampin, pyrazinamide, and ethambutol for a 2-month induction phase, followed by isoniazid and rifampin for a 4-month continuation phase. In 1 experimental arm evaluating treatment simplification, moxifloxacin replaced isoniazid during the 2-month induction phase. The continuation phase consisted of a 4-month, once-weekly regimen of rifapentine (1200 mg) and moxifloxacin. The second intervention arm evaluated treatment shortening in a 4-month TB treatment regimen. In this arm, moxifloxacin replaced isoniazid in the 2-month induction phase, and the 2-month continuation phase consisted of twice-weekly rifapentine (900 mg) and moxifloxacin. The primary end point of the study was a favorable outcome (survival, TB cure, and tolerance of TB medications) at 18 months. Of 827 subjects with smear-positive pulmonary TB enrolled, 730 were eligible for study and 28% were HIV-infected.

The 6-month experimental regimen, with a weekly continuation phase, was not inferior to the control arm. Favorable results were reported in 95% of subjects in the control arm compared with 96% of subjects in the experimental arm. In contrast, the 4-month experimental regimen was inferior to the control regimen, with only 83% of subjects achieving a favorable outcome. The use of quinolones in TB treatment remains controversial. The RIFAQUIN study indicates that replacing isoniazid with moxifloxacin does not achieve treatment shortening. For patients with quinolone-susceptible TB, isoniazid can be replaced with moxifloxacin, combined with weekly high-dose rifapentine, to simplify the continuation phase of TB treatment. Until further information about drug-drug interactions between antiretroviral drugs and rifapentine is available, HIV-infected patients are not candidates for this regimen because all HIV-infected patients with TB should be receiving antiretroviral therapy. In addition, prior studies of rifapentine in TB treatment of HIV-infected patients have revealed unacceptable rates of rifamycin resistance in instances of treatment breakthrough.

Optimal rifampin dose. Despite the desire to replace current TB regimens with new drugs to shorten treatment duration, current TB drugs may have some untapped potential. In a late-breaking presentation with the provocative title "What Is the 'Right' Dose of Rifampin?" Boeree and colleagues presented data suggesting that rifampin may be underdosed (Abstract 148LB). In a 14-day study, adults with smear-positive pulmonary TB received

1 of 5 possible doses of rifampin: 10 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, or 35 mg/kg—for the first 7 days. At day 7, standard doses of isoniazid, pyrazinamide, and ethambutol were added. Both the fall in colony-forming units and the time to TB culture negativity increased with higher doses of rifampin, suggesting higher potency with higher rifampin doses. Dose-limited toxicity attributable to rifampin was not observed in this 68-patient study. Early studies of rifampin, conducted more than 40 years ago, did not establish the maximal tolerated dose (MTD). These new data are intriguing in their suggestion that greater microbiologic potency could potentially be achieved without added toxicity, leaving the door open to the prospect of higher rifampin doses contributing to shorter TB treatment regimens. More study is needed to define the MTD of rifampin, to more fully characterize safety at these higher doses, and to understand the effects, if any, on enzyme inductions that result in drug-drug interactions with many antiretroviral and commonly used drugs.

Optimal raltegravir dose. Antiretroviral therapy is necessary for all HIV-infected patients with TB, and the compatibility of newer antiretroviral drugs, such as the HIV integrase strand transfer inhibitors, with TB therapy is important to understand. Previous drug interaction studies have shown that raltegravir levels are reduced in the presence of rifampin. In a study by Grinsztejn and colleagues, 155 patients starting TB treatment were randomized to receive raltegravir- (either 800 mg twice daily or 400 mg twice daily) or efavirenz-based antiretroviral treatment regimens (Abstract 853). The primary end point of the study was virologic response at 48 weeks. Treatment success rates were 63% in the arm receiving raltegravir 800 mg, 76% in the arm receiving raltegravir 400 mg, and 67% in the arm receiving efavirenz. The researchers concluded that raltegravir-containing regimens are compatible with standard TB therapy and that no dose adjustment of raltegravir is required. For patients unable to take an efavirenz-based regimen, this study tells us that raltegravir is an excellent option.

Drug interactions between a new investigational TB drug, PA-824, and efavirenz. Characterizing interactions between new TB drugs and antiretroviral drugs is critical because HIV-infected patients who acquire TB will either already be receiving antiretroviral therapy or in need of starting it. PA-824, an investigational nitroimidazole under study for TB treatment, undergoes metabolism through the P450 3A enzyme (CYP3A). Efavirenz, a CYP3A inducer, is recommended as the antiretroviral drug of choice for TB-infected patients starting antiretroviral therapy. Dooley and colleagues reported the results of an open-label crossover study examining interactions between PA-824 and efavirenz (Abstract 188LB). The AUC and trough concentrations of PA-824 were reduced by 35% and 46%, respectively, among healthy, HIV-uninfected adults who were also receiving efavirenz. The AUC and trough concentrations of efavirenz were unaffected by PA-824. As PA-824 continues to be developed for TB treatment, the clinical significance of this interaction and potential dose adjustments will need to be considered.

Rifampin-resistant TB and urinary lipoarabinomannan assays. The rapid combined TB and resistance to rifampicin assay (Xpert) is a revolutionary advance in TB diagnostics, providing results within 2 hours and improving on the sensitivity of TB smear for pulmonary TB diagnosis. However, there remains a need for complimentary rapid tests, because the test falls short of detecting all culture-positive TB cases. The lateral-flow, point-of-care, urinary lipoarabinomannan (LAM) test is a tool that could potentially fill this gap. The LAM test can detect the presence of a 12.5 kDa component in the mycobacterial cell wall in 20 minutes, with an estimated cost of $3.50. Shah and colleagues reported the results of a cross-sectional study examining TB diagnosis using an array of tests among HIV-infected adults in Uganda (Abstract 146). As expected, the sensitivity of Xpert alone was greater than that of the urinary LAM (76% vs 49%, respectively). However, adding urinary LAM to Xpert increased sensitivity from 76% to 85%. As reported in previous studies, LAM performs best with persons whose CD4+ cell counts are in the lower ranges. For example, in this study, among patients with CD4+ cell counts lower than 50/μL, Xpert sensitivity was 74%, versus 65% with LAM. In patients whose CD4+ cell counts were above 200/μL, Xpert sensitivity was 71%, versus 19% in LAM. In complimentary studies evaluating LAM, Van Rie and colleagues reported an 82% sensitivity of urinary LAM for smear-negative, Xpert-negative, culture-positive TB among HIV-seropositive adults with CD4+ cell counts above 10/μL (Abstract 841). In an outpatient evaluation of LAM, where patients had high CD4+ cell counts, sensitivity was low and there was a high false-negative rate (Abstract 842).

These studies substantially contribute to a growing body of data suggesting that the lateral-flow, point-of-care, urinary LAM test is a valuable addition to TB diagnostic tools for patients with low CD4+ cell counts. Hospitalized patients with the lowest CD4+ cell counts would benefit the most from access to the urinary LAM test, which could rapidly identify those with advanced TB, a group with high mortality rates that requires faster diagnosis and treatment.

Cryptococcal Meningitis

Cryptococcal meningitis remains one of the most common and deadly opportunistic infections (OIs) in resource-limited settings. Practitioners do not agree on the optimal timing of the initiation of antiretroviral therapy, because data are conflicting and generalizability of prior studies is limited by small sample sizes, inconsistent practices for intracranial pressure management, and use of substandard cryptococcal treatment regimens.

Boulware and colleagues presented the results of a randomized study conducted in Uganda and South Africa that provides the best data to date on this topic (Abstract 144). Antiretroviral therapy–naive adults experiencing their first episode of cryptococcal meningitis were randomized to start antiretroviral therapy 1 week to 2 weeks, in the early arm, or 4 weeks, in the deferred arm, after diagnosis. Amphotericin B and fluconazole (800 mg daily) were given for a 2-week induction period, followed by fluconazole alone. Clinicians performed serial lumbar punctures to monitor and manage elevated intracranial pressure.

The Data and Safety Monitoring Board (DSMB) stopped the study because of excess mortality in the early treatment arm after only 177 of the 500 planned participants were enrolled (hazard ratio [HR], 1.7; 95% CI, 1.1-2.8). The median time to start of antiretroviral therapy was 8 days in the early arm and 35 days in the deferred arm. The 26-week survival rate was 70% in the deferred arm and 55% in the early arm. Most deaths occurred within the first month of treatment and cryptococcal disease was the most common cause of death. Using a standard case definition, there was no difference between arms in the rates of cryptococcal immune reconstitution syndrome. No autopsies were reported, thus it is difficult to assess whether immune restorative effects of early antiretroviral therapy may have contributed to this finding. Independent risk factors for mortality included altered mental status (Glasgow Coma Scale score < 15) and a white blood cell count in cerebrospinal fluid of less than 3/μL. This study provides convincing evidence that cryptococcal meningitis is an exception to the rule that starting antiretroviral therapy early during acute OIs reduces incidence of AIDS and death. For patients with cryptococcal meningitis, the start of antiretroviral therapy should be delayed for 4 weeks after diagnosis

Prevention With Cotrimoxazole

In the developed world, cotrimoxazole prophylaxis can be safely discontinued after antiretroviral therapy restores immune function but the optimal strategy for its use after a response to antiretroviral therapy in resource-limited settings has not yet been evaluated in a randomized study. To address this question, researchers randomized 758 children living in malaria endemic areas in Uganda or Zimbabwe, who had received at least 96 weeks of antiretroviral therapy and had no prior history of *Pneumocystis jiroveci* pneumonia, were randomly assigned to stop or continue cotrimoxazole prophylaxis (Abstract 86). Hospitalization rates for malaria and non-malaria illness were higher in those who stopped than in those who continued (HR, 1.57; 95% CI, 1.09-2.26). Pneumonia, sepsis, and meningitis contributed to greater hospitalization rates in those who stopped cotrimoxazole prophylaxis. This study supports prior observational data from malaria endemic regions. Cotrimoxazole prophylaxis should not be stopped even among children who are responding to antiretroviral therapy, because it still confers significant clinical benefit.

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A list of all cited abstracts appears on pages 90-95 and is available online at www.iasusa.com.

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Aracelis D. Fernandez, MD, and Stephen Stafford, BA

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May: Pretreatment Counseling on Hepatitis C Virus (HCV) Protease Inhibitor-Based Therapy for HIV/HCV Coinfected Patients

Kara W. Chew, MD, MS, and Debika Bhattacharya, MD, MS, University of California Los Angeles

Two first-generation hepatitis C virus (HCV) protease inhibitors, boceprevir and telaprevir, each in conjunction with peginterferon alfa plus ribavirin, are in off-label clinical use for the treatment of HCV in HIV-coinfected persons. HIV practitioners need to understand potential adverse effects associated with these agents and counsel their patients before initiation of therapy.

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CROI 2013: Advances in Antiretroviral Therapy

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

The 20th Conference on Retroviruses and Opportunistic Infections (CROI) presented important highlights of advances in antiretroviral therapy. Investigators emphasized new approaches to finding a cure for HIV infection, with a special focus on an infant who received combination antiretroviral therapy at 30 hours of age and may have achieved a functional cure in the absence of continued antiretroviral therapy. Challenges and opportunities for sustainable antiretroviral therapy under the Patient Protection and Affordable Care Act (PPACA) were discussed, and investigators around the globe examined attrition through the cascade of care for HIV disease and its implications. Knowledge of barriers to antiretroviral therapy in resource-limited settings (RLSs) continues to expand, as do innovative strategies for improving antiretroviral therapy access and uptake in these settings. Encouraging results from expanded prevention of mother-to-child transmission programs, including option B+, were presented. Prevalence of transmitted (primary) drug resistance appears to be increasing in the United States, and new detection techniques may increase access to resistance testing in RLSs.

Keywords: *HIV, antiretroviral, therapy, treatment, CROI, cure, resource-limited, cascade of care*

Clinical Studies Investigating HIV-1 Cure Strategies

Persaud and colleagues presented data describing a possible functional cure of an HIV-1–infected infant (Abstract 48LB). The infant was born to an HIV-infected mother who had not received prenatal care and was diagnosed with HIV-1 infection during delivery. The delivery was precipitous and no antiretroviral prophylaxis was given to the mother. The child was transferred to a tertiary medical center at 30 hours of age and was started on full treatment doses of zidovudine, lamivudine, and nevirapine. Initial testing showed that the mother had a preserved CD4+ cell count of 644/μL and a plasma HIV-1 RNA level of 2423 copies/mL. The infant had a plasma HIV-1 RNA level of 19,812 copies/mL and detectable HIV-1 DNA in her peripheral blood cells, suggesting in utero transmission of HIV-1 infection. The infant's HIV-1 RNA levels were detectable in 3 sequential plasma specimens before declining to undetectable levels over the next 28 days and remained undetectable though 15 months of age. The infant was not brought in for medical care and antiretroviral therapy was discontinued. At 23 months of age, the infant was brought in for medical care and HIV-1 RNA was still undetectable in the absence of antiretroviral therapy.

Extensive testing was undertaken to assess a possible cure. The child had no HIV-specific antibody or cellular immune responses and levels of immune activation were within the normal range. No infectious virus was recovered, although the sensitivity of testing was limited by blood volume. Tests for proviral DNA were undetectable in various subsets except for 2 evaluations with very low levels, and HIV-1 RNA has remained undetectable since these evaluations. The investigators suggested that this is a functional cure of HIV-1 infection in this infant. Future investigations will attempt to replicate this functional cure in infants perinatally infected with HIV-1.

In a related abstract (Abstract 171LB), Luzuriaga and colleagues evaluated 5 teenagers infected with HIV as infants who received early antiretroviral therapy by 2 months of age, and 4 teenagers, also infected with HIV as infants, who started antiretroviral therapy later in childhood. Replication-competent virus was not found in the early antiretroviral therapy group and was found in all 4 subjects in the delayed treatment group. The early treatment group had lower proviral DNA levels and lower residual plasma viremia. HIV-specific antibody and CD8+ T-cell responses were identified in 1 of 5 subjects in the early treatment group and 4 of 4 in the delayed treatment group. These results suggest that early antiretroviral treatment of perinatally infected infants with HIV-1 leads to a marked decrease in HIV viral reservoir.

Very Early Antiretroviral Therapy and HIV-1 Reservoir Size

In a clinical study conducted by Ananaworanich and colleagues, pooled HIV-1 RNA testing was used to identify acute HIV-1 infection in nearly 53,000 people presenting for HIV testing in Thailand (Abstract 47). Of the 89 participants with acute HIV-1 infection identified, 75 were enrolled in a

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prospective trial in which they were given antiretroviral therapy within 5 days of presenting for HIV testing. Those who presented at the earliest phase of HIV-1 infection (Fiebig stage I: negative p24 antigen and positive HIV-1 RNA) had lower levels of HIV-1 DNA prior to initiation of antiretroviral therapy than those in Fiebig stage II or III. Only 2 of 24 (8%) participants in Fiebig stage I had detectable integrated HIV-1 DNA. After initiation of antiretroviral therapy, nearly all participants (93%) in Fiebig stages I to III developed undetectable integrated HIV-1 DNA levels.

Raltegravir Intensification

A debate continues as to whether ongoing cycles of HIV-1 replication typically occur in patients with effective virologic suppression on antiretroviral therapy. If ongoing replication exists, it may continually replenish the latent reservoir of HIV-1 infection, a major obstacle to curing HIV-1 infection; 2-long terminal repeat (2-LTR) circles are markers of ongoing replication. Hatano and colleagues randomly assigned participants taking effective antiretroviral therapy to receive either raltegravir or a placebo for 24 weeks (Abstract 42). The researchers measured 2-LTR circles using droplet digital polymerase chain reaction (ddPCR) technology, which is more sensitive at low levels than traditional assays. Raltegravir blocks the integration of HIV-1 complementary DNA (cDNA) into host DNA and promotes conversion of HIV-1 cDNA to 2-LTR circles. Raltegravir use resulted in higher 2-LTR circles after 2 weeks, 4 weeks, and 8 weeks, with no difference thereafter in 9 of 15 subjects. The researchers concluded that ongoing HIV-1 replication was blocked by raltegravir. This study confirms prior observations by Buzon and colleagues.[1]

Histone Deacetylase Inhibition

In an emerging strategy for HIV-1 infection cure known as "kick and kill," interventions "kick" the latent reservoir of HIV-1 infection into activation and replication allowing the immune system to "kill" the infected cell. A major focus of the kick portion of this strategy is histone deacetylase inhibitors (HDACis). In a prior study, vorinostat, an HDACi approved by the US Food and Drug Administration (FDA) for the treatment of cutaneous T-cell lymphoma, was shown to activate HIV-1, leading to a transient increase in intracellular unspliced HIV-1 RNA.[2] Lewin and colleagues presented data from a single-arm, open-label, 14-day trial of vorinostat given to 20 HIV-infected participants with virologic suppression who were taking effective antiretroviral therapy (Abstract 50LB). Vorinostat was generally well tolerated and no grade 3 or 4 adverse events were observed. Of the 20 participants, 18 experienced a substantial increase in intracellular HIV-1 RNA at least 1 time after vorinostat dosing. In the study group as a whole, HIV-1 RNA levels increased substantially as soon as 8 hours after the first dose of vorinostat and remained elevated up to 10 weeks after completion of dosing. A nonstatistically significant increase in HIV-1 RNA in rectal tissues was seen after 14 days of dosing, but levels of HIV-1 DNA in the blood or rectal tissue did not change during the trial. Data from this trial support the use of HDACis as activators of latent HIV-1 infection.

Wei and colleagues investigated the in vitro efficacy of romidepsin, another HDACi (Abstract 376). They found that romidepsin was 500 times more potent than vorinostat in inducing HIV-1 expression in vitro, supporting clinical trials of this drug as part of a cure strategy.

Interleukin-7 and Antiretroviral Therapy Intensification

Katlama and colleagues presented results from the ERAMUNE-01 (Therapeutic Intensification Plus Immunomodulation in HIV-Infected Patients) trial (Abstract 170aLB). Participants with well-controlled HIV-1 infection (n = 29) were randomly assigned to receive interleukin-7 (IL-7) in combination with antiretroviral therapy intensified by maraviroc and raltegravir, or intensified antiretroviral therapy alone. The goal was to evaluate which option would be most successful at reducing the HIV-1 viral reservoir, as measured by proviral DNA. HIV-1 DNA levels did not change in the group that received antiretroviral therapy intensification alone. CD4+ cell counts increased more dramatically in the arm that received IL-7 (median increase, 1400 cells/μL) than in the arm receiving intensification alone. The difference in CD4+ cell counts declined over time but was still statistically significantly higher 1 year later. In the IL-7 group, total HIV-1 DNA levels increased but $\log_{10}$ copies of HIV-1 DNA per million peripheral blood mononuclear cells (PBMC) did not change appreciably over time. Neither strategy examined in the study successfully reduced the HIV-1 viral reservoir, as measured by HIV-1 DNA.

Investigational Antiretroviral Drugs

CC Chemokine Receptor 5 Antagonists

Cenicriviroc is an investigational CC chemokine receptor 5 (CCR5) antagonist that also antagonizes CC chemokine receptor 2 (CCR2) and may lead to antiinflammatory effects in addition to antiretroviral activity. Gathe and colleagues presented data from a phase II study of cenicriviroc versus efavirenz. One hundred forty-three, HIV-infected, treatment-naive patients were randomly assigned to 1 of 3 study arms (2:2:1) in which they received cenicriviroc (100 mg or 200 mg daily) or efavirenz, each given with tenofovir and emtricitabine (Abstract 106LB). Eligible participants had a CD4+ cell count greater than 200/μL, plasma HIV-1 RNA levels greater than 1000 copies/mL, and documented CCR5-using HIV. In the cenicriviroc arms, 76% (100 mg group) and 73% (200 mg group) of patients achieved plasma HIV-1 RNA levels below 50 copies/mL compared with 71% of those in the efavirenz arm, using the FDA snapshot algorithm, a composite end point of virologic failure, treatment discontinuation, and missing data. The proportion

of patients who experienced virologic failure was higher in the cenicriviroc arms (12% and 14%, respectively) than in the efavirenz arm (4%). Of the 3 groups, more participants in the efavirenz arm discontinued treatment due to adverse events. These data suggest that the antiretroviral potency of cenicriviroc combined with 2 nucleos(t)ide analogue reverse transcriptase inhibitors (nRTIs) is not sufficient for use as an initial antiretroviral therapy regimen. Levels of soluble CD14 (sCD14), a marker of monocyte activation, were lower in the cenicriviroc arms, suggesting a possible antiinflammatory effect.

nRTIs

Tenofovir disproxil fumarate (tenofovir) is part of IAS–USA and US Department of Health and Human Services (DHHS; http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf) recommended initial antiretroviral therapy regimens.[3] This drug is well tolerated but leads to a loss in bone density and may cause renal dysfunction in some patients. Tenofovir alefenamide fumarate (tenofovir AF), an investigational prodrug of tenofovir, contains a lipid side chain that enhances intracellular concentrations of tenofovir and minimizes plasma concentrations. Its developers suggest that this will reduce the adverse bone and renal effects associated with tenofovir.

Zolopa and colleagues presented data from a phase II clinical trial comparing tenofovir AF and tenofovir, each given with elvitegravir, cobicistat, and emtricitabine (Abstract 99LB). One hundred seventy HIV-infected, treatment-naive participants were randomly assigned (2:1) to receive tenofovir AF or tenofovir. Similar proportions in each group (tenofovir AF, 88%; tenofovir, 90%) achieved HIV-1 RNA levels below 50 copies/mL at 24 weeks, and similar gains in CD4+ cell numbers were seen. Increases in serum creatinine levels were smaller in the tenofovir AF group than in the tenofovir group (0.07 mg/dL vs 0.12 mg/dL, respectively; $P = .02$), and the tenofovir group experienced larger decreases in bone density in the spine and hip. This study confirms the purported advantages of tenofovir AF over tenofovir. However, the clinical significance of the difference in serum creatinine levels is not clear. Phase III clinical trials of tenofovir AF are under way and should help clarify this finding.

Nonnucleoside Analogue Reverse Transcriptase Inhibitors

Data were presented by Anderson and colleagues on an investigational nonnucleoside analogue reverse transcriptase inhibitor (NNRTI), MK-1439 (Abstract 100). This compound retains activity against isolates with common mutations associated with efavirenz or nevirapine resistance, but not those associated with rilpivirine or etravirine resistance. The pharmacokinetic properties of MK-1439 support once-daily dosing. In a phase Ib study, treatment-naive subjects were randomly assigned to receive MK-1439 (25 mg or 200 mg) or a placebo once daily, without additional antiretroviral therapy drugs, for 7 days. The researchers observed a 1.5 $\log_{10}$ copy/mL decline in plasma HIV-1 RNA in the arms receiving MK-1439 and no change in the arm receiving placebos. The authors conclude that these results support further development of this compound.

Maturation Inhibitors

Maturation inhibitors affect gag processing; it has been shown that the maturation inhibitor bevirimat may also inhibit HIV-1 replication in vivo, although the compound did not complete clinical development, because of limited activity against a substantial proportion of circulating strains. Urano and colleagues presented data on numerous investigational maturation inhibitors that have in vitro activity against a substantially broader range of strains of HIV than bevirimat by retaining activity against HIV-1 isolates with naturally occurring polymorphisms that render bevirimat ineffective (Abstract 105). These data suggest that 1 or more of these compounds may be a viable candidate to enter clinical development.

Clinical Trials of Antiretroviral Drugs

Antiretroviral Therapy for Patients With Controlled HIV-1

Hatano and colleagues investigated the effects of antiretroviral therapy on treatment-naive patients with very low levels of HIV-1 RNA (Abstract 75LB). The researchers enrolled 16 participants, with a median HIV-1 RNA level of 77 copies/mL and a median CD4+ cell count of 615/μL. The participants started a regimen of raltegravir plus tenofovir and emtricitabine. After 24 weeks, CD4+ cell counts did not increase substantially, although HIV-1 RNA levels did decline substantially. Levels of immune activation decreased after initiation of antiretroviral therapy. These data suggest that HIV-infected participants with very low HIV-1 RNA levels in the absence of antiretroviral therapy are in a chronic state of immune activation, and that antiretroviral therapy initiation should be considered for these patients.

Maraviroc and Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome (IRIS) is a relatively common condition occurring in patients starting a new effective antiretroviral therapy regimen, especially those with low CD4+ cell counts. Maraviroc, a CCR5 antagonist, may have antiinflammatory effects.[4] Sierra-Madero and colleagues conducted a randomized, double-blind, placebo-controlled trial of maraviroc versus a placebo, each given with efavirenz, emtricitabine, and tenofovir (Abstract 182LB). The 276 study participants had CD4+ counts below 100 cells/μL (median, 30 cells/μL), a median HIV-1 RNA level of 5.3 $\log_{10}$ copies/mL, and were not required to have CCR5-using HIV-1. The primary end point of the study was the occurrence of IRIS, which was similar in the maraviroc- and placebo-receiving groups (24% and 23%, respectively; P = not significant). There was no difference in the severity of these events between the groups.

There was a slight increase in CD4+ cell counts in the maraviroc group at week 12 that was not sustained to week 24. This study does not support the immunomodulatory use of maraviroc to reduce IRIS events.

Maraviroc for Suboptimal CD4+ Cell Gains

Van Lelyveld and colleagues conducted a randomized placebo-controlled trial, adding maraviroc to an existing antiretroviral therapy regimen in order to increase CD4+ cell counts in participants with suboptimal CD4+ cell gain despite virologic suppression (Abstract 555). The median baseline CD4+ cell count was 237/µL. After 24 weeks, CD4+ cell gain did not differ between maraviroc and placebo recipients (+23 vs +15, respectively; $P = .50$). Changes in immune activation and sCD4 levels were not different between the 2 groups. These results do not support the use of maraviroc to increase CD4+ cell counts or as an immune modulator.

Dolutegravir for Treatment-Experienced Patients

Dolutegravir, an investigational integrase strand transfer inhibitor (InSTI), is in phase III clinical development. Previous trials have established its efficacy as part of combination antiretroviral therapy in treatment-naive and InSTI-experienced populations. Pozniak and colleagues reported interim data from SAILING, a double-blind placebo-controlled trial of dolutegravir (50 mg once daily) versus raltegravir (400 mg twice daily) with an optimized background regimen in treatment-experienced, InSTI-naive populations (Abstract 179LB). The 715 trial participants, 32% of whom were women, with a median age of 42 years, median baseline CD4+ counts of 200 cells/µL, and median HIV-1 RNA levels of 4.2 $\log_{10}$ copies/mL, were randomly assigned to the dolutegravir or the raltegravir group. At week 24, using the FDA snapshot algorithm, 79% of participants receiving dolutegravir achieved plasma HIV-1 RNA levels below 50 copies/mL compared with 70% of those receiving raltegravir (difference 9.7%; 95% confidence interval [CI], 3.1%-16.9%). CD4+ cell gains were similar between the 2 groups. The difference in efficacy was because of differences in virologic efficacy, although the drugs were well tolerated by subjects in both arms. One important difference was the emergence of InSTI-associated mutations. Nine subjects in the raltegravir group developed mutations in integrase, conferring resistance to raltegravir. Two subjects in the dolutegravir group developed the integrase R263K mutation, which resulted in minimal changes in phenotypic susceptibility to either InSTI. These data in combination with data from SPRING-2, a study comparing dolutegravir and raltegravir in treatment-naive patients, suggest that emergence of InSTI resistance is rare with dolutegravir use in InSTI-treatment-naive patients.

nRTIs for Highly Treatment-Experienced Patients

Newer antiretroviral drugs that have become available in the last 5 years have resulted in the ability to construct effective combination regimens for highly treatment-experienced patients. Nearly all clinical trials of antiretroviral therapy have included nRTIs as part of the studied regimen. Tashima and colleagues presented data from the AIDS Clinical Trials Group (ACTG) A5241 study, which investigated whether nRTIs were a necessary component of antiretroviral treatment regimens containing at least 2 fully active agents (Abstract 153LB). Treatment-experienced patients whose current antiretroviral regimen was failing had a new regimen chosen based on antiretroviral therapy history, resistance testing, and coreceptor tropism testing. An expert panel provided recommendations for the antiretroviral treatment regimens and nRTIs to be used. Participants with a continuous phenotypic score greater than 2 were randomly assigned to receive nRTIs or to omit nRTIs from their antiretroviral regimen.

Three hundred sixty racially and ethnically diverse participants, 25% of whom were women, with a median age of 46 years, a median CD4+ cell count of 200/µL, and a mean HIV-1 RNA level of 4.2 $\log_{10}$ copies/mL, were enrolled in the trial. Investigators hypothesized that omitting nRTIs was noninferior to including them, using a noninferiority margin of 15% and a primary end point of regimen failure, a composite of virologic failure or change in assigned nRTI strategy. Regimen failure occurred in 30% of participants in the no-NRTI arm and 26% in the nRTI arm (difference −3.2%; 95% CI, −12.5% to +6%). The no-NRTI arm was judged to be noninferior. Of note, virologic failure was similar in both arms, at 25%. There were 6 deaths in the nRTI arm and no deaths in the no-NRTI arm. These results were unexpected and require further investigation. The study suggests that nRTIs may be safely omitted in this patient population, which may reduce treatment cost and pill burden.

Comparison of Second-Line Therapies

Boyd and colleagues presented data from a randomized, open-label, clinical trial comparing raltegravir plus ritonavir-boosted (/r) lopinavir with 2 to 3 nRTIs plus lopinavir/r in patients in whom their initial regimens of NNRTIs plus 2 nRTIs had failed (Abstract 180LB). The 558 subjects had a mean HIV-1 RNA level of 4.3 $\log_{10}$ and a median CD4+ cell count of 190/µL. Genotypic testing was used to select the nRTIs for the majority of subjects (n = 492; 88%). At 48 weeks, virologic suppression (plasma HIV-1 RNA level < 200 copies/mL) in the raltegravir arm was noninferior to that in the nRTI arm, 83% and 81%, respectively (difference 1.8%; 95% CI, −4.7% to 8.3%). The researchers concluded that both types of regimen were reasonable choices for second-line therapy.

Pharmacokinetic Considerations

Antiretroviral Therapy in End-Stage Renal Disease

Teicher and colleagues presented data on the safety and pharmacokinetics of raltegravir in 10 HIV-infected subjects

with end-stage liver disease (Abstract 528). Patients' antiretroviral regimens were changed to raltegravir plus 2 nRTIs. Concentrations of raltegravir, protein-unbound raltegravir, and raltegravir glucuronide (the raltegravir metabolite) after 1 and 3 months were similar to those observed in patients without liver disease. Raltegravir was found to be safe and well tolerated.

Ramanathan and colleagues investigated the pharmacokinetics of tenofovir AF in 14 HIV-1–uninfected participants with severe renal impairment (creatinine clearance, 15 mL/min-29 mL/min) and in 13 HIV-1–uninfected participants with normal renal function (Abstract 529). Tenofovir AF concentrations were increased in participants with impaired renal function, but these differences were not thought to be clinically significant. The tenofovir concentrations were approximately 6 times higher in those with impaired renal function as compared to those without renal impairment but were still lower than those typically seen in patients with normal renal function receiving tenofovir disproxil fumarate. The investigators concluded that tenofovir AF should be safe for patients with severe renal impairment. A clinical trial evaluating the safety and efficacy of tenofovir AF in patients with severe renal impairment is currently under way.

Dolutegravir Interactions

Dolutegravir does not inhibit or induce cytochrome P450 (CYP450) or uridine diphosphate glucuronyltransferase (UDPGT) and has a low likelihood of drug-drug interactions. Piscitelli and colleagues investigated possible drug-drug interactions between dolutegravir and methadone or oral contraceptives (Abstract 535). HIV-1–uninfected participants receiving methadone chronically were enrolled in the study. They found that dolutegravir did not lead to appreciable changes in concentrations of methadone or its metabolites. Similarly, a second study enrolling HIV-uninfected women receiving oral contraception (ethinyl estradiol and norgestimate) found that levels of these hormones and their metabolites were not affected by dolutegravir.

Higher Dose Lopinavir/r in Pregnant Women

Drug concentrations of lopinavir are known to decrease in the second and third trimesters of pregnancy, and higher doses of lopinavir/r are recommended for pregnant women. Bonafe and colleagues conducted a randomized, open-label clinical trial to examine the safety, tolerability, and efficacy of higher dose lopinavir/r (600 mg/150 mg twice daily) compared with standard dose lopinavir/r (400 mg/100 mg twice daily) in 63 HIV-1–infected pregnant women between 14 weeks and 33 weeks gestation (Abstract 935). Of women randomized to the high- and standard-dose groups, 17% and 9%, respectively, discontinued treatment due to adverse effects ($P = .29$). Women who entered the study with HIV-1 RNA levels of 50 copies/mL or higher were more likely to achieve an HIV-1 RNA level below 50 copies/mL at the time of delivery in the high-dose group (89% vs 55%; $P = .01$). There was no difference among women who entered the trial with HIV-1 RNA levels below 50 copies/mL. The investigators concluded that higher dose lopinavir/r was needed for HIV-infected pregnant women with HIV-1 RNA levels of 50 copies/mL or higher but not for those with HIV-1 RNA levels below 50 copies/mL.

Abacavir and Ribavirin

Andrade and colleagues evaluated whether there are intracellular interactions between abacavir and ribavirin that explain poorer sustained virologic responses to hepatitis C virus (HCV) therapy in patients receiving abacavir (Abstract 538). They randomly assigned 28 HIV-uninfected participants to receive ribavirin alone or ribavirin with abacavir. When they compared intracellular ribavirin and ribavirin triphosphate concentrations, no appreciable difference was found between the 2 groups. The investigators did not find any evidence of intracellular interactions between these drugs.

Raltegravir and Rifampin

Sauvageon and colleagues investigated whether higher doses of raltegravir could be used to overcome the interactions between raltegravir and rifampin in a pharmacokinetic substudy of a larger trial of tuberculosis (TB) treatment in HIV-infected patients (Abstract 539). Participants taking a rifampin-containing TB regimen were randomly assigned to receive standard- (400 mg twice daily) or high-dose (800 mg twice daily) raltegravir. The investigators compared drug concentrations with those obtained after completion of TB treatment while on standard-dose raltegravir. Similar to results from other studies, there was a large variability in raltegravir concentrations, and high-dose raltegravir partially compensated for the lower concentrations observed when coadministered with rifampin. However, a separate presentation (Abstract 853) suggested that higher doses of raltegravir did not result in improved virologic control.

Political and Economic Context for Sustainable Antiretroviral Therapy

Kates, of the Kaiser Family Foundation in Washington, DC, provided an overview of the global and US political and economic challenges to antiretroviral therapy implementation (Abstract 119). Kates asserted that sustainable antiretroviral therapy is a misnomer, because only 24% of those living with HIV worldwide and 33% of those living with HIV in the United States are currently receiving antiretroviral therapy. The US government provided 68.2% of the international AIDS assistance from donor governments in 2011, but disbursements from the United States have been declining since 2009. Federal funding for the Ryan White HIV/AIDS Program has been stable, after adjustment for inflation, since 1999, despite an increase of more than 40% in HIV/AIDS prevalence in the United States during that time. The gap remains between those in need of and those receiving antiretroviral therapy. Maintenance of antiretroviral therapy

and expansion of existing programs are in jeopardy in an era of US budget sequestration and global reductions in funding of antiretroviral therapy in resource-limited settings (RLSs).

Kates discussed how the Patient Protection and Affordable Care Act (PPACA) will impact US domestic antiretroviral therapy programs and access to those programs. The PPACA will likely increase access to care because it raises the age limit for dependent coverage, eliminates lifetime and annual coverage limits, and removes limitations on preexisting conditions, a particularly relevant limitation for those living with HIV. Prescription drugs, including antiretroviral drugs, will no longer be subject to the coverage gap "donut hole" within Medicare Part D, and states can choose to define antiretroviral therapy as an essential health benefit required by insurers. However, the ability to opt out of Medicaid expansion in the PPACA, guaranteed by a US Supreme Court decision in 2012, could substantially impact this opportunity for expanded antiretroviral therapy access. Currently, 68% of people living with HIV in the United States reside in states that are likely to support Medicaid expansion. However, the majority of states opposed to Medicaid expansion are in the South, which means that current regional disparities in access to antiretroviral therapy could be exacerbated by the implementation of the PPACA. Kates emphasized that health insurance coverage does not ensure access to antiretroviral therapy and the important role that the Ryan White HIV/AIDS Program should play during this transition, by supplementing coverage for poorer patients and providing care for those who fall out of Medicaid expansion or who are not US citizens.

Cascade of HIV Care

Since the results of the HPTN (HIV Prevention Trials Network) 052 Study demonstrated that patients receiving potent antiretroviral therapy were less likely to transmit HIV to their partners, antiretroviral therapy has been seen as serving the dual purpose of saving the life of the infected partner and preventing transmission to uninfected individuals.[5] Treatment as prevention is limited, however, to those achieving virologic suppression on antiretroviral therapy. In 2010, it was estimated that only 28% of HIV-infected individuals in the United States had suppressed HIV-1 RNA levels.[6] The process of achieving virologic suppression proceeds through 5 stages: HIV diagnosis, linkage to care, retention in care, receipt of antiretroviral therapy, and virologic suppression. This progression is often called the cascade of care. The proportion of people who make it through the cascade and achieve virologic suppression is a metric of the efficacy of HIV testing and treatment programs. Several presentations highlighted successes and gaps in the cascade in different settings.

Greenberg reviewed national US data and used Washington DC's efforts to expand HIV testing and treatment as a case study, as discussed in the article "New Tools to Understand Transmission Dynamics and Prevent HIV Infections" by Buchbinder and Liu (Abstract 58). Session 31 included data from the United States, Canada, and France, highlighting the need for consistent definitions in discussions of the cascade of care and for examination of the cascade of care nationally and locally to address gaps. Althoff and colleagues applied relevant DHHS indicators of the cascade—percentage of patients retained in care, percentage of patients prescribed antiretroviral therapy, and percentage of patients with suppressed HIV-1 RNA levels—to data from 10 clinics participating in the NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) (Abstract 1026).

The investigators noted that those participating in NA-ACCORD were all engaged in care at some point. To be included in the cohort, participants must have 2 HIV clinic visits within a 12-month period. Thus, these data do not reflect early steps in the cascade, such as testing and linkage to care. Of 25,235 patients, 87% met DHHS definitions for retained in care, 85% were prescribed antiretroviral therapy, and 76% achieved virologic suppression. Statistically significant disparities in age, race and ethnicity, and HIV transmission risk category existed for all indicators after adjustment. Among patients with access to HIV care, only one-quarter did not achieve virologic suppression, but this success was attenuated for younger people, African Americans, and heterosexual individuals.

Data on the cascade of care in Kings County, Washington, were presented by Dombrowski and colleagues (Abstract 1027). Their unique strategy used laboratory data on CD4+ cell counts and HIV-1 RNA levels in addition to case investigations to define indicators at various steps in the cascade and accounted for patient migration in and out of care. They confirmed a linkage-to-care rate of 78% of people living with HIV, of which 54% were retained and engaged in continuous care and 52% were virologically suppressed. These data are higher than the national estimate of 28% virologic suppression.[6] The investigators speculated that their ability to account for in-and-out migration and use of laboratory data as a surrogate for retention in care may have led to a more accurate depiction of the care cascade. The reliability of laboratory data as a surrogate for engagement in care is currently under investigation, and Kings County is now using a lack of laboratory data after 6 months as a trigger for outreach efforts to prevent patients from being lost to follow-up.

The US Medical Monitoring Project (MMP) is a national supplemental surveillance system that monitors the clinical outcomes of HIV-infected adults engaged in care across 23 health department jurisdictions in the United States. Quinn and colleagues used MMP data from January through April of 2009 to examine the association between insurance type and continuous virologic suppression, defined as all HIV-1 RNA levels of 200 copies/mL or lower within the past 12 months (Abstract 1028). Sixty percent of patients in the cohort met criteria for durable virologic suppression, and after adjustment for sociodemographic

and clinical factors, this was associated with insurance coverage through Medicare (odds ratio [OR], 1.13; 95% CI, 1.05-1.21) and the military (OR, 1.26; 95% CI, 1.09-1.45). Virologic suppression was also inversely associated with black race, younger or older age (compared with those 40 years to 49 years of age), homelessness, and more advanced disease stage (AIDS or nadir CD4+ cell count < 500/µL). The investigators concluded that these data support the expansion of quality HIV care delivery models, though confounding by the sociodemographic factors associated with various types of insurance is also probable.

Montaner and colleagues used the robust longitudinal dataset available in British Columbia to examine the evolution of the cascade of care during the period from 1996 to 2010 (Abstract 1029). They found that the estimated percentage of those with undiagnosed HIV infection fell from 53% to 14% during the study period. In 2009, linkage to care was 79%, retention in care was 56%, and an estimated 38% of HIV-infected individuals were virologically suppressed, defined as having no detectable (using assay threshold at the time) HIV-1 RNA over 3 or more months within the calendar year. Sensitivity analyses revealed that estimates of virologic suppression varied widely, from 38% to 55%, by the definition of suppression applied to the data. It is remarkable that despite universal access to care in Canada, there is still substantial attrition through the care cascade. The investigators are examining the sociodemographic and geographic predictors of achievement of virologic suppression.

Supervie and Constagliola used several French national datasets, including HIV surveillance data, French national health insurance data, and the French hospital database on HIV (Agence Nationale de Recherche sur le Sida [ANRS]-CO4 study), to estimate engagement throughout the HIV care cascade in France (Abstract 1030). Of all HIV-infected adults older than 15 years in France in 2010, it is estimated that 81% were diagnosed, 74% were in care, 60% were taking antiretroviral therapy, and 52% were virologically suppressed. Disparities occur early in HIV care by HIV transmission risk group, with consistently higher engagement at all levels for injection drug users and lowest engagement for non–French national heterosexual men, although the investigators did not report statistical tests for differences between these groups.

Data from the Ryan White HIV/AIDS Program were used by Doshi and colleagues to examine the cascade of care for 546,156 Ryan White HIV/AIDS Program clients in 2010 (Abstract 1031a). Of 291,449 persons with documented HIV seropositive status receiving Ryan White HIV/AIDS Program–funded medical care, 80% were prescribed antiretroviral therapy, 76% were retained in care, and 60% had a most-recent viral load below 200 copies/mL. Retention in care was statistically significantly associated with female sex, Hispanic or multiracial race and ethnicity compared with white race, and all age groups between 13 years and 54 years compared with those older than 65 years. Blacks and American Indian or Alaska natives were statistically significantly less likely to be retained in care.

Horberg and colleagues used data from the Kaiser Permanente Medical Care Program to illustrate a flaw in the cascade of care: progression to subsequent steps in the cascade is not necessarily dependent on achievement of success at earlier stages (Abstract 1033). They argue that, depending on how the variables are defined, one can fail to be engaged in care but still receive antiretroviral therapy or achieve virologic control. They analyzed achievement of cascade stages by forcing each stage to be a subset of the previous or by allowing stages to be independent. In the Kaiser Permanente Medical Care Program in 2010, 97% of 16,816 known HIV seropositive patients were linked to care and 78% were retained in care. Of those patients retained in care in 2010, defined as at least 2 medical visits in 2010 with at least 60 days between visits, 66% filled 3 months worth of antiretroviral therapy prescriptions. However, if the calculation is not restricted to those retained in care, 83% received antire-troviral therapy. Similarly, for virologic suppression, 61% of HIV-infected patients had last-measured HIV-1 RNA levels below 200 copies/mL, if this stage is taken as a subset of all prior stages. If the cascade steps are independent, 80% of HIV-infected patients in the Kaiser program in 2010 had a last-measured HIV-1 RNA level below 200 copies/mL. There were also statistically significant differences in achievement of various stages in the cascade of care by sex and age.

Data from a single site in Johannesburg, South Africa, was used to examine attrition in 3 cohorts of individuals: those testing seropositive for HIV, those linking to HIV care, and those starting antiretroviral therapy between March 2010 and March 2012 (Abstract 1103). The investigators defined lost to follow-up (LTFU) as at least 1 month late for linkage to care for those who tested HIV seropositive and at least 3 months late for the pre–antiretroviral therapy and on antiretroviral therapy cohorts. Of 229 patients testing HIV seropositive, 54.6% were not linked to care. Of 134 pre–antiretroviral therapy patients, 17.2% were LTFU prior to antiretroviral therapy initiation and 13 of 152 (8.6%) were LTFU while on antiretroviral therapy. Predictors of LTFU included transportation-related barriers for the HIV-seropositive testing cohort, and young age and South African birth for the pre–antiretroviral therapy cohort. These findings are concerning but, because they come from a single site, do not account for the substantial in-and-out migration that may be impacting the LTFU measures.

Taken collectively, findings on the cascade of care presented at CROI illustrate several key points. First, uniformity of definitions and methodology for assessment of the numbers of patients reaching each stage is crucial. As demonstrated, percent attainment can be affected by the definitions of engagement in care and virologic suppression (Abstract 1033) and the type of dataset used, as illustrated by the use of laboratory data to determine care engagement (Abstract 1027). Even in settings with integrated medical

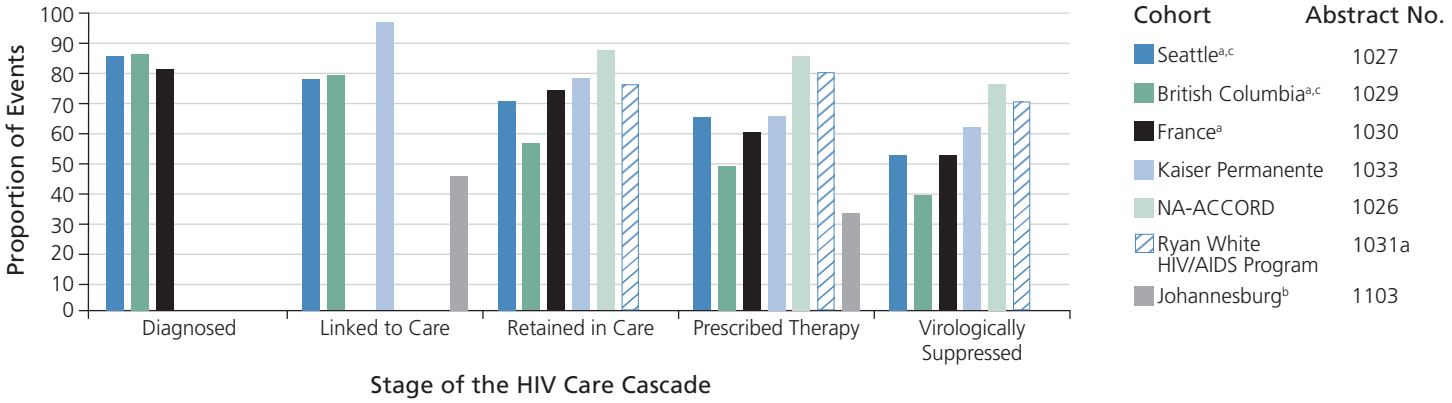

Figure. Attrition through the cascade of care reported at the 20th Conference on Retroviruses and Opportunitic Infections (CROI 2013) varies widely by cohort and metrics utilized. [a]The Seattle, British Columbia, and French cohorts began calculations with the number of HIV seropositive individuals diagnosed. The remaining cohorts began with the number of known diagnoses linked to care, thus the denominators are not comparable between the first 3 and latter 4 studies. [b]The Johannesburg cohort percentage of prescribed antiretroviral therapy is defined as the percentage of individuals retained from seropositive HIV test through 1 year on antiretroviral therapy. [c]In the Seattle and British Columbia cohorts, "virologically suppressed" was defined as a plasma HIV-1 RNA level below 200 copies/mL for the most recent value reported for the observation period in 2010.

systems and success in diagnosis and linkage to care, such as Seattle, Washington (Abstract 1027), British Columbia (Abstract 1029), Canada, and France (Abstract 1030), substantial health disparities by race and ethnicity, sex, and HIV transmission category exist. Finally, as the moderators emphasized, these data must be used to address gaps throughout the care cascade and to translate lessons from programs with good care cascades to other settings (Figure).

Antiretroviral Therapy in RLSs

Engagement in Care in RLSs

Teasdale and colleagues from the International Center for AIDS Care and Treatment Programs (ICAP) presented data on the cascade of care and mortality from 34,892 patients in care at 41 ICAP-affiliated health care facilities in Rwanda between 2005 and 2010 (Abstract 92). They examined LTFU and mortality in patients pre–antiretroviral therapy and on antiretroviral therapy and found that LFTU was 11.2% and 4.4% and mortality was 4.4% and 6.3% at 2 years for pre– and on antiretroviral therapy, respectively. Both adverse outcomes were associated with male sex, and receiving care at a rural facility was associated with mortality pre– and on antiretroviral therapy. There is a strong likelihood that deaths were underreported in this clinical cohort without active case finding. Regardless, retention was higher in this cohort than in others reporting pre–antiretroviral therapy LTFU but remains a challenge for individuals pre–antiretroviral therapy who had higher CD4+ cell counts and World Health Organization (WHO) clinical disease stages at enrollment.

Guffey and colleagues asked a similar question regarding LTFU for individuals with immediate (within 180 days of enrollment) antiretroviral therapy initiation versus delayed initiation for 118,935 adults enrolled in a public sector cohort in Lusaka, Zambia (Abstract 93). To mitigate confounding by disease severity, the investigators examined LTFU, defined as 60 days or more late for a clinical or pharmacy visit, in 6419 individuals falling within a narrow disease status band: a CD4+ cell count of 175/μL to 225/μL and WHO disease stage I or II. This allowed for inclusion of individuals falling on either side of the antiretroviral therapy initiation threshold of 200 cells/μL in Zambia. Despite similar baseline characteristics, they found LTFU rates of 10.2 per 100 person-years (95% CI, 14.1-15.7) in the immediate antiretroviral therapy start group (n = 4810) and 33.9 per 100 person-years (95% CI, 31.8-36.1) in the delayed antiretroviral therapy start group (n = 1609). In a Kaplan-Meier analysis of the proportion of LTFU by antiretroviral therapy initiation status, it was evident that the discrepancy between the 2 groups occurred within the first year of enrollment, with rates of LTFU leveling out after that. The investigators acknowledged that unreported deaths or transfers may be misclassified as LTFU. Questions from the audience also raised the concern that people may not have initiated antiretroviral therapy because they were LTFU, particularly considering the 60-day follow-up definition.

Hoffman and colleagues from ICAP examined another aspect of engagement in care in RLSs, late enrollment into care (Abstract 94). They determined the proportion of patients enrolling into care late, defined as entering into care after being eligible for antiretroviral therapy (CD4+ cell count ≤ 350/μL or WHO stage III or IV by 2010 WHO guidelines), in 302,777 patients drawn from 193 ICAP-affiliated HIV care clinics in 4 countries in sub-Saharan Africa. The percentage of individuals enrolling late decreased substantially from 68% in 2006 to 55% in 2011, and the median CD4+ cell count at enrollment rose from 238/μL to 286/μL during the same period; both tests for trends were statistically significant ($P < .0001$). This decrease in

risk for late enrollment was observed across all patient demographic groups (sex, age, marital status, enrollment point of entry, and country). A second analysis of factors associated with late enrollment was conducted for 45,113 patients in 193 clinics providing services in 2011. The investigators included program-level and regional data in this analysis and found that increased population knowledge of HIV and testing uptake were protective against late enrollment. The investigators concluded that, though late enrollment is declining, it was still substantial (55%) in 2011, and that efforts to increase HIV knowledge and testing at the population level could have an impact.

MacPherson and colleagues presented data from a possible intervention to address the above issues in engagement in HIV care, particularly regarding delays in antiretroviral therapy initiation (Abstract 95LB). Using a cluster-randomized trial design of 14 neighborhoods in Blantyre, Malawi, they randomized 7 regions to home-based HIV testing with referral to facility-based HIV care (control arm) and 7 regions to home-based testing with the option of home assessment of HIV serostatus and initiation of antiretroviral therapy if HIV infected and eligible for antiretroviral therapy initiation by national guidelines (intervention arm). Community-based counselors were selected and trained within each cluster to perform testing, assessment, and initiation of 2 weeks of antiretroviral therapy for those in the intervention arm. After 2 weeks of therapy, those patients in the intervention arm opting for home initiation were required to engage in care at a local clinic. Patients in the intervention arm were more likely to disclose their HIV seropositive status to the counselors (risk ratio [RR], 1.86; 95% CI, 1.16-2.97) and more likely to initiate antiretroviral therapy (RR, 2.94; 95% CI, 2.10-4.12). The investigators are conducting a more in-depth analysis of these late-breaking data, including important results on the number of individuals who initiated antiretroviral therapy at home but did not subsequently link to care and other adverse outcomes. Regardless, home-based antiretroviral therapy initiation appeared acceptable to many participants and increased treatment initiations in this context.

Retention and Adherence in RLSs

Session 48 covered similar themes of retention and adherence in RLSs. Bangsberg began the session with a review of the current literature. He highlighted that any analysis generated from programmatic data without sampling those LTFU may generate biased information, overestimating survival and underestimating engagement in care. Studies in RLSs demonstrate that many people who are disengaged from care have died, and many others have transferred to other clinics that are more convenient.[7] Adherence in RLSs remains good and may be enhanced by some technology interventions. However, initiating antiretroviral therapy at higher CD4+ cell counts and duration on antiretroviral therapy are both risk factors for poor adherence and suggest that programs may have more trouble as they mature and CD4+ cell count thresholds for antiretroviral therapy initiation rise.

Transportation cost and distance to clinic are frequently noted barriers to maintenance in care in RLSs. Seidner and colleagues sought to measure and validate transportation time and distance using 4 different measures of transportation for 188 patients in the UARTO (Ugandan AIDS Rural Treatment Outcomes) study (Abstract 1101). They found a high correlation between global positioning system (GPS) measures of distance to clinic: GPS straight-line distance and GPS tracked distance using the distance measured by a clinic staffer driving the patient home by his or her regular route ($R^2 = 0.92$). There was poor correlation between GPS straight-line distance and either self-reported travel time or self-reported travel cost. They validated these measures using linear regression models for the association between transportation measure and days missing from clinic per year. Both GPS measures (straight-line and tracked distance) had a statistically significant correlation ($P < .001$) with days missing, but the self-reported measures did not. The investigators suggest that objective measures of distance to clinic should be used to stratify patients in rural RLSs by level of risk for loss to follow-up.

Ugoji and colleagues examined predictors of patient retention in care, defined as 1 or more clinic visits during the 1-year review period, for 5176, randomly selected, HIV seropositive patients from a retrospective review of quality of care in 2010 at 37 Nigerian treatment facilities (Abstract 1102). They found that 1 of 4 pre–antiretroviral therapy patients and 3 of 4 patients on antiretroviral therapy were retained in care. After controlling for patient-level characteristics known to be associated with LTFU (age, sex, antiretroviral therapy status, baseline CD4+ cell count, and WHO stage), several treatment-site characteristics were found to be statistically significantly associated with retention in care, including rural site, younger age of treatment site, stability of site clinicians, and support group linkages. Interestingly, the presence of leadership-supported quality improvement teams and a high nurse-to-patient ratio were inversely associated with retention in care. These findings are encouraging for the ability of programs to enhance retention with support groups, even in decentralized and newly established rural clinics.

Retention in care prior to antiretroviral therapy initiation was examined using routinely collected data from 17 primary health care clinics in a decentralized HIV program in KwaZulu-Natal, South Africa (Abstract 1104). Overall, 31,767 patients 15 years of age or older met inclusion criteria of a seropositive rapid HIV test and a CD4+ cell count at a participating site between January 2007 and March 2011, with follow-up through March 2012. Based on CD4+ cell count criteria for initiation (≤ 200/μL prior to April 2010, or ≤ 350/μL thereafter), 13,761 (43%) were eligible for antiretroviral therapy immediately, 5404 (17%) became eligible during follow-up, and 7630 (24%) were LTFU without subsequent CD4+ cell count monitoring to determine eligibility. Of the 19,165 patients

eligible for antiretroviral therapy at any point, only 66% initiated antiretroviral therapy during the observation period. Patients who were eligible for antiretroviral therapy after 2 or more CD4+ cell count measurements were more likely to initiate antiretroviral therapy than those eligible at the first CD4+ cell count, after adjustment for sex, age, CD4+ cell count, and year of eligibility (adjusted odds ratio [aOR], 1.39; 95% CI, 1.33-1.45). The investigators felt that LTFU and failure to initiate antiretroviral therapy after the first CD4+ cell count could be mitigated by interventions at the first clinic visit.

Myer and colleagues asked whether HIV-infected women have better outcomes on antiretroviral therapy when other HIV-infected family members are enrolled at the same site (Abstract 1105). They included women initiating antiretroviral therapy with up to 5 years of follow-up from 12 ICAP-affiliated sites in 8 African countries. Of these 2877 women, 10% had an HIV-infected child enrolled in care at the same site, and 24% had an HIV-infected partner enrolled. Comparing women with co-enrollment of either a child or partner with those without co-enrollment, they found no differences in mortality. However, LTFU was statistically significantly lower among women with either a child or a partner co-enrolled in the same program (adjusted hazard ratio [aHR], 0.26; 95% CI, 0.15-0.46 for children co-enrolled; aHR, 0.41; 95% CI, 0.30-0.56 for partner co-enrolled). The investigators acknowledge that without active patient tracking, it is likely that some of those LTFU actually died and mortality is underestimated for the cohort.

Geng and colleagues investigated reasons for disengagement from care for patients on antiretroviral therapy at 14 clinics in Kenya, Uganda, and Tanzania (Abstract 1106). Of 6687 patients on antiretroviral therapy who were more than 3 months late for their last appointment (ie, LTFU), they generated a random sample of 1024 (15%) patients and attempted to ascertain their current status. Of 907 patients whose outcome was ascertained, 27% had died, 65% were in care, and 35% had disengaged from care. Those who were disengaged were asked open-ended questions regarding reasons for disengagement categorized as structural: transportation difficulty or expense (29% reported), work interference (23%), or lack of money to access care (12%); clinic-based: fear of scolding for missed appointment (13%), spending too much time at clinic (4%), and staff not being nice (3%); and patient-based: felt well and did not need care (23%), seeing a traditional healer instead (19%), and family obligations (16%). There were substantial between-country differences in the number of participants reporting structural and patient-based barriers, but all participants reported similar prevalence (13%-21%) of clinic-based barriers. These data shed light yet again on the high percentage of those LTFU who are deceased, and barriers to care for those disengaged, particularly transportation-based issues and feeling well, that could be mitigated.

Standard adherence measures can predict virologic rebound on antiretroviral therapy but usually do so after the fact. A wireless adherence monitor attached to a pillbox sends a signal via a cellular phone network each time it is opened, allowing real-time tracking of potential lapses in antiretroviral therapy. Haberer and colleagues used this technology in 447 individuals initiating antiretroviral therapy within the UARTO study and detected 134 virologically suppressed individuals with a signal lapse longer than 48 hours (Abstract 1107). Of these, virologic rebound (HIV-1 RNA levels, 430-24,278 copies/mL) was seen in 9 lapses, and this was associated with lapse duration (OR, 4.4 for lapses > 6 days; P = .03). Eight of nine patients with lapses resuppressed HIV-1 RNA levels on subsequent measurements after intervention by the study team. The investigators believe that this technology is feasible and could potentially replace some routine HIV-1 RNA monitoring.

Overall, the data presented on engagement in care and adherence in RLSs highlight several challenges: (*a*) the lack of uniformity of definitions for engagement in care and outcomes to allow comparison across studies and cohorts, (*b*) the likely underestimation of mortality that occurs whenever outcome ascertainment in LTFU is not completed, and (*c*) the need for innovative technology-based and other strategies to improve the HIV care continuum, from testing to virologic suppression, in RLSs.

Prevention of Mother-to-Child Transmission of HIV

This year's N'Galy-Mann lecture was presented by Mofenson of the National Institute of Child Health and Human Development (Abstract 15). Her address provided an overview of the global scale-up of prevention of mother-to-child transmission (PMTCT) programs since the 1990s. The historical trajectory of PMTCT—from monotherapeutic options to lifelong antiretroviral therapy for pregnant women—provided a hopeful yet sobering view of ongoing PMTCT, primarily in RLSs. Mofenson argued that maternal antiretroviral therapy, even at coverage rates of 90%, would not be sufficient to achieve the WHO goal of less than 5% mother-to-child transmission (MTCT) globally by 2015. She delineated the crucial programmatic interventions needed to eliminate pediatric HIV infection, including overall reductions in incident HIV infections among women, universal access to family planning services, early antenatal services, and availability of safe alternatives to breast feeding when appropriate. The following sections summarize the most salient PMTCT data to be presented at this year's CROI.

Uptake and Retention in PMTCT Programs

Data from the implementation of WHO options A, B, and B+ for PMTCT were presented in a number of oral and poster abstracts. Options A and B are CD4+ cell count–driven protocols for PMTCT. In both options, all pregnant women with CD4+ cell counts below 350/μL receive combination antiretroviral therapy during pregnancy and

continue for their lifetimes. In Option A, women presenting with a CD4+ cell count above 350/μL receive prophylaxis with zidovudine monotherapy in the antepartum period; single-dose (sd) nevirapine, zidovudine, and lamivudine in the intrapartum period; and zidovudine with lamivudine for 7 days postpartum. In Option B, women with CD4+ cell counts above 350/μL receive antiretroviral therapy from week 14 of pregnancy until 1 week following cessation of breast feeding. A third option, Option B+, provides lifetime antiretroviral therapy to all pregnant women irrespective of CD4+ cell count results.

In an oral abstract session dedicated to PMTCT, Barr and colleagues described the implementation of an Option B+ PMTCT program in Malawi (Abstract 82). Designed by the Malawian Ministry of Health, the program modified WHO Option B+ by offering antiretroviral therapy to all pregnant or breast-feeding women. Program implementation began in the third quarter of 2011, and data are presented through year-end 2012. From a programmatic perspective, the implementation of Option B+ resulted in the successful integration of antenatal and antiretroviral therapy programs, the decentralization of antiretroviral therapy programs and expansion into rural settings, and the complete replacement of sd nevirapine protocols with antiretroviral therapy. Quantitatively, a 49% increase in the total antiretroviral therapy coverage in known HIV seropositive pregnant women was demonstrated, from 13,910 women in the 2 quarters preceding program implementation to 20,687 women in the most recent 2 quarters of program implementation, which represents an almost 800% increase in the use of antiretroviral therapy in pregnant women. The authors also noted that 41% of those starting antiretroviral therapy were breast-feeding mothers and described this as an unexpected and "client-driven phenomenon."

In the same session, a South African study compared 3 programmatic strategies for uptake of PMTCT: standard of care (in which antenatal care and antiretroviral therapy are provided in separate settings); enhanced linkage (in which a lay counselor acts as a patient navigator to link patients to the antiretroviral therapy program); and an integrated approach (in which antiretroviral therapy and antenatal services are collocated at the same site). Not surprisingly, the integrated approach resulted in far higher rates of linkage to care and antiretroviral therapy initiation. Antiretroviral therapy initiation rates were 21% in the standard of care group, 49% in the enhanced linkage group, and 86% in the integrated approach group. Integration of care also resulted in a statistically significant reduction in time from antiretroviral therapy eligibility to time of antiretroviral therapy initiation: 29 days in the standard of care, 15 days in enhanced linkage, and 7 days in the integrated model (Abstract 83).

An analysis from the United Kingdom and Ireland compared rates of MTCT for 2 periods, 2000 to 2006 and 2007 to 2011 (Abstract 906). Analyzing data from more than 6000 women, the authors note a substantial decrease in MTCT across the 2 periods, from 1.28% in the early period to 0.68% in the later period. This decline in MTCT was accounted for by near universal use of antiretroviral therapy in pregnant women.

Timely HIV testing during pregnancy is an essential inflection point in the HIV care cascade. Using insurance claims, investigators calculated the percent coverage of HIV testing among commercially insured women who gave birth in the United States between 2009 and 2010 (Abstract 904). Extracting from a database of more than 20,000,000 women, 177,930 deliveries were identified. An insurance claim for HIV testing within 293 days before delivery was identified in 75.7% of women. No data on prevalence of HIV infection in this population was presented, and the authors noted that the study group may not be representative of the US female population. A study from rural Uganda estimated the incidence of HIV infection among pregnant women: 863 women who presented for nonemergent delivery with a prior seronegative HIV test at least 3 months prior to delivery were enrolled. Six new HIV diagnoses were made, yielding an incidence rate of 1.6 per 100 person-years, comparable to background rates in the population (Abstract 903).

Efficacy of PMTCT

Prevention of HIV transmission during breast-feeding is a crucial component of PMTCT efforts and overall child wellness goals. Fowler and colleagues presented 18-month follow-up results from HPTN 046 (Abstract 84LB). HPTN 046 is a large, randomized study comparing 6 months versus 6 weeks of infant nevirapine for prevention of postnatal HIV transmission. The study is being conducted in Zimbabwe, South Africa, Tanzania, and Kenya. All infants received 6 weeks of nevirapine after birth. At 6 weeks, 1505 HIV seronegative infants were randomized to continue nevirapine or receive placebo for a total of 6 months.

Women were instructed to exclusively breast-feed up to the 6-month point. In both arms, 29% of mothers were receiving antiretroviral therapy at randomization, and the median maternal CD4+ cell count was more than 500/μL. Self-reported adherence to study medication was 88% to 96%, and 95% of mothers reported cessation of breast-feeding at 12 months. At 18 months, data for the primary safety and efficacy end points were available for 679 infants randomized to extended nevirapine and 683 to placebo. No differences were seen in overall mortality or HIV infection–free survival between the arms. Postnatal transmission was observed in 2.2% of infants in the extended nevirapine arm and 3.1% in the placebo arm ($P = .28$). Statistically significantly higher rates of HIV transmission were observed in those women not receiving antiretroviral therapy. In women with a CD4+ cell count of above 350/μL who were not receiving antiretroviral therapy, transmission rates at 6 months were 0.7% in the extended nevirapine arm and 2.8% in the placebo arm ($P = .014$). Thirty-six percent of transmissions occurred before 6

months, and 18% occurred after reported cessation of breast-feeding, underscoring the risk conferred by early and abrupt cessation of breast-feeding in this study setting. No differences in rates of adverse events were observed between the arms.

The authors conclude that extended nevirapine is a safe and effective strategy for postnatal prevention of HIV transmission in women who are not on antiretroviral therapy. The strategy may be a bridge to universal implementation of maternal antiretroviral therapy.

Preliminary data from the French ANRS 12174 study were presented (Abstract 912). ANRS 12174 is a randomized, controlled study comparing the safety and efficacy of lamivudine-based with lopinavir/r–based prophylaxis in breast-fed infants of mothers deemed ineligible for antiretroviral therapy. The study is ongoing in Burkina Faso, Uganda, Zambia, and South Africa. Infant prophylaxis is administered for 12 months, during which mothers continue breast-feeding. Preliminary blinded data from 763 of the 1273 children enrolled show a total of 9 transmission events and an overall transmission rate of 1.3 per 100 child-years. The mortality rate thus far is reported to be 2.6 per 100 child-years. None of the deaths are attributable to HIV seroconversion or HIV-related disease. Six of the transmission events occurred after 6 months of breast-feeding. Although the study is ongoing, the authors note that the low rate of postnatal transmission observed is within the WHO target for reduction of breast-feeding transmission.

Data from the Kisumu Breastfeeding Study compared infant death rates in Kenyan women receiving PMTCT Option B with those receiving PMTCT Option B+ (Abstract 921). Data were collected prospectively between 2003 and 2009 in this open-label study. Maternal antiretroviral therapy discontinuation occurred in 82% of women in the Option B arm. The investigators found a statistically significant increase in risk of HIV transmission and infant death in the Option B arm compared with the Option B+ arm, 10.1% and 2.4%, respectively (P = .04).

A study of temporal trends in virologic failure among pregnant women receiving antiretroviral therapy in a European cohort showed reductions in virologic failure over time (Abstract 909). The authors analyzed data from 396 women who received a minimum of 28 days of antiretroviral therapy during pregnancy. Virologic failure was defined as any HIV-1 RNA level above 200 copies/mL at any point from conception to delivery. Between 2000 and 2001, virologic failure was observed in 34% of women, compared with 3% between 2010 and 2011. In a partially adjusted analysis, virologic failure was associated with use of an unboosted protease inhibitor (PI), younger age, previous deliveries, duration of HIV infection, as well as calendar year of delivery. Despite the high rates of viral resistance in the early analysis period, 63% of women with virologic failure subsequently achieved suppression.

A related analysis from Canada estimated the proportion of pregnant women who maintained virologic suppression to delivery (Abstract 908). Of 178 women with virologic suppression during pregnancy, 9.5% had a detectable HIV-1 RNA level (> 250 copies/mL) at delivery. In a multivariate analysis, only poor adherence was associated with loss of virologic control. Despite the surprisingly high rates of virologic failure reported in this study, no MTCT events occurred.

Safety and Complications of PMTCT

Sibiude and colleagues presented long-term teratogenicity data from more than 13,000 children enrolled in the French Perinatal Cohort study (Abstract 81). The analysis included women and their children enrolled since 1985 and represents approximately 70% of HIV-infected women in metropolitan France. Children who were uninfected at birth were followed up for 2 years, whereas infected children were followed up for 18 years. Of the total cohort, 370 women were exposed to efavirenz in the first trimester. Efavirenz exposure in the first trimester was not associated with an overall increase in birth defects. However, efavirenz exposure in the first trimester was associated with an increase in neurologic defects, with an aOR of 2.3 (95% CI, 1.1-9.1; P = .03). Four neurologic birth defects were observed: pachygyria, cerebral cyst, agenesis of the corpus callosum, and hydrocephaly. No neural tube defects were identified. All neurologic defects occurred in children exposed to efavirenz since conception. Zidovudine exposure in the first trimester was associated with an overall increased risk of a birth defect, with an aOR of 1.4 (95% CI, 1.1-1.8; P = .002). There was a statistically significant association between zidovudine exposure in the first trimester and congenital heart defects, with an aOR of 2.5 (95% CI, 1.6-4.2; P = .001); the majority of these were ventricular septal defects. Didanosine was associated with head and neck defects (aOR, 1.93; 95% CI, 1.1-3.3; P < .05). The investigators noted that the analysis did not control for maternal drug use. Referencing the recent change to WHO guidelines, the authors urged caution in the use of efavirenz in the first trimester and the ongoing need for surveillance of the benefits and risks of PMTCT.

A study conducted in Kisumu, Kenya, compared risk of birth defects and infant mortality among infants exposed to nevirapine versus nelfinavir (Abstract 924). Only women with a CD4+ cell count above 250/μL were included in the analysis. A total of 392 women and 401 births were included: 215 women received nevirapine and 177 women received nelfinavir. All women were treated with a zidovudine plus lamivudine nRTI backbone. Overall, there were 394 live births and 7 stillbirths (1.8%). Rates of preterm delivery and low birth weight were 12.2% and 9.6% of live births, respectively. No statistically significant differences were observed between nevirapine- and nelfinavir-exposed infants.

Expansion of PMTCT programs has been associated with the emergence of mutations associated with drug resistance. A study from Brazil showed high rates of these mutations in both antiretroviral therapy–naive and –experienced pregnant women (Abstract

905). Two hundred thirteen pregnant women presenting for care with a HIV-1 RNA level above 2000 copies/mL were included in the analysis; 77% were antiretroviral therapy–naive and 24% were primigravida. Drug resistance mutations were found in 10% of antiretroviral therapy–naive women and in 37% of antiretroviral therapy–experienced women. The K103N accounted for 79% of the mutations detected. Overall, 80% of antiretroviral therapy–naive women achieved an HIV-1 RNA level below 400 copies/mL at 34 weeks gestation, compared with 57% of antiretroviral therapy–experienced women. Suboptimal antiretroviral therapy in pregnancy is known to lead to the emergence of resistance. In a study from Thailand, zidovudine monotherapy was associated with a 16% rate of zidovudine-associated resistance mutations (Abstract 937).

Antiretroviral Therapy Resistance

In a symposium presentation entitled ARV Drug Resistance: Global Challenges, Hamers discussed the implications of antiretroviral resistance to global antiretroviral therapy success (Abstract 121). The presentation addressed a number of crucial issues in the emergence of drug resistance globally, including the implications of antiretroviral therapy scale-up on acquired and transmitted drug resistant virus; the impact of novel treatment strategies, including preexposure prophylaxis (PrEP), treatment as prevention, and early antiretroviral therapy initiation on the emergence of drug resistance mutations; and the implications of limited access to HIV-1 RNA level testing and sequencing technologies on resistance trends in low- and middle-income countries. Noting that antiretroviral therapy resistance has stabilized or decreased in resource-rich settings, Hamers attributed this trend to the availability of potent antiretroviral therapy, effective HIV-1 RNA level monitoring, widespread availability of resistance testing, and access to individualized second-line and salvage regimens.

Transmitted drug resistance (TDR) is an epidemiologic warning sign of future compromise to antiretroviral therapy efficacy. Since the rollout of antiretroviral therapy, aggregated data from East and southern Africa show an average annual rate of increase in TDR of 29% and 14%, respectively. This increase in resistance is driven mainly by NNRTI resistance. Data also suggest that TDR is associated with a doubled risk of future virologic failure.

Mathematical modeling has been used to predict the impact of antiretroviral therapy scale-up on TDR prevalence in Africa. Expansion of antiretroviral therapy treatment criteria to all patients with a CD4+ cell count below 500/µL is predicted to increase TDR prevalence to 19%. Nevertheless, a benefit-to-harm analysis favors antiretroviral therapy expansion. Treatment initiation based on a CD4+ cell count threshold of below 500/µL was modeled for 2 urban settings in Uganda and Kenya and found to be associated with 1 case of TDR for every 22 and 32 new cases of HIV infection averted, respectively (Abstract 1116). Acquired drug resistance mutations are also on the rise. Lack of timely identification of virologic failure, coupled with a paucity of second-line options, leads to accumulation of resistance in patients maintained on failing regimens. Hamers argued that large-scale expansion of antiretroviral therapy programs will result in progressively increasing rates of resistance, unless virologic monitoring, resistance sequencing, and second-line options become available concomitantly.

Acquired Drug Resistance

In a large study from Senegal, investigators calculated rates of resistance in the ANRS 1215 cohort (Abstract 592). Subjects included in the analysis initiated therapy with either an NNRTI- or an unboosted indinavir–based regimen, had a minimum of 6 months follow-up, and had at least 1 HIV-1 RNA measurement. Virologic failure was defined as 2 consecutive HIV-1 RNA level measurements above 1000 copies/mL; 366 subjects were included, of which 89% achieved virologic suppression. Cumulative risk of failure at 6 months, 12 months, and 24 months was 5%, 16%, and 25%, respectively. Resistance testing was available in 64% of subjects with virologic failure. NNRTI-associated mutations were noted in 77% of patients failing NNRTI-based therapy. PI-associated mutations were noted in 21% of those on a failing PI-based therapy, despite the observation that PI-based therapy was associated with a greater risk of virologic failure. The authors also provide data on the success of second-line regimens in those for whom the first regimen had failed: 81% achieved virologic suppression. However, at 6 months, 12 months, and 24 months, virologic failure was again noted in 18%, 20%, and 27%, respectively, of subjects on second-line therapy.

A similar study conducted in Namibia calculated the prevalence of resistance after 12 months of follow-up on an initial antiretroviral therapy (Abstract 593). Patients enrolled in treatment programs since 2009 and who had undergone pretreatment genotyping were included in the analysis. NNRTI-based therapy was prescribed to almost all participants. Of the 394 subjects enrolled, 80% remained on their initial antiretroviral therapy at 12 months; of these, 94% achieved virologic suppression. Of the total study population, 7% had resistance mutations at baseline and 5% of those with virologic failure at 12 months had detected resistance mutations. No PI resistance was noted, but high-level NNRTI resistance was prevalent. Virologic failure with resistance was associated with the presence of resistance mutations at baseline and strongly associated with markers of poor adherence.

Canadian researchers analyzed the prevalence of resistance mutations in previously suppressed patients who rebounded to low-level viremia, defined as an HIV-1 RNA level between 50 copies/mL and 1000 copies/mL. Two hundred patients with no baseline resistance mutations were included in the analysis. Approximately 5000 sequencing attempts were made. The success of sequencing increased with

HIV-1 RNA strata from 75% in the 51 copies/mL to 249 copies/mL strata to 90% in the 749 copies/mL to 1000 copies/mL strata. Mutations were found in 20% of patients. The most common mutation detected was M184V (16%), followed by K103N (10.5%). HIV-1 RNA strata did not predict the presence of mutations.

TDR

In an oral abstract session, investigators from the Centers for Disease Control and Prevention (CDC) presented data on TDR rates from 10 US surveillance sites (Abstract 149). Persons with newly diagnosed HIV infection between 2007 and 2010, with no prior history of antiretroviral treatment, and with viral sequencing evaluations available were included in the analysis. The surveillance sites included 6 states, mostly in the southern United States, and 4 municipalities. Of the 77,000 newly diagnosed cases reported to the CDC, sequencing data was available for 18,144 (23%). Overall, 16.2% of sequences harbored mutations. Single, dual, and triple class mutations were identified in 13.6%, 2.1%, and 0.5% of sequences, respectively. NNRTI mutations were most frequent, detected in 8.1% of specimens, followed by nRTI-associated mutations in 6.7% and PI-associated mutations in 4.5%. Seventy-two percent of NNRTI mutations were K103N. The most common nRTI mutations identified were M41L (24.8%), T69N (19.5%), and M184V (8.2%); transmitted resistance to tenofovir was minimal (0.9%). The investigators calculated an annual percentage change in rates of TDR. Statistically significant increases in single class resistance and NNRTI resistance were found, with an estimated annual percentage increase of 4.3% (P = .01) and 5.2% (P = .03), respectively.

Investigators from the HOPS (HIV Outpatient Study) analyzed trends in resistance between 1999 and 2011 among antiretroviral therapy–naive individuals undergoing commercial genotypic testing prior to antiretroviral therapy initiation (Abstract 615). Of 711 samples analyzed, 10.4% harbored major drug resistance mutations. Mutations associated with nRTIs were observed in 8.9%, with NNRTIs in 7.8%, and with PIs in 3.2% of samples. Of note, no temporal trends in prevalence of TDR were observed in the reported time period. A similar analysis was conducted in Spain (Abstract 619). Rates reported were lower overall than in the US data cited above, but similarly, the researchers did not detect any temporal trends in TDR prevalence. An analysis of TDR in Guatemala, Panama, and Nicaragua showed prevalence rates of 7.5%, 9.0%, and 10.1%, respectively (Abstract 617).

Increased rates of TDR over time were reported in a study of clinical samples obtained at a single center in New York City (Abstract 616). The patients were primarily immigrants with subtype B strains. A statistically significant increase in TDR from 9% (2000-2005) to 18% (2006-2011) was observed. Overall TDR rates were 15%. High TDR rates were also reported in an adolescent HIV clinic in New York City (Abstract 952b). There were 331 behaviorally infected adolescents, with duration of infection of less than 1 year, enrolled in the clinical program between 2007 and 2011. Genotypic analysis data were available for 64% of these patients prior to initiation of antiretroviral therapy. Prevalence of resistance mutations was 19%; NNRTI-associated, nRTI-associated, and PI-associated resistance mutations accounted for 64%, 21%, and 15%, respectively.

Transmission of multiple drug–resistant HIV strains has been reported previously. Authors from Spain report on a multi-nRTI– and NNRTI-resistant strain causing a cluster of infections in men who have sex with men (Abstract 618).

Drug Resistance Mutation Detection Techniques

A novel technique using a single-tube, allele-specific assay for detection of tenofovir and emtricitabine resistance mutations was presented in Abstract 597. The clinical application of this assay would be useful in determining eligibility for tenofovir and emtricitabine–based PrEP. The authors compared the results of the single tube, allele-specific assay to a PCR sequence–based assay. Of the 75 specimens analyzed, the single-tube assay showed a high sensitivity, detecting 100% of all relevant tenofovir and emtricitabine resistance mutations at codon 65, 98.7% at codon 184, and 92% at codon 70.

ANRS researchers reported on the operative characteristics of sequencing assays in dried blood spot (DBS) samples compared with paired plasma specimens (Abstract 606). Subjects included were those for whom their initial antiretroviral regimen was failing as indicated by an HIV-1 RNA level of above 1000 copies/mL. Sequencing was successful in 89 of 93 DBS samples. Sensitivity of the various assays used to sequence from DBS ranged from 82% to 93%. These findings suggest that resistance testing may become feasible within the constraints of existing laboratory infrastructures in RLSs.

Subtype- and Class-Specific Resistance Mutations

Investigators showed a decrease in darunavir-associated resistance mutations between 2006 and 2012 (Abstract 590). More than 78,000 specimens submitted to a commercial laboratory in the United States were analyzed. In 2006, 77.7% of specimens harbored no darunavir resistance mutations compared with 92.8% in 2012. The presence of more than 3 darunavir–associated resistance mutations were found in 7.5% of sequences in 2006 and in 2.6% in 2012. Among specimens with any resistance to PIs, presence of darunavir resistance mutations also decreased, as did phenotypic evidence of resistance to darunavir.

Data on integrase resistance from nearly 2000 sequences submitted to a commercial US laboratory were presented in Abstract 591. These clinical specimens were submitted specifically for InSTI resistance testing, suggesting clinical concern for InSTI failure. InSTI-associated resistance was observed in

25.6% of samples. InSTI-associated resistance was more frequent in older subjects and those with a higher resistance score to other classes of antiretrovirals ($P < .001$).

Investigators evaluated the ability of proviral *env* sequencing in virologically suppressed subjects to predict phenotypic tropism during viral rebound at treatment interruption (Abstract 586). Seventy-two subjects enrolled in 2 ACTG treatment interruption trials (ACTG 5102 and 5170) under went sequencing of the V1 through V5 regions while virologically suppressed. At time of treatment interruption, a commercial tropism assay was performed. Concordance between the proviral genotype assay results and phenotypic tropism assay results was 91.7%; sensitivity of genotype for predicting R5 tropism was 96.6% and specificity was 69.2%. In another study, mutations conferring resistance to maraviroc were assessed in 951 maraviroc treatment–naive individuals with R5 tropic virus by phenotype (Abstract 587). The investigators found genotypic evidence of resistance to maraviroc in 9.7% of subjects and suggested that genotypic analysis of tropism may overestimate phenotypic evidence of resistance to maraviroc.

Abstract 598 reports on the development of a standardized rule set for interpretation of resistance mutations in HIV-2. The tool is available at http://www.HIV-grade.de.

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6. The Challenge of Marginalization in the Fight against HIV, and the Resiliency of Individuals and Communities. Paul Semugoma.

15. MTCT: From Epidemic to Elimination. Lynne Mofenson.

16. HIV-1 Eradication Strategies: Design, Assessment, and Clinical Consequences. Robert Siliciano.

24LB. Long-acting Parenteral Formulation of GSK1265744 Protects Macaques against Repeated Intrarectal Challenges with SHIV. Chasity Andrews, A Gettie, K Russell-Lodrigue, L Moss, H Mohri, W Spreen, C Cheng-Mayer, Z Hong, M Markowitz, and D Ho.

25LB. A Tenofovir Disoproxil Fumarate Intravaginal Ring Completely Protects against Repeated SHIV Vaginal Challenge in Nonhuman Primates. James Smith, R Rastogi, R Teller, P Srinivasan, J Mitchell, J McNicholl, M Hendry, P Mesquita, P Kiser, and B Herold.

26LB. Pre-exposure Prophylaxis for HIV in Women: Daily Oral Tenofovir, Oral Tenofovir/Emtricitabine, or Vaginal Tenofovir Gel in the VOICE Study (MTN 003). Jeanne Marrazzo, G Ramjee, G Nair, T Palanee, B Mkhize, C Nakabiito, M Taljaard, J Piper, K Gomez Feliciano, M Chirenje, and VOICE Study Team.

27. No Excess in HIV Incidence after Stopping Oral Emtricitabine/Tenofovir Pre-exposure Prophylaxis: The iPrEx Trial. Robert Grant, J Guanira, S Buchbinder, C Mosquera, V Veloso, E Kallas, M Mehrotra, V McMahan, R Amico, D Glidden, and iPrEx Study Team.

28. Hormonal Contraception and Risk of HIV: An Analysis of Data from the Microbicides Development Programme Trial. Angela Crook, H Rees, G Ramjee, A Kamali, S Kapiga, M Chisembele, M Gafos, A Nunn1, R Hayes, and S McCormack.

30. Community-level Reductions in Estimated HIV Incidence: HIV Prevention Trials Network 043, Project Accept. Thomas Coates, S Eshleman, S Chariyalertsak, A Chingono, G Gray, J Mbwambo, L Richter, D Donnell, E Piwowar-Manning, M Kulich, and HPTN 043 Project Accept Study Team.

31. Which HIV Testing and Counseling Model Works Best in African Outpatient Departments? Results from the Strengthening HIV Test Access and Treatment Uptake Study. AD McNaghten, A Schilsky Mneimneh, T Farirai, N Wamai, M Ntiro, J Sabatier, N Makhunga-Ramfolo, S Mwanasalli, A Awor, J Moore, and Project STATUS Study Team.

33. Protective Effect of Hepatitis B Virus–active cART against Primary Hepatitis B Virus Infection. M Heuft, G van den Berk, T Smissaert, W Blok, R Regez, L Dijksman, and Kees Brinkman.

35. Pharmacokinetic Interactions of Darunavir/ritonavir, Efavirenz, and Tenofovir with the Hepatitis C Virus Protease Inhibitor Faldaprevir in Healthy Volunteers. J Sabo, Jens Kort, M Haschke, C Ballow, B Girlich, U Feifel, B Lang, M Schobelock, and M Elgadi.

36. High Early Virological Response with Telaprevir-Pegylated-Interferon-Ribavirin in Treatment-experienced Hepatitis C Virus Genotype 1/HIV Co-infected Patients: ANRS HC26 TelapreVIH Study. Laurent Cotte, J Braun, C Lascoux-Combe, C Vincent, S Pol, M-A Valentin, K Lacombe, D Nau, J-P Aboulker, J-M Molina, and ANRS HC26 Study Group.

37. ANRS-HC27 BocepreVIH Interim Analysis: High Early Virologic Response with Boceprevir + Pegylated Interferon + Ribivirin in Hepatitis C Virus/HIV Co-infected Patients with Previous Failure to Pegylated Interferon + Ribivirin. Isabelle Poizot-Martin, E Bellissant, L Piroth, A Renault, Y Quertainmont, E Rosenthal, L Alric, D Guyader, M Bourliere, J-M Molina, and ANRS-HC27 BOCEPREVIH Study Group.

38. 12 Weeks of ABT-450/Ritonavir, Non-nucleoside Inhibitor and Ribavirin Achieved SVR24 in >90% of Treatment-naïve Hepatitis C Virus GT1 Patients and 47% of Prior Non-responders. Eric Lawitz, D Cohen, F Poordad, K Kowdley, G Everson, B Freilich, D Jensen, M Heckaman, T Pilot-Matias, and B Bernstein.

39. Risk of Virologic Relapse in Hepatitis C Virus GT1-infected Subjects after 8, 12, and 24 Weeks of ABT-450/r + ABT-267 + ABT-333 + Ribavirin: Identifying Optimal Treatment Duration. Martin King, W Xie, L Larsen, D Cohen, T Podsadecki, and B Bernstein.

40LB. STARTVerso 4: High Rates of Early Virologic Response in Hepatitis C Virus Genotype 1/HIV Co-infected Patients Treated with Faldaprevir + Pegylated Interferon and Ribavirin. Douglas Dieterich, V Soriano, M Nelson, J Rockstroh, K Arasteh, S Bhagani, A Talal, C Tural, R Vinisko, and J Kort.

42. Increase in 2-LTR Circles after Raltegravir Intensification in HAART-suppressed Patients with High CD4 + T Cell Counts: A Randomized, Controlled Trial. Hiroyu Hatano, M Strain, R Scherzer, E Sinclair, S Palmer, M Busch, P Bacchetti, P Hsue, D Richman, and S Deeks.

43. Characterization of Non-induced HIV-1 Proviruses Dampens the Hope for HIV-1 Eradication. Ya-Chi Ho, L Shan, J Wang, N Hosmane, J Blankson, and R Siliciano.

47. Early ART Intervention Restricts the Seeding of the HIV Reservoir in Long-lived Central Memory CD4 T Cells. Jintanat Ananworanich, C Vandergeeten, N Chomchey, N Phanuphak, V Ngauy, R-P Sekaly, M Robb, N Michael, J Kim, N Chomont, and RV254/SEARCH 010 Study Group.

48LB. Functional HIV Cure after Very Early ART of an Infected Infant. Deborah Persaud, H Gay, C Ziemniak, YH Chen, M Piatak, T-W Chun, M Strain, D Richman, and K Luzuriaga.

50LB. The Safety and Effect of Multiple Doses of Vorinostat on HIV Transcription in HIV + Patients Receiving cART. J Elliott, A Solomon, F Wightman, M Smith, S Palmer, M Prince, J Watson, J Hoy, J McMahon, and Sharon Lewin.

52. HIV and SIV Pathogenesis at the Interface of Gut Mucosal Immune Defense and Microbiota. I Grishina, L Hirao, L Nagy, S Sankaran, A Baumler, M Marco, H Cheng, and Satya Dandekar.

53. Treating Microbial Translocation in Progressive HIV/SIV Infections. N Klatt, Z Klase, M Quinones, D Hazuda, M Miller, J Segre, J Lifson, E Haddad, J Estes, and Jason Brenchley.

54. The Enteric Virome in AIDS. S Handley, L Thackray, G Zhao, R Presti, J Brenchley, R Veazey, T Stappenbeck, D Wang, D Barouch, and Herbert Virgin.

55. Drivers of the HIV Epidemic in the Southern US. Adaora Adimora.

57. How Should We Spend Our Prevention Dollars? Carlos del Rio.

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59. HIV + Adults Are at Greater Risk for Myocardial Infarction, Non-AIDS Cancer, and End-stage Renal Disease, but Events Occur at Similar Ages Compared to HIV– Adults. Keri Althoff, C Wyatt, C Gibert, KA Oursler, D Rimland, M Rodriguez-Barradas, K McGinnis, M Skanderson, K Gebo, A Justice, for Veterans Aging Cohort Study.

60. Combined Effect of Interleukin-6 and D-dimer on the Risk of Serious Non-AIDS Conditions: Data from 3 Prospective Cohorts. Birgit Grund, J Baker, S Deeks, J Wolfson, D Wentworth, A Cozzi-Lepri, C Cohen, A Phillips, J Lundgren, J Neaton, and INSIGHT SMART/ESPRIT/SILCAAT Study Group.

62. Age and Noncalcified Coronary Plaque in the Multicenter AIDS Cohort Study. Wendy Post, L Jacobson, X Li, F Palella, L Kingsley, M Witt, T Brown, M Plankey, M Budoff, and J Margolick.

63. Increased Coronary Atherosclerotic Plaque Vulnerability Features on Computed Tomography Angiography among HIV + Subjects vs Matched HIV– Controls. M Zanni, J Lo, B Wai, B Shah, D Hark, E Marmarelis, S Abbara, and Steven Grinspoon.

64. Elevated Numbers of CD163+ Macrophages in Hearts of SIV + Rhesus Macaques with Cardiac Disease Are Decreased Using PA300. Joshua Walker, T Burdo, A Miller, K Misgin, M Sulciner, M McGrath, and K Williams.

65. Comparison of Aspirin Use and Incident Myocardial Infarction Rates in HIV+ and HIV– Patients in a Large US Healthcare System. Sujit Suchindran, S Regan, J Meigs, S Grinspoon, and V Triant.

66LB. Monocyte Activation, but Not T Cell Activation, Predicts Progression of Coronary Artery Calcium in a Contemporary HIV Cohort. Jason Baker, K Huppler Hullsiek, A Singh, E Wilson, K Henry, P Patel, J Brooks, H Hodis, M Budoff, I Sereti, for CDC SUN Study Investigators.

75LB. Prospective ART of Asymptomatic HIV + Controllers. Hiroyu Hatano, S Yukl, A Ferre, E Sinclair, P Hunt, P Bacchetti, M Busch, B Shacklett, J Wong, and S Deeks.

81. Birth Defects and ART in the French Perinatal Cohort, a Prospective Exhaustive Study among 13,124 Live Births from 1994 to 2010. Jeanne Sibiude, L Mandelbrot, S Blanche, J Le Chenadec, N Boullag-Bonnet, A Faye, C Dollfus, R Tubiana, B Khoshnood, J Warszawski, and ANRS CO1/CO10/CO11.

82. Uptake and Retention in Malawi's Option B+ PMTCT Program: Lifelong ART for All HIV+ Pregnant or Lactating Women. Beth Tippett Barr, E Mhango, L Tenthani, G Zomba, S Makombe, M Eliya, D Midiani, S Gupta, F Chimbwandira, and A Jahn.

83. Optimization of ART Initiation in Pregnancy through Linkage of Services vs Integration of ART into Antenatal Care. Landon Myer, V Manuelli, E Abrams, J McIntyre, and L-G Bekker.

84LB. Efficacy and Safety of 6 Months vs 6 Weeks Nevirapine for Prevention of Postnatal HIV-1 Transmission 18 Month Follow-up: HPTN 046 Trial. Mary Glenn Fowler, H Coovadia, E Brown, L Stranix-Chibanda, D Moodley, R Kisenge, P Richardson, S Zwerski, L Mofenson, and B Jackson.

86. Randomized Comparison of Stopping vs Continuing Cotrimoxazole Prophylaxis among 758 HIV + Children on Long-term ART: The Anti-Retroviral Research for Watoto Trial. Mutsa Bwakura-Dangarembizi, L Kendall, S Bakeera-Kitaka, P Nahirya-Ntege, R Keishanyu, A Kekitiinwa, E Natukunda, S Walker, D Gibb, A Prendergast, and ARROW Study Group.

90. HIV Prevalence and Awareness of Infection in 2008 and 2011 among Men Who Have Sex with Men: 20 US Cities. Cyprian Wejnert, B Le, J Zhu, T Finlayson, A Oster, A Smith, G Paz-Bailey, for NHBS Study Group.

91. Age and Racial Disparities in Per-contact Risk of HIV Seroconversion among Men Who Have Sex with Men: US. Hyman Scott, E Vittinghoff, and S Buchbinder.

92. Determinants of Mortality and Loss to Follow-up among Adult Patients in Pre-ART Care and on ART: Rwanda. Chloe Teasdale, V Mugisha, C Wang, H Nuwagaba-Biribonwoha, E Tayebwa, E Ingabire, P Ingabire, M Lahuerta, R Sahabo, and E Abrams.

93. ART Initiation Substantially Improves Retention among Patients Enrolling in Care: Lusaka, Zambia. M Li, Brad Guffey, P Musonda, I Sikazwe, A Mwango, B Chi, and J Stringer.

94. CD4 Count and Late Enrollment into HIV Care: Comparison between 2006 and 2011 in 4 Sub-Saharan African Countries. Susie Hoffman, Y Wu, W El-Sadr, M Lahuerta, H Nuwagaba-Biribonwoha, V Mugisha, M Hawken, E Chuva, D Nash, B Elul, and LSTART Team and Identifying Optimal Models of HIV Care Collaboration.

95LB. Home Assessment and Initiation of ART following HIV Self-Testing: A Cluster-Randomized Trial to Improve Linkage to ART in Blantyre, Malawi. Peter MacPherson, D Lalloo, A Choko, J van Oosterhout, D Thindwa, E Webb, B Squire, S Makombe, R Hayes, and E Corbett.

96. Population HIV Viral Load Estimate in Swaziland: Assessing ART Program Effectiveness and Transmission Potential. Jessica Justman, T Ellman, D Donnell, Y Duong, J Reed, G Bicego, P Ehrenkranz, L Wang, N Bock, and R Nkambule.

97. Molecular Characterization of the Source of New Infections in a High-risk Population in Uganda: Implications for Test and Treat as Prevention. Chris Parry, J Levin, J Nazziwa, G Asiki, J Mpendo, H Njai, J Seeley, A Kamali, L Nieslen, and PK Kaleebu.

99LB. Comparative Study of Tenofovir Alafenamide vs Tenofovir Disoproxil Fumarate, Each with Elvitegravir, Cobicistat, and Emtricitabine, for HIV Treatment. Andrew Zolopa, R Ortiz, P Sax, I Brar, R Elion, H Wang, C Callebaut, S Ramanathan, M Fordyce, and S McCallister.

100. Safety and Antiviral Activity of MK-1439, a Novel NNRTI, in Treatment-naïve HIV+ Patients. Matt Anderson, J Gilmartin, M Robberechts, I De Lepeleire, E Tetteh, Y Guo, D Schurman, F Wagner, J Wagner, and J Butterton.

105. Potent Antiviral Activity of 2nd Generation Maturation Inhibitors Against Bevirimat-resistant Polymorphic HIV-1 Isolates. E Urano, S Ablan, D Martin, T Nitz, E Freed, and Carl Wild.

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107. Interferon-inducible Siglec, CD169, Is the Mature Dendritic Cell Receptor Essential for HIV-1 Trans-infection. W Blay Puryear, H Akiyama, S Geer, N Ramirez, X Yu, B Reinhard, and Rahm Gummuluru.

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113. What Have the Epidemiological Studies Taught Us about Hormonal Contraceptives and HIV-related Risks? Chelsea Polis and R Heffron.

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140. Substantial Burden of Non-AIDS Cancers in Persons with HIV: Early Results from a Computerized HIV and Cancer Registry Match in Pune, India. Sheela Godbole, K Nandy, M Gauniyal, S Koyande, P Virgo, K Bhatia, R Paranjape, A Risbud, S Mbulaiteye, and R Mitsuyasu.

141. Timing and Predictors of Cancer Incidence following Initiation of ART: Centers for AIDS Research Network of Integrated Clinical Systems, 1996-2011. Elizabeth Yanik, S Napravnik, S Cole, C Achenbach, S Gopal, D Dittmer, M Kitahata, M Mugavero, M Saag, J Eron, and Ctr for AIDS Res Network of Integrated Clin Systems.

144. ART Initiation within the First 2 Weeks of Cryptococcal Meningitis Is Associated with Higher Mortality: A Multisite Randomized Trial. David Boulware, D Meya, C Muzoora, M Rolfes, K Huppler Hullsiek, A Musubire, K Taseera, H Nabeta, C Schutz, G Meintjes, and Cryptococcal Optimal ART Timing Trial.

146. Comparative Performance of Rapid Urinary Lipoarabinomannan Assays and Xpert MTB/RIF in HIV+ TB Suspects: Uganda. Maunank Shah, W Ssengooba, D Armstrong, L Nakiyingi, M Holshouser, J Ellner, M Joloba, Y Manabe, and S Dorman.

147LB. A Multicentre Randomized Clinical Trial to Evaluate High-dose Rifapentine with a Quinolone for Treatment of Pulmonary TB: The RIFAQUIN Trial. Amina Jindani, M Hatherill, S Charalambous, S Mungofa, S Zizhou, J van Dijk, J Shepherd, P Phillips, A Nunn, D Mitchison, and RIFAQUIN Trial Team.

148LB. What Is the "Right" Dose of Rifampin? Martin Boeree, A Diacon, R Dawson, A Venter, J du Bois, K Narunsky, M Hoelscher, S Gillespie, P Phillips, R Aarnoutse, and PanACEA Consortium.

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152. Renal Insufficiency among Women Treated with Tenofovir/Emtricitabine/Lopinavir/Ritonavir or Tenofovir/Emtricitabine/Nevirapine. A Mwafongo, K Nkanaunena, Mina Hosseinipour, S Lockman, M Hughes, J Currier, and ACTG 5208.

153LB. Omitting NRTI from ARV Regimens Is Not Inferior to Adding NRTI in Treatment-experienced HIV+ Subjects Failing a Protease Inhibitor Regimen: The ACTG OPTIONS Study. Karen Tashima, L Smeaton, A Andrade, J Eron, C Fichtenbaum, R Gandhi, V Johnson, K Klingman, K Hollabaugh, R Haubrich, and A5241 Study Team.

154LB. Simeprevir with Pegylated Interferon/Ribavirin in Patients Co-infected with Chronic Hepatitis C Virus and HIV-1: Week-24 Interim Analysis of the TMC435-C212 Study. Douglas Dieterich, J Rockstroh, C Orkin, F Gutierrez, M Klein, J Reynes, W Jessner, O Lenz, M Peeters, and M Beumont-Mauviel.

155LB. Suppression of Viral Load through 4 Weeks Post-Treatment Results of a Once-daily Regimen of Simeprevir + Sofosbuvir with or without Ribavirin in Hepatitis C Virus GT 1 Null Responders. Eric Lawitz, R Ghalib, M Rodriguez-Torres, Z Younossi, A Corregidor, I Jacobson, K Callewaert, W Symonds, G Picchio, and K Lindsay.

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157LB. High Efficacy of Sofosbuvir with Weight-based Ribavirin for 24 Weeks in Difficult-to-Treat Patients. Anu Osinusi, D Bon, E Herrmann, G Teferi, R Talwani, H Masur, W Symonds, J McHutchison, A Fauci, S Kottilil, and NIAID SPARE Study Team.

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165. Viral Load Measures: Patients, Populations, and Interpretations. Irene Hall.

170aLB. Impact of Interleukin-7 and Raltegravir + Maraviroc Intensification on Total HIV DNA Reservoir: Results from ERAMUNE 01. Christine Katlama, S Lambert, L Assoumou, L Papagno, F Lecardonnel, G Tambussi, B Clotet, M Youle, D Costagliola, B Autran, and ERAMUNE-01 Study Group.

171LB. Absent HIV-specific Immune Responses and Replication-competent HIV Reservoirs in Perinatally Infected Youth Treated from Infancy: Towards Cure. Katherine Luzuriaga, YH Chen, C Ziemniak, G Siberry, M Strain, D Richman, T-W Chun, C Cunningham, and D Persaud.

173LB. Multifocal Detection of HIV-1 RNA in Lymphatic Tissues during Early Viral Recrudescence after Treatment Interruption. Meghan Rothenberger, M Stevenson, G Beilman, J Chipman, A Khoruts, C Fletcher, C Reilly, S Wietgrefe, A Haase, and T Schacker.

179LB. Dolutegravir vs Raltegravir in ART-experienced, Integrase-naïve Subjects: 24-Week Interim Results from SAILING (ING111762). Anton Pozniak, H Mingrone, A Shuldyakov, C Brites, J Andrade, D Hagins, C Beltran Buendia, D Dorey, S Griffith, and S Min.

180LB. SECOND-LINE: Ritonavir-boosted Lopinavir with 2-3N(t)RTI or Raltegravir in HIV+ Subjects Virologically Failing 1st-line NNRTI/2N(t)RTI. Mark Boyd and SECOND-LINE Study Team.

182LB. Efficacy and Safety of Maraviroc to Prevent Immune Reconstitution Inflammatory Syndrome in High-risk Subjects Initiating ART: 24-Week Results of a Randomized, Placebo-controlled Trial. Juan Sierra-Madero, A Tierney, M Rassool, L Azzoni, I Sereti, J Andrade, L Mosqueda-Gomez, A Pineirua, I Sanne, M Lederman, and CADIRIS Study Team.

186LB. Effect of Statins on Immune Activation and Inflammation in HIV+ Subjects on ART: A Randomized Placebo Controlled Trial. Grace McComsey, Y Jiang, S Debanne, B Clagett, J Robinson, D Labbato, N Storer, M Lederman, and N Funderburg.

187LB. Pitavastatin 4 mg Provides Greater Low-density Lipoprotein Cholesterol Reduction Compared to Pravastatin 40 mg over 12 weeks of Treatment in HIV+ Adults with Dyslipidemia. Craig Sponseller, R Morgan, S Campbell, J Aberg, and M Thompson.

188LB. Safety and Pharmacokinetics of PA-824, an Investigational Anti-TB Drug, and Co-administered Efavirenz, among Healthy Subjects: ACTG Study A5306. Kelly Dooley, A Luetkemeyer, J-G Park, R Allen, D Sutherland, F Aweeka, S Koletar, Y Cramer, J Bao, D Haas, and A5306 Study Team.

264. Endothelial Activation Biomarkers Increase after HIV-1 Acquisition, and Soluble VCAM-1 Levels at Set Point Predict Disease Progression and Mortality. Susan Graham, N Rajwans, K Tapia, W Jaoko, B Estambale, S McClelland, J Overbaugh, and C Liles.

285. TLR8 Ligands Inhibit HIV Infection of Macrophages through a Vitamin D and Cathelicidin Dependent Autophagic Mechanism. Grant Campbell and S Spector.

344. The Impact of Male Circumcision on the Penis Microbiome: Analyses from Rakai, Uganda. Cindy Liu, B Hungate, A Tobian, D Serwadda, R Lester, G Kigozi, R Galiwango, M Wawer, R Gray, and L Price.

345. Enhanced Penile Skin Barrier Function in Circumcised Men and Implications of HIV Transmission. Minh Dinh, R Veazey, and T Hope.

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898. Unmet Need for Family Planning, Contraceptive Failure, and Unintended Pregnancy among Women Living with HIV Infection: Zimbabwe. Sandra McCoy, R Buzdugan, L Ralph, A Mushavi, A Mahomva, C Watadzaushe, J Dirawo, C Frances, and N Padian.

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