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Topics in Antiviral Medicine™

A publication of the IAS–USA

Highlights of the 19th Conference on Retroviruses and Opportunistic Infections

Topics in Antiviral Medicine™

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International Antiviral Society–USA

Topics in Antiviral Medicine™

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Announcements

Topics in
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Continuing Medical Education

The articles in this issue are associated with CME credit.

Instructions

This journal-based continuing medical education (CME) activity provides a review of advances in the treatment of HIV and hepatitis C virus (HCV) infection. It offers a maximum of 8 CME credits. To complete the activity, the learner is instructed to:

- Read the articles
- Review a selection of the references
- Reflect on how the information might be applied to clinical practice
- Complete the posttest and CME claim form and send both to the IAS–USA office.

Learning Objectives

On completion of this activity, the learner will be able to describe the important new data presented at the 19th CROI and the potential clinical implications for patients in the areas of:

- Pathogenesis of HIV disease
- Vaccine research
- Epidemiology of HIV and prevention efforts
- Antiretroviral therapy: new drugs and new strategies, complications, and concurrent infections

Accreditation Statement

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

The IAS–USA designates this journal-based CME activity for a maximum of 8 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Intended Audience

This activity is intended for physicians involved in the care of patients infected with HIV, HCV, or other viruses. It is also relevant to nurse practitioners, physician assistants, nurses, and other health professionals who provide care for people with viral diseases.

Conflicts of Interest and Financial Disclosures

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Posttest Questions

Check the box next to the best answer to each of the questions below. To earn CME credit, you must receive a passing score of 80% or more correct.

1. What proportion of HIV–infected persons in the United States have fully suppressed viral loads, according to the latest Centers for Disease Control and Prevention (CDC) data?

- ❑ **A.** 88%
- ❑ **B.** 67%
- ❑ **C.** 43%
- ❑ **D.** 28%
- ❑ **E.** 11%

2. Which of the following is the leading hypothesis to explain disparate results in different preexposure prophylaxis (PrEP) and microbicide efficacy trials?

- ❑ **A.** Poor statistical power in the negative studies
- ❑ **B.** High rates of loss to follow-up in the negative studies
- ❑ **C.** Poor drug adherence in the negative studies
- ❑ **D.** Toxicity of oral and topical tenofovir on vaginal tissue in the negative studies
- ❑ **E.** Overestimates of PrEP efficacy in the positive studies

3. For men who have sex with men (MSM), serosorting (having unprotected sex only with partners of the same perceived HIV serostatus) is:

- ❑ **A.** As risky as 100% condom use
- ❑ **B.** Twice as risky as 100% condom use
- ❑ **C.** 10 times as risky as 100% condom use
- ❑ **D.** Not associated with harm for HIV-infected men
- ❑ **E.** Associated with an increased risk of bacterial sexually transmitted infections (STIs), only among HIV-infected men

4. Which of the following statements about HIV testing is **true**?

- ❑ **A.** Home self-testing for HIV is associated with an increase in high-risk sexual behavior
- ❑ **B.** Home self-testing for HIV is associated with a decrease in high-risk sexual behavior
- ❑ **C.** Patients newly diagnosed with HIV are as likely as partner notification services to notify previous partners of their HIV serostatus
- ❑ **D.** Newly diagnosed patients are more likely than partner notification services to notify previous partners of their HIV serostatus, but only if Internet tools are available
- ❑ **E.** Learning of one's own HIV-seropositive status, without regard to disclosure interventions, has been shown to be the single biggest factor in reducing unprotected sex between serodiscordant partners

5. Which of the following statements about HIV-related disparities is **true**?

- ❑ **A.** In the United States, African American MSM report fewer sex partners and less drug use than white MSM
- ❑ **B.** In the United States, African American MSM have higher rates of sexual concurrency than white men
- ❑ **C.** In the United States, early antiretroviral therapy initiation rates are similar across races
- ❑ **D.** Globally, HIV incidence rates appear to be decreasing more rapidly in women than in men
- ❑ **E.** Globally, HIV prevalence rates appear to be decreasing more rapidly in women than in men

6. An increased risk of stroke in patients with HIV infection is associated with:

- ❑ **A.** Detectable levels of HIV RNA
- ❑ **B.** Latest CD4+ count less than 100 cells/μL
- ❑ **C.** NNRTI use
- ❑ **D.** Cytomegalovirus (CMV) disease
- ❑ **E.** A and B
- ❑ **F.** A, B, C, and D

7. Adding a hepatitis C virus (HCV) protease inhibitor (PI) to pegylated interferon/ribavirin in HCV/HIV-1-coinfected, HCV-treatment-naive patients increased sustained virologic response (SVR, or cure of HCV) by approximately what percentage?

- ❑ **A.** 5%
- ❑ **B.** 10%
- ❑ **C.** 30%
- ❑ **D.** 50%
- ❑ **E.** PIs cannot be used in HIV-coinfected patients due to drug–drug interactions

8. In pharmacokinetic studies of healthy volunteers, which of the following antiretroviral agents did **not** substantially alter plasma concentrations when coadministered with the HCV PI boceprevir?

- ❑ **A.** Raltegravir
- ❑ **B.** Ritonavir-boosted (/r) darunavir
- ❑ **C.** Lopinavir/r
- ❑ **D.** Nevirapine
- ❑ **E.** Atazanavir/r

9. Low 25-hydroxyvitamin D (25[OH]D) levels were reported in association with all of the following except:

- ❑ **A.** Lower CD4+ cell counts
- ❑ **B.** Higher levels of inflammatory markers
- ❑ **C.** Increased carotid intima-media thickness (IMT) in children
- ❑ **D.** Mortality in resource-limited settings

10. Which of the following statements about the rapid mycobacterial lipoarabinomannan test Determine TB-LAM is correct?

- ❑ **A.** The test can be used on cerebrospinal fluid (CSF)
- ❑ **B.** The test is more sensitive at higher CD4+ cell counts
- ❑ **C.** The test can be used on urine
- ❑ **D.** The test must be used on specimens that already demonstrate mycobacterial growth
- ❑ **E.** The test detects rifampin resistance

11. "Positive selection" is used to describe:

- ❑ **A.** Modulation of viral replication by cell-mediated immunity
- ❑ **B.** Modulation of viral replication by humoral immunity
- ❑ **C.** Selective pressure on cellular genes by viral pathogenicity
- ❑ **D.** Impact of antiretroviral drugs on cellular gene expression

12. SAMHD1 is a newly identified antiviral restriction that is counteracted by:

- ❑ **A.** Vif
- ❑ **B.** Vpu
- ❑ **C.** Reverse transcriptase
- ❑ **D.** Vpx

13. TRIM5α is a species-specific antiviral restriction that targets:

- ❑ **A.** Integrase
- ❑ **B.** Reverse transcriptase
- ❑ **C.** Capsid
- ❑ **D.** Envelope

14. Which drug is being used to reactivate viral latency in patients?

- ❑ **A.** Vorinostat
- ❑ **B.** Raltegravir
- ❑ **C.** Darunavir
- ❑ **D.** Topiramate

15. SAMHD1 is a myeloid cell restriction that antagonizes viral replication by:

- ❑ **A.** Reducing deoxynucleotide triphosphate levels in the cell
- ❑ **B.** Blocking envelope-CD4 interaction
- ❑ **C.** Targeting viral capsids to endosomes
- ❑ **D.** Inducing methylation of the viral genome

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❒ ≤1 ❒ 1.5 ❒ 2 ❒ 3 ❒ other _____

Evaluation

Please complete the following evaluation form for this journal activity:

	Excellent	Very Good	Good	Fair	Poor
Please rate the activity in terms of meeting the stated learning objectives (see p. 22 for objectives)	❍	❍	❍	❍	❍
Please rate the extent to which the information presented was supported by the evidence	❍	❍	❍	❍	❍
Please rate the overall quality of the article	❍	❍	❍	❍	❍
Please rate the activity's freedom from commercial bias	❍	❍	❍	❍	❍
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Please list 3 specific measurable changes you will make in your practice based on the information presented in the article:

1. _____
2. _____
3. _____

Other comments (please feel free to comment on any aspect of *Topics in Antiviral Medicine*):

_____

_____

What percentage of your patients has HIV infection?
❒ 0% ❒ 1%–10% ❒ 11%–25% ❒ 26%–50% ❒ 51%–75% ❒ 76%–90% ❒ 91%–100%

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

What percentage of your patients are members of an underrepresented minority group?
❒ 0% ❒ 1%–10% ❒ 11%–25% ❒ 26%–50% ❒ 51%–75% ❒ 76%–90% ❒ 91%–100%

Are you a member of an underrepresented minority group? ❒ Yes ❒ No

Cases on the Web

www.iasusa.org/cow

Cases on the Web (COW) is a series of case-driven continuing medical education activities sponsored by the IAS–USA. The *COW* program was created to offer convenient online access to top-quality education in the management of HIV and other viral infections.

NEW Prevention of Mother-to-Child Transmission in Highly Treatment-Experienced HIV-Infected Women

Theresa Barton, MD, and Laura N. Armas-Kolostroubis, MD
CME Credit Available: 1.25 *AMA PRA Category 1 Credits*™
Level: Advanced

The use of antiretroviral therapy and prophylaxis has dramatically reduced HIV transmission to infants. However, ongoing use of antiretroviral agents can lead to increases in viral resistance, especially as women are switched to second-line or third-line treatment regimens. Dr Barton and Dr Armas-Kolostroubis address maintaining low perinatal transmission rates in the presence of resistant HIV infection, which requires knowledge of recommendations for treatment and prophylaxis in pregnant women with drug resistance as well as safety of alternative agents in neonates.

NEW Sexually Transmitted Infections in the HIV-Infected Patient

Linda M. Gorgos, MD, MSc
CME Credit Available: 1.75 *AMA PRA Category 1 Credits*™
Level: Advanced

Sexually transmitted infections (STIs) among HIV-infected persons are an important source of morbidity that impacts personal and public health. Effective detection includes routine assessment of sexual-risk behavior and regular screening for STIs regardless of symptoms. Dr Gorgos addresses a comprehensive approach to treatment of infected individuals and their partner(s) and discusses emerging challenges, including the management of gonococcal infections in the context of rising antimicrobial resistance.

NEW Drug Interactions With Medications for Treating Hepatitis C Virus Infection

John J. Faragon, PharmD, BCPS
CME Credit Available: 1.5 *AMA PRA Category 1 Credits*™
Level: Advanced

The availability of boceprevir and telaprevir, each approved in 2011 by the FDA, has led to increased successful response rates in treating hepatitis C virus (HCV) infection. Dr John Faragon discusses the effects of HCV protease inhibitors (PIs) and other drugs on the cytochrome P450 enzyme system, outlines strategies for preventing and managing interactions between HCV PIs and select coadministered drugs used in primary care settings, and provides sources of information about drug interactions between HCV drugs, HIV antiretroviral drugs, and selected other drugs.

Preexposure Prophylaxis for HIV Infection

Jason R. Faulhaber, MD
CME Credit Available: 1.5 *AMA PRA Category 1 Credits*™
Level: Advanced

There may finally be a viable breakthrough in the prevention of new HIV infections, as data from recent studies have demonstrated. These studies evaluated the use of preexposure prophylaxis (PrEP) as oral medication or topical microbicide to reduce the risk of HIV acquisition. Dr Jason Faulhaber describes the role of health care practitioners in altering the future of HIV transmission.

Osteomalacia and Osteoporosis in the HIV-infected Patient

Michael Yin, MD, MS, and Emily Stein, MD, MS
CME Credit Available: 1.5 *AMA PRA Category 1 Credits*™
Level: Advanced

The incidence of age-related comorbidities affecting bone mineral density has increased among HIV-infected individuals. HIV primary care practitioners will need to learn about the effects of antiretroviral drugs on vitamin D levels, bone metabolism, and the diagnosis and management of osteomalacia and osteoporosis. Dr Michael Yin and Dr Emily Stein describe the differences between these disease processes and the challenge of treating them.

CME CREDIT

These internet enduring material activities have been approved for *AMA PRA Category 1 Credit*™.

COMING SOON

Look for these new *Cases on the Web* activities in coming months.

- **Novel HIV-1 Resistance and Tropism Testing**—When available, HIV drug-resistance testing should be used to guide the selection of an optimal antiretroviral regimen. Technologic advances in HIV sequencing and sequence detection have revolutionized the study of antiretroviral drug resistance and HIV diversity, and are increasingly moving from the laboratory to clinical practice.
- **Management of Chronic Hepatitis C in Advanced Liver Disease**—Hepatitis C virus is a leading cause of chronic liver disease worldwide. The disease is largely asymptomatic until advanced liver disease ensues, and patients are often diagnosed after years of infection. Newer treatments offer a higher chance of cure, but may be challenging and sometimes contraindicated in patients with advanced disease.

For information about *Cases on the Web*, please contact the IAS–USA.
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Review of Basic Science Advances in HIV

Mario Stevenson, PhD

The Conference on Retroviruses and Opportunistic Infections (CROI) is held annually to provide a forum for scientists to hear the most recent advances in the field of HIV and AIDS research. Although the conference has a primary mission to showcase advances in the prevention and management of HIV-1 infection and opportunistic infections (in particular, tuberculosis and hepatitis C virus [HCV]), there continues to be a strong basic research component. Research on cellular factors that influence the interplay between the virus and the host cell, and especially, cellular factors that antagonize viral replication, had the greatest presence at the conference. In the area of retroviral pathogenesis, research on viral reservoirs and mechanisms of viral persistence in the face of antiretroviral therapy generated considerable interest. Research on mechanisms of viral persistence is beginning to reveal strategies, some of which were the focus of presentations at CROI, to eliminate long-lived viral reservoirs.

Cellular Restrictions

In his plenary lecture, Emerman discussed how primate lentiviruses, including HIV-1 and HIV-2/simian immunodeficiency virus (SIV), have been shaped through evolutionary conflict with their primate hosts (Abstract 19). In the last century, HIV-1 has been acquired from chimpanzees at least 4 times and humans have acquired HIV-2 at least 8 times from sooty mangabeys. Therefore, Emerman focused his discussion on why humans are infected with some lentiviruses and not others, and how lentiviruses that infect humans have adapted to their human hosts.

Emerman's research has focused on ancient viral pathogens and how their antiviral defenses deal with modern viruses. These antiviral defenses are proteins that are encoded by primates. These include APOBEC 3, SAMHD 1, and tetherin. APOBEC 3 and SAMHD 1 act on the reverse transcription step of viral replication, but at different levels. APOBEC 3 deaminates viral complementary DNA (cDNA), rendering it incompetent to serve as a template for production of functional viral transcripts and proteins. SAMHD 1 is a nuclear protein that shuttles into the cytoplasm and reduces nucleotide pools to render the cell poorly permissive for reverse transcription.

Tetherin acts at the site of viral budding and interferes with the detachment of the maturing virus particle from the surface of the infected cell. Viruses have evolved evasion strategies to circumvent cellular defenses such as tetherin and establish infection within the host cell. Emerman used the "arms race" as an analogy to describe the conflict between the antiviral factor and the virus-encoded antagonist. This conflict results in rapid evolution of both cellular defense factors and the viral antagonists of those factors. Over generations, host escape from the viral antagonist essentially neutralizes the ability of the virus to protect itself from the host-encoded defense factor. This forces a viral readaptation that allows the viral antagonist to once again neutralize the host defense factor.

In the absence of viral infection, the antiviral gene does not acquire mutations because it is not under selective pressure. However, the presence of a new virus forces the accumulation of mutations that influence the interaction with the viral antagonist. This process, by which viral infection drives polymorphisms within cellular genes, is referred to as positive selection. Emerman described studies that cloned genes from primate lentiviruses and antiviral genes representing 30 million years of viral and antiviral evolution. These viral and cellular genes were then subjected to functional analysis including antiviral activity and ability to neutralize cellular defense proteins. This analysis allowed an estimation of when the virus entered the primate lineage, how acquisition of an antiviral gene influenced the fitness of the host, and how the virus evolved to adapt to its new host. Using APOBEC 3DE, which is poorly active against HIV-1, as an example, Emerman was able to determine the timing of an ancient viral infection occurring between 2 million to 5 million years ago. The positive selection of host antiviral genes can be used to gauge whether a virus is imparting some fitness cost on the host. For example, although SIV from African green monkeys (SIV_{agm}) is considered nonpathogenic, the ongoing adaption between APOBEC 3G and SIV Vif indicates that the virus is not benign in its host and that there is a fitness disadvantage as a consequence of the infection.

Finally, Emerman discussed how his evolutionary analysis can be used to provide insight into the adaption of a virus to a new host. For example, HIV-1 Vpu antagonizes the antiviral action of tetherin. Chimpanzee SIV (SIV_{cpz}), the immediate ancestor of HIV-1, encodes a Vpu protein that does not counteract tetherin; other SIV lineages, including sooty mangabey SIV (SIV_{sm}), do not contain Vpu, but counteract tetherin via the Nef accessory protein. Although SIV Nef could counteract tetherin in chimpanzees, on transfer to humans, SIV Nef was unable to neutralize human tetherin—the site of its interaction had been deleted during human evolution. Therefore, HIV-1 altered Vpu in the transmembrane domain so that SIV

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Nef could interact with and neutralize tetherin. This occurred only in pandemic (group M) HIV-1 and not in nonpandemic (group O) HIV-1, indicating that the current epidemic may be explained in part by changes in the transmembrane domain of Vpu that allow HIV-1 to neutralize tetherin.

Viruses adapt to the new host not only by evolving a new function within an existing gene (such as the case with vpu and HIV-1) but also by evolving a new viral gene to combat a host restriction. HIV-2, macaque SIV (SIV_{mac}), and SIV_{sm} harbor a *vpx* gene that is not contained within HIV-1 or SIV_{cpz} or gorilla SIV (SIV_{gor}) lineages. Recently, *vpx* has been demonstrated to degrade a cellular antagonist called SAMHD 1. SAMHD 1 limits infection of myeloid cells (dendritic cells and monocytes) by depleting deoxynucleotide triphosphate (dNTP) pools, thereby limiting reverse transcription of the virus. Although HIV-2 and SIV_{sm} lineages encode a Vpx, HIV-1 does not. Therefore, in the ancestral primate lentivirus that gave rise to the HIV-1 and HIV-2 predecessors, the ancestral *vpr* gene acquired the ability to degrade SAMHD 1.

Further along the evolutionary pathway, the HIV-2 predecessor acquired a new gene that specialized in its ability to degrade SAMHD 1. Although no Vpx-like activity has so far been detected in HIV-1, this virus retains the ability to infect macrophage without the apparent ability to degrade SAMHD 1. In summary, the conflict between lentiviruses and their hosts involves antagonism of viral infection by cellular defenses and neutralization of those defenses by viral accessory proteins. Viruses adapt to selective evolution of host cell defenses by acquiring a new gene with specialized ability to counteract the host defense or by adapting to be able to neutralize the cellular defense.

Research in the area of antiviral restrictions has accelerated in pace with the recent identification of a novel antiviral restriction that selectively acts to block viral reverse restriction in myeloid-lineage cells. In the past year, the research groups of Benkirane[1] and Skowronski[2] independently identified SAMHD1 as the cellular target of the Vpx protein encoded by HIV-2 and most SIV. As discussed in the symposium on host cell factors, SAMHD 1 is a newly discovered antiviral restriction that specifically antagonizes lentivirus replication in myeloid cells including monocytes and dendritic cells (Abstract 63). In the absence of Vpx, infection of primary lymphocytes and T-cell lines is not affected. However, infection of these myeloid cells is absolutely dependent on a functional Vpx and in its absence, viral replication is blocked at the reverse transcription step.

Vpx (like Vpr) is packaged within virions. Therefore, it is clear that the Vpr and Vpx proteins act at an early stage in viral replication before de novo synthesis of viral proteins. In earlier work by Sharova and colleagues[3] heterokaryon analysis in which permissive HeLa cells were fused with nonpermissive macrophages indicated that Vpx was counteracting a dominant-negative restriction. This research provided the impetus for studies to identify the Vpx-associated restriction. SAMHD 1 appears to have biologic properties that underscore the belief that it is the restriction targeted by Vpx. For example, SAMHD 1 is degraded in the proteasome in the presence of Vpx. Silencing of SAMHD 1 increases infection of nonpermissive cells. Expression of SAMHD 1 in permissive cells rendered them nonpermissive to HIV-1 infection. SAMHD 1 is a deoxynucleoside triphosphate triphosphohydrolase and mutations in this gene have previously been shown to be associated with Aicardi-Goutières Syndrome (AGIS). SAMHD 1 appears to restrict infection by depleting the intracellular pool of deoxynucleoside triphosphates, which, in the presence of Vpx, is increased. Presumably, a reduction in intracellular dNTP levels by SAMHD 1 leads to a less permissive environment for reverse transcription of viral cDNA.

The restrictive activities of SAMHD 1 have been conserved throughout the evolutionary history of primates. Degradation of SAMHD 1 by Vpx appears to be species-specific. For example, Vpx from red-capped mangabey SIV (SIV_{rcm}) is unable to degrade human SAMHD 1 but efficiently degrades rhesus SAMHD 1. The cellular differentiation state appears to be essential for the Vpx phenotype and SAMHD 1 restriction activity appears to be specific for differentiated, nondividing cells. All of the biochemical and biologic data obtained to date suggest that SAMHD 1 restricts lentivirus infection only in myeloid cells. Benkirane raised the possibility that SAMHD 1 also restricts viral infection in quiescent CD4+ T cells. SAMHD 1 appears to be expressed efficiently in quiescent CD4+ T cells and does not require activation to increase expression. However, Vpx does not appear to have the capability to degrade SAMHD 1 in quiescent CD4+ T cells. Although SAMHD 1 exhibits properties that would be predicted by the Vpx-associated restriction, it is unlikely to act independently. For example, expression levels of SAMHD 1 do not collaborate with levels of antiviral restriction and expression of SAMHD 1 in T-cell lines such as SUP-T1 does not reconstitute the restriction. Research continues in order to fully understand the biochemical nature of the restriction and cofactors of SAMHD 1 that are necessary for its full biologic activity.

Although a number of studies have demonstrated that SAMHD 1 is active against all primate lentiviruses including HIV-1, HIV-1 does not encode Vpx. Although HIV-1 contains a *vpr* gene, there is no evidence that HIV-1 Vpr is able to neutralize SAMHD 1—a central question is why HIV-1 has not evolved a strategy to do so. Littman and researchers demonstrated that HIV-1 infection of myeloid cells does not normally induce an interferon response.[4] However, if Vpx is introduced in the form of virus-like particles, the infection induces an interferon response. It is tempting to speculate that HIV-1 has deliberately avoided evolving a strategy to neutralize SAMHD 1 to stay below the radar of the interferon response. This suggests a fundamental difference in the biologic properties of HIV-1 and HIV-2/SIV. Given this information, it is therefore puzzling that HIV-1 retains the capability to infect myeloid lineage cells even though it is

unable to restrict SAMHD 1. It is possible that HIV-1 has adapted to undergo reverse transcription in low-dNTP environments and is therefore only partially analogized by SAMHD 1. There is much work to be done in understanding how myeloid lineage cells impact primate lentivirus pathogenesis. Clearly, these viruses have evolved strategies to infect myeloid lineage cells and to evade myeloid-specific restrictions (at least in the case of HIV-1 and SIV). This supports the notion that myeloid lineage cells play a crucial role in the biology of these viruses.

In the same session, Luban outlined the state of research on TRIM5α, as a restriction factor that recognizes HIV-1 capsid (Abstract 65). The existence of this restriction was first suggested by the realization that HIV-1 inefficiently infects monkeys, which correlated with an inability of HIV-1 to replicate within cells of many monkey species. While working in Sodroski's laboratory, Stremlau identified TRIM5α as the factor that restricts HIV-1 infection of monkey cells.[5] Around the same time, Luban's lab identified cyclophilin A as a factor that restricts HIV-1 infection of owl monkey cells.[6] Both proteins recognize viral capsids through a domain that regulates species-specific restriction. Amino acid differences within this domain result in changes in activity such that HIV-1 is recognized by monkey TRIM5α, but not by human TRIM5α. Some structural insight into some of the domains within TRIM5α, such as RING and B-box domains, has been obtained, but there is no structural information on the complete protein. This has hampered attempts to gain detailed insight into how TRIM5α acts on the viral capsids. The most plausible model is that TRIM5α interacts with the capsid to promote premature uncoating. TRIM5α has also been shown to associate with proteasome components, suggesting that another part of the restriction mechanism may involve the proteasome. Ubiquitinylation of any viral component has yet to be observed.

Luban went on to discuss the possibility that TRIM5α, through recognition of the capsid lattice, serves as an innate pattern recognition receptor that alerts the infected cell to the incoming viral particle. In support of this hypothesis, Luban presented data that over-expression of TRIM5α activates innate immune transcription factors such as activating protein 1 (AP-1) and nuclear factor κB (NF-κB), and TRIM5α knock-down inhibits lipopolysaccharide (LPS) signaling in human dendritic cells. Further, challenge of dendritic cells with retroviruses restricted by TRIM5α activated inflammatory cytokines. TRIM5α appears to activate AP-1 and NF-κB through the transforming growth factor β-activated kinase 1 (TAK1) and TAK2/TAK3 complex. This kinase complex has ubiquitin binding components (TAK1-binding protein-3 [TAB3]). Using purified individual components, TRIM5α was shown to synthesize unattached lysine-63–linked ubiquitin chains that are unattached to any substrate. TRIM5α perhaps stimulates these chains to activate TAK1 phosphorylation. Luban went on to demonstrate that HIV-1 capsid lattices stimulate this activity. Collectively, these data indicate that TRIM5α is a pattern recognition receptor and that the retroviral capsid lattice is the pathogen-associated molecular pattern (PAMP).[7] Furthermore, the TAK1 complex is activated by TRIM5α-mediated restriction. Therefore, in addition to the premature uncoating and proteasome mechanisms previously shown in TRIM5α-mediated restriction, an additional aspect to this restriction involves K63-linked ubiquitination, activation of TAK1, and an additional level of restriction. How activation of TAK1 contributes to TRIM5α restriction is under investigation.

A new dimension on the TRIM5α story is the possibility that TRIM5α plays a role in pathogenesis. Monkey TRIM5α does not effectively target SIV capsids. However, there is a growing body of literature to suggest that TRIM5α may modulate control of SIV replication in rhesus monkeys,[8] although this is not seen consistently.[9] There are less solid data regarding the impact of TRIM5α polymorphisms in humans, although some papers suggest that these polymorphisms impact HIV-1 acquisition and disease progression. To this end, Abstract 237 described a G249D polymorphism that is a common variant in Asians and is associated with an increased susceptibility to HIV-1. There are also data to suggest that TRIM5α may play a role in control of HIV-1 infection in individuals who have particular human leukocyte antigen (HLA) genotypes and who mount strong cytoxic T lymphocyte (CTL) responses to *gag*. CTL escape variants acquired mutations that impact viral fitness by increasing susceptibility to TRIM5α restriction.

Viral Reservoirs and Persistence

Much attention has focused on the mechanism with which HIV-1 persists in the face of antiretroviral therapy and this topic received extensive coverage at the conference. A reservoir of quiescent, latently infected CD4 + T cells is considered to be the single biggest obstacle to viral eradication. When HIV-1 is in a latent state, it is not affected by the antiretroviral drugs currently used in the management of HIV-1-infected individuals. A number of groups have been exploiting approaches to reactivate viral latency with the expectation that reactivated virus can be killed by immune surveillance or attacked with retroviral reagents.

Lewin (Abstract 106) reviewed latency and its maintenance, as well as clinical studies aimed at clearing the latent viral reservoirs. She described a clinical study using vorinostat (suberoylanilide hydroxamic acid [SAHA]), an histone deacetylase (HDAC) inhibitor that has been shown to activate HIV from latency in vitro. Vorinostat is licensed for the treatment of cutaneous T-cell lymphoma and is undergoing numerous phase II trials for other malignancies. The toxic effects of vorinostat are well described, at least in short-term studies, but it is unknown whether there is any toxicity associated with long-term use.

In a trial to reactivate latent HIV, 20 patients received 14 days of vorinostat. Blood samples were collected frequently and rectal biopsy was conducted at day 0 and day 14. The major

endpoints were cell-associated viral RNA, as well as other indicators of viral activity, such as cell-associated HIV DNA. The study group was very well-suppressed, with a median CD4+ cell count of 710/µL. Some adverse events were reported in 8 of 9 patients. These events have been previously observed in vorinostat trials but reversed on discontinuation of the drug. In rectal biopsies, there was no evidence of T-cell activation at day 0 and day 14. Viral markers are currently being assessed.

In another trial conducted by Margolis and colleagues (Abstract 157LB), patients received a single dose of vorinostat. The primary endpoints were cell-associated viral RNA and frequency of latently infected T cells. Thirteen patients have been enrolled. Extensive baseline viral characteristics were determined for each patient at enrollment. Quiescent lymphocytes were purified and treated ex vivo with vorinostat to ensure that their cells responded to the treatment. Lymphocytes from each of the 6 enrolled patients showed an increase in cell-associated HIV-1 RNA after treatment with vorinostat ex vivo. Following administration of vorinostat, there was a similar induction of cell-associated viral RNA in patients following a single 400-mg dose of vorinostat. There was no significant change in the level of single-copy viral RNA in all patients. This study provides proof-of-concept that a single dose of vorinostat induces expression of full-length viral RNA within resting CD4+ T cells and provides a framework with which to establish an optimal dosing schedule for the drug.

An important consideration in developing strategies to eradiate the latent viral reservoir by reactivation is the expectation that viral cytopathic effects or immune surveillance would accelerate destruction of the reactivated cell. Abstract 153 examined the ability of CD8+ cells to kill latently infected resting T cells that were treated with vorinostat in vitro. CD4+ cells were obtained from patients on suppressive antiretroviral therapy and were used to generate latent infection in vitro. Cells were then reactivated with vorinostat—of the 1% to 3% of cells in latent infection, the majority were reactivated with treatment. Autologous CD8+ cells were then obtained from the same patients and cocultured with SAHA-reactivated cells at a 1-to-1 ratio. CD8+ cells from an elite controller with a high level of cytotoxic T-cell activity efficiently killed HIV-1-infected cells over an 8-day interval. However, CD8+ T cells from patients receiving antiretroviral therapy did not effectively kill latently infected T cells after virus reactivation. Furthermore, there was no obvious cytopathic effect in these cultures. Stimulation of patient CD8+ cells with HIV *gag* peptides enhanced the CTL responses and led to killing of vorinostat-treated cells. It should be noted that latently infected cells were transduced with Bcl-2 in order to maintain their viability, but this could also have affected their susceptibility to cytopathicity and CTL lysis. Nevertheless, Bcl-2 transduced cells died when virus was reactivated by CD3/CD28 co-stimulation. These sobering data suggest that reactivation of viral latency in vivo will be insufficient to accelerate the death of the reactivated cell and will require additional measures to boost cytotoxic T-cell responses in patients undergoing purging protocols to eliminate the latent reservoir.

Despite these apparent setbacks, the field of research in viral reservoirs is engendered with a sense of purpose in pursuing strategies that will achieve viral eradication. Ultimate success will depend on a complete understanding of the nature of the viral reservoirs that persist in the face of antiretroviral therapy, and that understanding will inform the most effective strategies to eliminate those reservoirs.

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A list of all cited abstracts appears on pages 87-93.

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Update on Progress in HIV Vaccine Development

David I. Watkins, PhD

The 19th Conference on Retroviruses and Opportunistic Infections heralded the arrival of a new crop of potent, broadly neutralizing antibodies against HIV. This advance has given the entire vaccine field enormous hope that it will be possible one day to develop an antibody-based vaccine for HIV. However, substantial obstacles still exist in the induction of these antibodies by vaccination, given the enormous number of somatic mutations needed to develop these highly efficient antibodies. It is likely that follicular helper T cells will be involved in the development of these antibodies, and this will be a key area of interest in the future. Cellular immune responses will also be an important part of any vaccine regimen. Evidence showed that protection provided by an attenuated vaccine correlated with the frequency of vaccine-induced helper cells and killer cells, underlining the importance of these key immune cells. An alternative approach to the development of potent neutralizing antibodies was presented as part of an update on the Thai Phase III Vaccine Trial RV144. Data were shown suggesting that binding antibodies may play a role in protection from HIV infection.

Neutralizing Antibodies and the Structure of the Envelope Glycoprotein

Burton opened the conference with his delivery of the 17th Bernard Fields lecture, in which he gave a tongue-in-cheek discussion of the state of the development of an antibody-based vaccine (Abstract 15). He used a Tootsie Pop as an example of the envelope spike. To get to the chocolate inside the candy, one has to get through a sugar coating. He used the tongues of several British scientists to demonstrate how a neutralizing antibody might bind to the envelope spike and access the chocolate. Though unorthodox, the demonstration was unquestionably tasteful.

Burton then showed his more serious side with models of the trimeric gp120 structure and its glycan shield. Because of the enormous diversity of the envelope protein, the task of making an antibody-based vaccine will be difficult. However, there have been encouraging developments in the definition of new broadly neutralizing, potent monoclonal antibodies, and Burton showed that we now have a new series of such antibodies. These will be useful tools for understanding the targets of effective neutralizing antibodies and for providing proof that it is possible to make a potent, broadly neutralizing antibody against HIV. However, enormous hurdles still need to be surmounted in the area of inducing such antibodies by vaccination. Most of these neutralizing antibodies have undergone considerable somatic mutation to arrive at the final potent effector molecules. Determining how a vaccine regimen will induce this still remains the holy grail of HIV vaccine development. Sodroski presented new data from single-particle cryoelectron microscopy to further elucidate the prefusion structure of the trimeric HIV envelope glycoprotein (Abstract 76).

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The Emerging Importance of Helper T Cells

Renewed interest in the antibody response to HIV has spawned several new studies of the helper-cell subset that is thought to be crucial in the development of these responses: follicular helper T cells. Koup's group presented preliminary data on the description of this cell type in macaques (Abstract 42). This was followed by a parallel presentation describing these cells in humans by Streeck's group (Abstract 43). Ranasinghe (from Streeck's group) also presented interesting data related to the role of major histocompatibility complex (MHC) class II molecules in viral suppression in humans (Abstract 44). After extensive mapping of the targets of CD4+ cell responses in humans, the group's studies revealed that numerous MHC class II molecules could bind several different HIV-derived peptides. Interestingly, the MHC class II molecules that bound the most HIV-derived peptides were correlated with lower plasma HIV RNA levels. This interesting observation suggests that MHC class II-restricted CD4+ cell responses may play a crucial role in controlling viral replication.

Clues from the Attenuated Vaccine

New data from the Picker group showed that the magnitude of CD8+ and CD4+ Simian Immunodeficiency Virus(SIV)-specific T cells induced by live attenuated virus (LAV) vaccination correlated with a better outcome after pathogenic viral challenge (Abstract 92). Furthermore, the number of these vaccine-induced T cells in the lymph nodes proved to be the best predictor of successful control of the challenge virus. Vaccine-induced lymph node CD8+ T cells had an activated effector phenotype and seemed to be maintained by virus replicating in programmed death-1 (PD-1) high CD4+ memory T cells in the lymph nodes. LAV could be readily detected in PD-1 high CD4+ cells during the vaccine phase. These lymph node T-cell responses, therefore,

appeared to be the key to controlling pathogenic virus replication soon after intravenous challenge.

RV144 Vaccine Trial

In contrast with the notion that neutralizing antibodies are required for protection, the results of the Thai Phase lll Vaccine Trial (RV144) suggest that vaccine-induced antibodies that bind, but do not neutralize, can make a difference in protection against HIV. Michael presented results from the correlation analysis of the RV144 trial (Abstract 167). Six different aspects of the vaccine-induced immune responses in 205 uninfected vaccinated individuals were compared with immune responses from 41 infected vaccinees. The results suggested that antibody responses against the viral envelope may have been involved in the borderline protection observed. Michael presented new monoclonal antibodies that had been isolated from these vaccinees and showed that they had tier 1 neutralizing abilities and antibody-dependent cellular cytotoxicity activity. Future studies will include testing these monoclonal antibodies in passive transfer studies in macaques.

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Antiretroviral Use for Prevention and Other Factors Affecting the Course of the HIV-1 Epidemic

Susan P. Buchbinder, MD

Antiretroviral therapy has tremendous potential to alter the HIV-1 epidemic trajectory. However, gaps in the continuum from HIV diagnosis, through linkage to care and uptake and adherence to antiretroviral therapy, are substantially limiting to the actual impact. In the United States, gaps in HIV diagnosis and care are greatest among African Americans, substance users, and persons living below the poverty line. Globally, HIV diagnosis rates are highest in women, but HIV incidence may be declining more rapidly in men, due to lower transmission rates from female partners and greater uptake of medical male circumcision. The 2012 Conference on Retroviruses and Opportunistic Infections explored gaps in the continuum of care and potential strategies to address them, and also addressed the disparate results from preexposure prophylaxis efficacy trials. The role of injectable contraceptives in increasing the risk of HIV acquisition in women was debated, as was the potential harm that could arise from limiting this contraceptive method due to increased maternal mortality. Similarly, the potential benefits and harms of serosorting were explored. Investigators explored scale-up of prevention strategies to have the biggest and most cost-effective impact on the global epidemic.

Antiretroviral Strategies for HIV Prevention

Antiretroviral Therapy

Following the announcement last year of the dramatic reduction in heterosexual transmission when antiretroviral therapy is initiated early in the course of HIV infection,[1] a great deal of attention was focused on using antiretroviral therapy as a method of reducing HIV infection rates at a population level at the 2012 Conference on Retroviruses and Opportunistic Infections (CROI). El-Sadr reviewed recent data demonstrating both the promise and the challenges of using antiretroviral therapy for HIV prevention (Abstract 18). She displayed gaps in the continuum of care from HIV diagnosis to linkage to care, retention in care, uptake of antiretroviral therapy, and suppression of viral load. In the United States, it is estimated that only 28% of HIV-1 infected persons have fully suppressed viral loads. In Mozambique, there are similar challenges with gaps in each step in the continuum of care. In one study, only 5% of 7000 HIV-seropositive persons had fully suppressed viral loads; this study did not take into account the large proportion of HIV-infected persons who may not yet be diagnosed. Other troubling data from Mozambique showed that 43% of those diagnosed with HIV were not enrolled in care, and 69% of persons eligible for antiretroviral therapy did not initiate treatment.

El-Sadr reviewed innovative strategies for addressing gaps at each stage in the continuum of care. Home-based voluntary HIV testing, in which health workers go door to door to offer HIV antibody testing, has been shown to increase the uptake and efficiency of HIV testing, uncovering a larger number of HIV-infected individuals than clinic-based strategies. HIV self-testing was shown to be accurate and highly acceptable in a study in Malawi. Couples-based HIV testing is another approach to delivery of testing. To enhance linkage to care, point-of-care CD4+ testing—particularly when paired with home-based testing—doubled the rate of uptake of antiretroviral therapy among eligible HIV-seropositive persons. However, a sizeable proportion of persons do not remain in care, and even if in care, some may not opt to take antiretroviral therapy. In a study of more than 7000 patients tested for HIV in South Africa, 35% were HIV-seropositive. Of the 743 patients eligible for antiretroviral therapy, 20% repeatedly refused treatment, despite a median CD4+ count of 110 cells/μL for the eligible group. The most common reason for refusal was the statement that the person was feeling well, suggesting additional education on the benefits of antiretroviral therapy among asymptomatic persons may be needed.

Failure to remain in care has hampered efforts to control the epidemic. In a meta-analysis of 36 African cohorts reviewed by El-Sadr, retention on antiretroviral therapy was 86% at 6 months but only 72% at 36 months. Although this rate of retention in therapy is higher than published data from North America, additional work must be done to improve the health of HIV-infected persons and decrease the risk of transmission to their uninfected partners. Text messaging has been used successfully in Kenya to modestly improve adherence to antiretroviral therapy and, in some cases, result in full viral suppression. Use of community treatment groups, in which one individual collects medications for other members of the group, has resulted in very low rates of attrition and excellent health outcomes. To obtain maximal individual and societal benefits from antiretroviral therapy, El-Sadr proposes that efforts focus on several different populations. Persons with the lowest

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CD4+ cell counts may benefit most from early treatment, and the risk of HIV transmission among persons with low CD4+ cell counts appears to be substantially higher than the risk among persons with higher CD4 + cell counts. Given the HPTN (HIV Prevention Trials Network) 052 results,[1] treatment for HIV serodiscordant couples may be particularly effective. One strategy to efficiently identify serodiscordant couples is to test the partners of identified HIV-infected persons, as approximately half will have an HIV uninfected partner. HIV-seronegative pregnant women are at 4-fold higher risk of acquiring HIV infection than non-pregnant women, suggesting that particular attention should be focused on testing the male partners of pregnant women and offering treatment as necessary.

There are few data available about the effectiveness of antiretroviral therapy on HIV acquisition at a population level. Tanser and colleagues presented data from the Africa Centre for Health and Population Studies, a rural research community in Hlabisa, South Africa, that uses a unique population-level tracking of antiretroviral therapy uptake and HIV seroincidence (Abstract 136LB). The investigators demonstrated a strong dose-response relationship between antiretroviral therapy coverage and reduction in HIV acquisition. In geographic areas with 20% to 30% antiretroviral therapy coverage, HIV acquisition rates were 22% lower than in communities with lower rates of coverage. For communities with 30% to 40% coverage, HIV incidence was 38% lower. Future community randomized clinical trials will provide additional data on population-level impact of treatment as prevention.

Preexposure Prophylaxis

A major focus of this year's conference was preexposure prophylaxis (PrEP), which uses antiretrovirals in HIV-uninfected persons to lower the risk of HIV acquisition. Clinical trials to date have used either tenofovir disoproxyl fumarate with or without emtricitabine. New results were released from several PrEP efficacy trials at CROI 2012.

To date, there has been only one efficacy trial of PrEP in MSM: the iPrEx (Chemoprophylaxis for HIV Prevention in Men) study, which was conducted in North and South America, Africa, and Asia. Most recently, Grant reported a 42% reduction in the risk of HIV acquisition through the end of study follow-up.[2] At CROI 2012, Anderson and colleagues presented data on iPrEx and the Strand study, a trial of tenofovir levels in peripheral blood mononuclear cells (PBMCs) when tenofovir was administered 2, 4, or 7 days per week under directly observed therapy (Abstract 31LB). In the Strand study, all participants receiving tenofovir had detectable drug in their PBMCs at the end of a 6-week course of the drug, regardless of randomization arm. In contrast, only 8% of participants in the iPrEx trial who were randomized to the emtricitabine/tenofovir arm who became HIV-1-infected had detectable drug at the time HIV infection was diagnosed, suggesting a high proportion were non-adherent or incompletely adherent to the daily regimen. Anderson then modeled the efficacy of different dosing regimens by combining data from iPrEx and Strand and concluded that 4 or more doses per week would be associated with a greater than 90% reduction in HIV acquisition. However, the drug levels used to model these efficacy thresholds were based on data from dosing delivered under direct observation; efficacy would be projected to be lower with lower levels of adherence expected from unobserved dosing. Furthermore, these models use data from men who have sex with men (MSM); additional data are needed to confirm these findings and extrapolate to other populations.

Disparate results have been reported from PrEP efficacy trials in heterosexuals. Several presentations focused on the potential reasons for these results. Baeten and colleagues presented an update on the Partners PrEP study, an efficacy trial of daily oral tenofovir, emtricitabine/tenofovir, or placebo in 4758 serodiscordant heterosexual couples in Kenya and Uganda (Abstract 29). Final analysis of data from the pre-unblinding phase of this study confirmed high levels of efficacy in reducing HIV infections in the tenofovir (efficacy 67%; 95% confidence interval [CI], 44%-81%) and the emtricitabine/tenofovir (efficacy 75%; 95% CI, 55%-87%) arms. There were no statistically significant differences in efficacy between the 2 active medications, nor between women and men. Both drug regimens appeared safe and well-tolerated. Donnell and colleagues from the same study reported on the relative risk reduction associated with detectable tenofovir levels in women and men randomized to receive active drug who became infected, compared with those who remained uninfected (Abstract 30). Overall, 82% of the uninfected participants had detectable drug in plasma, a statistically significantly higher proportion than that among participants who became infected. Donnell calculated 86% and 90% relative risk reduction of HIV acquisition among those with detectable drug in the tenofovir and emtricitabine/tenofovir arms, respectively.

In the same session, Van Damme and colleagues presented data on the FEM-PrEP (Study to Assess the Role of Truvada in Preventing HIV Acquisition in Women) trial, a study of 2120 enrolled women at risk of HIV acquisition in Tanzania, Kenya, and South Africa (Abstract 32LB). This study was stopped early because the Data and Safety Monitoring Board (DSMB) determined that it was unlikely that efficacy would be demonstrated. This was the first scientific presentation of data from this study. In total, there were 68 post-enrollment infections, with 33 in the active treatment arm (receiving emtricitabine/tenofovir), and 35 in the placebo arm. One likely contributor to the lack of efficacy seen in this trial was the low rate of adherence to the study drug, although the magnitude of this factor is as yet unknown. Although 95% of the women reported that they always or usually took their study drug, only 26% of those who became infected and 35% of those who remained uninfected had detectable tenofovir in stored plasma specimens from their last preseroconversion time point.

Baeten discussed hypotheses for the difference in results between these studies (Abstract 67). He pointed out that 3 studies of oral tenofovir/emtricitabine (iPrEx, Partners PrEP, and TDF2 [FHI TDF West African trial]) and one of vaginal tenofovir gel (CAPRISA [Centre for the AIDS Programme of Research in South Africa] 004) have demonstrated efficacy in preventing HIV infection in MSM and heterosexuals, and 2 studies, 1 of oral tenofovir/emtricitabine (Partners PrEP) and 1 of vaginal tenofovir gel (VOICE [Vaginal and Oral Interventions to Control the Epidemic]), have not demonstrated efficacy in preventing HIV infection in women. Baeten categorized potential explanations as statistical, biologic, or behavioral, ruling out the first explanation based on the robustness of evidence from the trials that demonstrated efficacy. Potential biologic explanations for the lack of efficacy with oral PrEP include cofactors that could lower the threshold for infection, even in the presence of PrEP, such as sexually transmitted infections (STIs), genital inflammation, intravaginal practices, or the incidence of acute infection in partners. All of these cofactors may have been higher in the negative than in the positive trials. Potential biologic explanations for disparities in results of vaginal tenofovir gel may be related to dosing schedules. Whereas tenofovir was prescribed pericoitally in CAPRISA 004, it was recommended for daily use in VOICE. It is possible that these higher levels of this hyperosmolar vaginal gel could have caused epithelial disruption, overwhelming any potential efficacy of the drug. Adherence is frequently cited as a potential behavioral factor causing divergent results in different trials. This is supported by data from each of the positive trials that link higher level of adherence to greater degree of efficacy. Baeten emphasized that additional investigation is required to determine whether and to what extent each of these possible explanations contributed to different outcomes in different trials.

In the same session, Buchbinder presented what is known about the potential for intermittent dosing of PrEP (Abstract 68). She pointed out that, although treatment of HIV-seropositive persons may substantially lower the risk of HIV transmission, there have been substantial challenges in the United States and globally with HIV testing, linkage to care, and uptake and adherence to antiretroviral therapy, as outlined in El-Sadr's presentation described above. The best way to substantially reduce HIV infections globally involves treatment as well as prevention, and PrEP may play a role in this effort. She reviewed 4 types of "intermittent PrEP": (1) fixed dosing (on a regular schedule, but less than daily); (2) event-based dosing (pericoitally); (3) combined fixed and event-based dosing (regular dosing less than daily, with postcoital doses to augment drug levels); and (4) periodic dosing (daily dosing, but only during periods of risk). Less than daily dosing has the potential to reduce cost and toxicity, as well as improve adherence and tolerability. Potential downsides of less than daily dosing include increased potential for antiretroviral drug resistance, decreased efficacy, and potential worsening of adherence or tolerability. After reviewing what is known to date about these issues, she pointed out that all PrEP regimens require ruling out HIV infection before (re)initiation of PrEP, and monitoring for renal toxicity on an ongoing basis. Fixed intermittent dosing may be feasible for preventing HIV infection, given data from trials indicating that high levels of efficacy may be achievable with less than daily dosing. However, the substantial hazard with fixed intermittent dosing is that, if doses are missed, there is less "forgiveness," and drug levels may not be sufficient to prevent infection. She posited that episode-driven regimens may be successful if they are built into all sexual acts (eg, microbicides), but are unlikely to be successful if they are not, because individuals may not leave adequate time before sexual exposure to take PrEP, and may not recognize which sexual episodes contain risk. She noted the questions about the likely success of intermittent PrEP, and suggested that long-acting agents and extended delivery methods may obviate the need for intermittent PrEP.

Microbicides

Delivering antiretrovirals topically (eg, microbicides) rather than systemically (eg, oral PrEP) has the potential to increase drug levels at the locations where infection occurs, while also reducing the risk of systemic toxic effects. On the other hand, because tenofovir may be detectable in cervicovaginal lavage fluid (CVL) for up to 30 days after vaginal administration, there is concern that resistance to tenofovir could emerge in the vaginal compartment, either during the "tail" of tenofovir postdosing, or when tenofovir is delivered postinfection but prior to diagnosis. Johnson presented the results of sensitive resistance screening of HIV-1 from genital tract samples of women participating in the CAPRISA 004 efficacy trial, on behalf of Wei and colleagues (Abstract 33). In this trial of 899 women enrolled in South Africa, topically administered 1% tenofovir gel was associated with a 39% reduction in HIV-1 infection rates (95% CI, 6%-60%). This trial used a "BAT 24" dosing regimen. Women were instructed to use the gel within 12 hours Before and up to 12 hours After sexual intercourse, but no more than Twice per 24-hour period. As in previously described studies of oral tenofovir, efficacy in this microbicide trial was highly associated with adherence. Only 40% of women who became HIV-infected had any tenofovir detectable in CVL specimens at the seroconversion visit, compared with 96% of the women remaining uninfected. No tenofovir resistance was detected in the plasma of infected women from the CAPRISA 004 trial. In evaluating tenofovir resistance in CVL specimens, only 3 of the 21 specimens with detectable HIV-1 had detectable tenofovir, and only 1 of these had a K65R mutation detectable. The woman with the K65R mutation had very high levels of tenofovir and recent HIV infection; the investigators suggested that this indicated that tenofovir was administered shortly after infection. None of the resistant virus was detectable in expressed RNA,

only in the proviral DNA. Johnson suggested that this implies a low risk of resistance emergence in the vaginal compartment, but acknowledged that these women were closely monitored to decrease the likelihood of using the gel postinfection.

McGowan and colleagues presented data from MTN (Microbicide Trials Network) 007, a randomized controlled trial (RCT) of a reduced glycerin (RG) formulation of 1% tenofovir gel for rectal use (Abstract 34LB). A previous phase I study (MTN 006) had demonstrated substantial gastrointestinal symptoms with a hyperosmolar preparation of tenofovir gel (>3000 mOsm/kg). With the RG formulation used in the MTN 007 trial, the osmolarity was substantially reduced, to 836 mOsm/kg, which is closer to iso-osmolar levels (290 mOsm/kg) and therefore potentially less likely to induce the abdominal pain, bloating, and diarrhea reported in the previous study. In MTN 007, 65 HIV-seronegative men and women were randomly assigned to receive a single dose followed by 7 consecutive daily doses of 2% nonoxynol-9 (N-9), the "positive" control; 1% RG tenofovir gel; hydroxyethyl cellulose (HEC), the placebo; or no product. Tolerability was high in all study arms, with rare grade 3 symptoms, and rare evidence of mucosal toxicity, except in the nonoxynol-9 arm. McGowan noted significant differences in the cytokine/chemokine profile, T-cell phenotype, and rectal microflora between the nonoxynol-9 and tenofovir arms, and hypothesized that these may contribute to differences in toxicity profiles between these agents.

Making a case for the relevance of rectal microbicides for heterosexuals, DiNenno and colleagues presented data on the prevalence and factors associated with unprotected anal intercourse in more than 10,000 heterosexual men and women enrolled in the 2010 US National HIV Behavioral Surveillance System (NHBS; Abstract 1100). After excluding persons who reported ever having used injection drugs, 28% of the remaining women and 33% of the remaining men reported heterosexual unprotected anal intercourse in the prior 12 months. For both men and women, factors associated with unprotected anal intercourse on multivariate analysis were household income at or below poverty, use of noninjection drugs, and exchange of sex with their partner.

New Antiretroviral Agents, New Delivery Methods

Romano presented an overview of new strategies and agents for oral and topical PrEP (Abstract 69). The limitations of the current tenofovir-based regimens are that they focus on one mechanism of action (ie, reverse transcriptase inhibition), with mixed results potentially caused by potency or adherence issues. The next generation of PrEP regimens may include combination antiretroviral approaches and new delivery methods to increase potency and adherence, which could be combined with agents to prevent other STIs or with contraceptives. Romano gave examples of trials focused on HIV prevention, including: (1) HPTN 069: oral daily regimens of maraviroc (an entry inhibitor) with or without emtricitabine, tenofovir, or emtricitabine/tenofovir (a nucleoside analogue reverse transcriptase inhibitor [nRTI]); (2) MTN-013/IPM (International Partnership for Microbicides) 026: combination dapivirine (a nonnucleoside analogue reverse transcriptase inhibitor [NNRTI]) and maraviroc delivered as an intravaginal ring; and (3) SSAT (St Stephen's AIDS Trust) 040: injectable rilpivirine long-acting (NNRTI). Of note, Jackson and colleagues reported that the rilpivirine long-acting intramuscular (IM) injection appeared to be safe and well-tolerated when given as a single dose, with prolonged plasma and genital tract exposure (Abstract 35). This trial also pointed to the importance of understanding how drugs penetrate different genital tract compartments. Rilpivirine levels in CVL were equal to or higher than plasma, levels in rectal tissue were equivalent to levels in plasma, and vaginal tissues had somewhat lower levels than in plasma.

Nel and colleagues presented data from an RCT of the investigational drug dapivirine (TMC120) vaginal microbicide rings in 280 African HIV–seronegative women (Abstract 1089). In this trial, women inserted active or placebo vaginal rings once every 28 days over a 12–week period. Safety was excellent, with infrequent adverse events that were balanced between the 2 arms. Acceptability was high, with more than 90% of women reporting no ring removals, and 97% reporting comfort and intent to use the vaginal ring in the future if safe and effective.

Non-Antiretroviral Prevention Strategies

Medical Male Circumcision

Three previously reported RCTs had demonstrated that medical male circumcision (MMC) resulted in a 50% to 60% reduction in HIV acquisition among men. No substantial protective effect has been seen for the female partners of circumcised HIV-infected men. Two presentations at this year's conference addressed the population-level impact of MMC. First, Gray and colleagues presented population-level data on the impact of voluntary MMC on HIV infection rates in Uganda (Abstract 36). Comparing the HIV incidence from the period prior to the MMC RCT, during which non-Muslim men had very low MMC rates (1999), to the period post-trial (2004-2011), the study found substantial reductions in HIV incidence among non-Muslim men, with no corresponding reduction among Muslim men or non-Muslim women. After adjusting for secular changes in the distribution of age and sexual risk practices, the study found a 27% reduction in HIV incidence (95% CI, 10%-40%) among non-Muslim men, likely attributable to the uptake of MMC.

Auvert and colleagues measured the population-level impact of MMC on herpes simplex virus type-2 (HSV-2) in Orange Farm, South Africa (Abstract 37). The prevalence of HSV-2 among circumcised men was 16.5% in comparison with HSV-2 prevalence of 31% among uncircumcised males, leading

to a weighted prevalence reduction (adjusting for age) of 23% (95% CI, 9%-35%). This reduction was significantly lower than the reduction in HIV prevalence (50%; 95% CI, 44%-62%; $P < .001$), suggesting that MMC may be more effective in preventing HIV than HSV-2 acquisition.

Seroadaptive Sexual Practices

Vallabhaneni and colleagues presented an analysis of the impact of seroadaptive practices (changing sexual practices based on the perceived HIV serostatus of sex partners) on the risk of HIV acquisition (Abstract 140). She and her colleagues pooled data from more than 12,000 HIV-seronegative MSM recruited from US or Canadian sites, participating in 1 of 4 longitudinal cohort studies conducted from 1995 to 2007. In this analysis, Vallabhaneni categorized participants for each 6-month interval based on their highest reported risk during that interval. Seroadaptive practices included having unprotected anal sex, but with the following limitations (in hierarchical order): (1) having only 1 HIV-seronegative partner, (2) engaging only in insertive anal sex with all partners, (3) having only (numerous) HIV-seronegative partners, and (4) restricting sexual activity with partners who were HIV-seropositive or of unknown serostatus to insertive anal sex. A total of 663 infections occurred during more than 60,000 6-month intervals of follow-up. Compared with having unprotected anal sex without any seroadaptive practices, each of the seroadaptive practices was associated with a lower risk of HIV-1 seroconversion. However, compared with reporting no unprotected anal sex, serosorting (having only HIV-negative partners) was associated with a doubling of risk, and having unprotected anal sex without seroadaptive practices with more than a 3-fold increased risk. Vallabhaneni suggested that seroadaptive practices may be recommended as a harm reduction strategy for men engaging in unprotected receptive anal sex with HIV-seropositive partners or partners with unknown serostatus. However, men should be counseled that serosorting is associated with a doubling of risk compared with not reporting any unprotected anal sex, and serosorting should not be relied upon as a "safe" alternative to 100% condom use.

Golden and colleagues reported on trends in serosorting and their relationship to HIV, syphilis, and gonorrhea incidence over time among patients attending the Seattle King County Sexually Transmitted Diseases (STDs) clinic (Abstract 1092). Both HIV-seropositive and seronegative men have been engaging in statistically significantly less serodiscordant unprotected anal sex, but significantly more seroconcordant unprotected anal sex (serosorting) over time in their clinic. These trends correlate with increased rates of early syphilis in HIV-seropositive men and gonorrhea in both HIV-seropositive and -seronegative MSM. In accordance with Vallabhaneni's previously described results, Golden found that HIV-seronegative men reporting serosorting were at intermediate risk of seroconversion—lower than men reporting unprotected anal sex with an HIV-seropositive or unknown serostatus partner, but higher than men reporting no unprotected anal sex. In a separate longitudinal analysis of a cohort of almost 800 MSM recruited in San Francisco, Vallabhaneni reported that 61% of the HIV-seronegative men and 35% of the HIV-seropositive men said they intended to serosort (Abstract 1093). However, when the men who intended to serosort were seen 6 months after enrollment, HIV-seropositive and -seronegative men using substances (eg, methamphetamines, alcohol, poppers, downers) were statistically significantly more likely to report having had unprotected anal sex with a partner of unknown or discordant serostatus to their own. This highlights the role that substance use plays in disinhibition of safer sex plans.

Heffelfinger and colleagues reported on the proportion of HIV-seropositive MSM who were unaware of their HIV serostatus and risk factors for unprotected anal sex with a potentially serodiscordant partner (Abstract 1091). Of the 1562 HIV-seropositive men enrolled in the NHBS in 2008, 56% were aware of their HIV-seropositive status, and 44% were not. Predictors of being unaware of an HIV-seropositive status included being non-white, being younger than 30 years of age, ever having used injection drugs, and several measures of lower socioeconomic status (eg, being uninsured, having less education, and income at or below poverty). Independent predictors of engaging in unprotected anal sex with an HIV-seronegative or unknown serostatus partner were being unaware of HIV-seropositive status, binge drinking in the last 30 days, and being US-born. Freedman and colleagues, using data from the Medical Monitoring Project (MMP) conducted by the US Centers for Disease Control and Prevention (CDC), reported that only 5% of HIV-infected patients in clinical care reporting unprotected sex with an HIV-seronegative or unknown serostatus partner were not virally suppressed (Abstract 1090).

Superinfection

Serosorting for HIV-infected persons will limit the spread of new HIV infections, but may also result in increased rates of superinfection. This may in turn lead to worsened clinical outcome in HIV-infected persons. Two presentations measured rates of HIV-1 superinfection, based on deep sequencing strategies. Redd and colleagues presented data on superinfection rates among men and women within the longitudinal cohort in Rakai, Uganda (Abstract 58). In the analysis of 149 participants who seroconverted from 1997 to 2002 with a follow-up specimen available in 2008, 7 superinfection events were detected. All superinfection events were observed in the gp41 region. All initial infections were subtype D, with 3 superinfections being intersubtype (all type subtype A), and the other 4 being intrasubtype. The incidence of superinfection (1.44/100 person-years) was similar to the rate of initial HIV infection in the same cohort (1.15/100 person-years). Ronen and colleagues presented data on superinfection in the Mombasa,

Kenya, female sex worker cohort (Abstract 59LB). This analysis is still underway, with 117 of 149 qualifying specimens having been tested. At the time of the presentation, the incidence of superinfection in this cohort was 3.25/100 person-years, with HIV incidence in the same cohort of 3.06/100 person-years. Audience members pointed out that these are likely to be underestimates of superinfection, as they will not identify transient cases of superinfection or differences that occur in regions of the genome that were not sequenced. Although previous studies suggested that the risk of superinfection may be greatest soon after HIV infection, Ronen's data captured episodes that occurred up to 5 years after initial infection. Both investigators have plans to examine the impact of superinfection on the clinical course of HIV disease. The implication of these results for the development of HIV vaccines is not yet clear.

Trends in HIV Diagnosis and Factors Contributing to HIV Outcomes

HIV Testing

Branson reviewed the current algorithm for HIV testing, pointing to its problems (Abstract 114). The current testing algorithm has been in use since 1989 and requires repeat screening antibody tests, confirmed by a specific test, typically a Western blot or enzyme immunoassay (EIA). This system means that the confirmatory test (a first-generation assay) is being used to confirm a third- or fourth-generation assay, despite the fact that third-generation assays turn positive on average 2 weeks earlier than a Western blot, and fourth-generation assays 5 days earlier than third. Another problem with the current algorithm is that it does not adequately differentiate HIV-1 from HIV-2 infection. NNRTIs and some protease inhibitors (PIs) are ineffective in treating HIV-2 infection, and HIV-2 is not detectable with current viral load testing. Therefore, HIV-2-infected persons who are treated and monitored as though they have HIV-1 infection are often not correctly diagnosed until their condition inexplicably deteriorates, despite an undetectable viral load. In fact, in New York City, 93% of HIV-2 cases had been read as HIV-1 positive on Western blot, as had 60% of HIV-2 cases reported to the CDC.

The CDC and Public Health Laboratories developed a new testing algorithm (Figure 1). In this algorithm, patients should be screened with a fourth-generation HIV-1/2 immunoassay. If that test is negative, patients are determined to be negative for both antibody and p24 antigen. Positive tests are then tested using an assay to differentiate IgG for HIV-1 from HIV-2. This will confirm a positive result. If this confirmatory test is negative, RNA testing is done to detect acute HIV-1 infection. If negative, HIV-1 infection has been ruled out. The new algorithm has been validated to be both more sensitive and more specific than the current algorithm, and to produce fewer indeterminate test results. This leads to yet another benefit: the current algorithm can take days to weeks to produce a definitive diagnosis, but running a test through the new algorithm can provide definitive results within 2 hours.

In the same session, Sullivan provided an overview of what is known about the impact of disclosure of serostatus to one's sexual partners (Abstract 117). He differentiated 3 types of disclosure. Firstly, for newly HIV-diagnosed individuals, partner notification by health departments has been shown to identify other HIV-seropositive persons who were unaware of their HIV infection. Most data suggest that health care practitioners play an important role in successful notification; individuals notify substantially fewer partners without the help of a practitioner, even when the newly diagnosed person has access to other tools, such as online anonymous notification. Secondly, in evaluating strategies to reduce the risk of HIV transmission from known HIV-infected persons, data show that knowledge of HIV-seropositive status is the most important predictor of safer sex practices. The benefits of disclosure per se are not consistently documented. Finally, Sullivan pointed to the potential hazard of serodisclosure of HIV-seronegative status to sex partners, if that encourages persons to have unprotected sex with others also believed to be HIV-seronegative. Several studies have demonstrated the important role of presumed HIV-seronegative partners in driving new infections, as some of these partners are newly infected and therefore may be highly infectious. Sullivan closed with promising data on the potential role of voluntary couples-based counseling and testing as a way to disclose serostatus within a partnership and

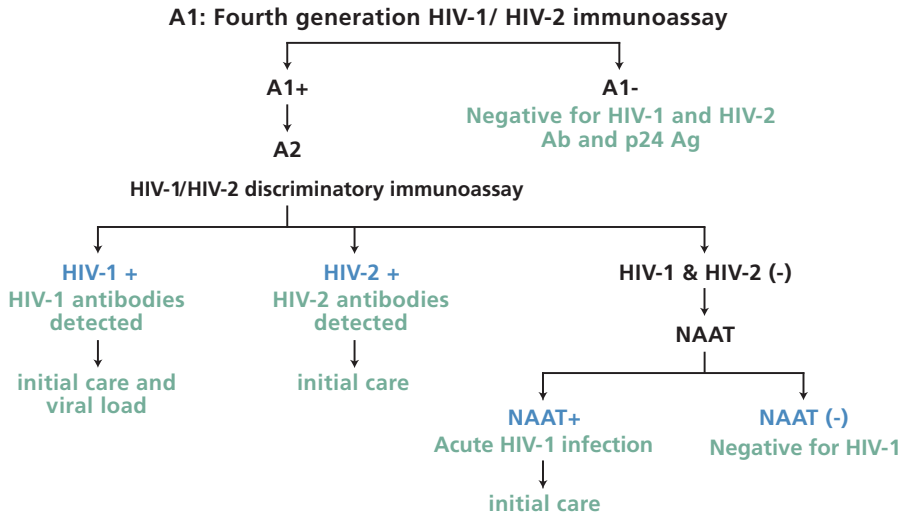

Figure 1. HIV Testing Algorithm from the 2010 Centers for Disease Control and Prevention American Public Health Laboratories HIV Diagnostic Conference. Ab indicates antibody; Ag, antigen; NAAT, nucleic acid amplification test.

encourage strategies to reduce the risk of HIV transmission.

McNairy introduced a themed discussion session focused on novel testing and linkage to care (Session 29). She pointed to the differences in HIV diagnosis rates in the United States (now up to 80%) compared with resource-limited settings (estimated at less than 40%). There is substantial heterogeneity in the proportion of diagnosed persons who are linked to care. In the United States, estimates range from 69% to 77%, and in resource-limited settings, they range from 33% to 88%. Two presentations focused on new strategies to provide HIV testing outside of clinical care settings. Katz and colleagues presented on the acceptability and ease of use of home self-testing among MSM in Seattle (Abstract 1131). Of 133 participants enrolled to date, 89% stated that they would test more frequently if the home test were available. Cost of the test was a determinant of whether or not the person anticipated testing at all, as well as the frequency of testing; more than half of the participants stated that they would only pay $20 or less for a test kit. More than 90% of the men stated that the oral fluid-based self-test kit was easy to use. Katz also described a case of a participant who tested a sex partner (despite all participants being instructed not to test partners); the sex partner was newly diagnosed by this test as HIV-seropositive. The HIV-seropositive sex partner stated to the clinic staff that he thought it was acceptable to learn of his HIV status in that way. He waited 2 months before seeking confirmatory testing, but stated that knowledge of his possible HIV-seropositive status motivated him to use condoms with his sex partners.

Van Rooyen and colleagues presented data from a study of home-based voluntary counseling and testing, combined with point-of-care CD4+ testing in KwaZulu-Natal, South Africa (Abstract 1135). Their team was able to perform HIV testing on 91% of the adults living in the targeted households. Of the 673 men and women tested, nearly 32% were being tested for the first time. Test results showed 30% were HIV-seropositive, of whom 37% were newly diagnosed. Median CD4+ count at diagnosis was 425 cells/μL, substantially higher than reported in clinic-based testing. By 3 months after testing, 88% of the HIV-seropositive men and women were linked into care. Fatch and colleagues evaluated factors associated with never having received an HIV antibody test in rural Uganda (Abstract 1137). Overall, 60% of the populations sampled had never been HIV tested. Lower socioeconomic status (eg, lack of education, low income) was significantly associated with lack of testing for both men and women. Women were also at increased risk if they suffered from food insecurity or drank alcohol.

HIV-Related Disparities in the United States

Several abstracts focused on temporal trends in receipt of medical care, antiretroviral therapy, and clinical outcomes. Hogg and colleagues reported on data from the NA-ACCORD (North American AIDS Cohort Collaborative on Research and Design) (Abstract 137). They noted increases in total life expectancy for HIV-infected 20-year-olds from 54 years to 67 years in the period from 1996 to 2007. Total life expectancy for HIV-seronegative persons in North America was approximately 80 years. Factors associated with lower life expectancy for HIV-infected persons included African American race, injection drug use, and lower CD4+ cell count. There were no substantial differences in life expectancy between HIV-infected men and women.

Skarbinski and colleagues at the CDC reported data from the MMP, a probability-based estimate from 23 US cities, states, and territories to estimate the proportion of HIV-seropositive persons in care who are on antiretroviral treatment and virally suppressed (Abstract 138). From these data, researchers estimated that 89% of HIV-infected persons in the United States who are in care have been prescribed antiretroviral therapy in the previous year, and 72% are virally suppressed. In a multivariate model, factors associated with lower rates of treatment included younger age (18 years–29 years), being black, being a woman who has sex with men, having a more recent HIV diagnosis, or having a higher CD4+ cell count. Factors associated with lack of viral suppression included younger age (18 years–49 years), being black or of "other" race, having CD4+ count greater than 500 cells/μL, and having income at or below the poverty line. Presenters also estimated that expanding national guidelines for initiating antiretroviral therapy to all HIV-infected patients would only increase the proportion of persons in care on antiretroviral therapy by 3%. The conclusion from these data was that gaps in effective treatments exist for particular subpopulations (eg, young, black, women who have sex with men, and persons of low socioeconomic status). These disparities must be addressed, and increasing awareness of HIV serostatus, linkage to care, and retention in care need to be addressed as well.

Truong and colleagues also noted disparities in early antiretroviral initiation among patients in San Francisco, as measured through a citywide surveillance unit (Abstract 139). In 2010, the San Francisco Department of Public Health and the Positive Health Program of the San Francisco General Hospital recommended that all HIV-infected patients be offered antiretroviral therapy, regardless of CD4+ cell count. Truong documented the substantial increase in earlier diagnosis and treatment of HIV-seropositive persons in San Francisco from 2004 to 2010. The most dramatic change in 2010 was in the proportion of persons initiating antiretroviral therapy at the time of diagnosis. The mean difference in CD4 + count between diagnosis and treatment was 44 cells/μL in 2009 and 7/μL in 2010. However, substantial disparities were noted in the proportion not receiving antiretroviral therapy, with lower proportions among younger HIV-seropositive persons, non-white races, those with income at or below the poverty line, and persons not having private insurance.

Millett built on his earlier work by

presenting a meta-analysis of racial disparities in HIV risk, infection, and care among MSM in the United States (Abstract 1094). He and colleagues reported data from more than 145 US studies that included more than 150,000 black MSM and more than 500,000 MSM of other races. Despite reporting substantially significantly fewer male sex partners, less substance use, and similar rates of partner concurrency and serodiscordant unprotected anal sex compared with other MSM, black MSM were found to have double the risk of HIV infection. Among MSM with known HIV infection, black MSM reported fewer clinical visits, less antiretroviral therapy utilization, lower antiretroviral therapy adherence, and lower CD4+ cell counts than other MSM. Among MSM less than 30 years old, black MSM reported earlier sexual debut, and greater likelihood of having older male sex partners or having been sexually abused as a child. Millett pointed to the need to move beyond risk-based interventions in black MSM populations and address structural issues, engagement in care, and intergenerational sex.

Trends in the Global HIV Epidemic

Wawer and colleagues presented data on temporal trends in HIV incidence, prevalence, and prevention services in Rakai, Uganda, from 1994 through 2011 (Abstract 141). In parallel with the rise in uptake of antiretroviral therapy and MMC after 2005, there was an overall steep decline in HIV incidence and a lesser decline in HIV prevalence. The decline in incidence was greater in men than in women (10-fold vs 2-fold, respectively). Moreover, although HIV prevalence in men has leveled off in recent years, HIV prevalence in women appears to be rising. Wawer highlighted 2 possible explanations for these sex-based differences. MMC reduces HIV incidence primarily in men. Antiretroviral therapy uptake is greater in women than men, leading to a more substantial reduction in transmission to male partners, but an increased life expectancy for women, compared with men. In combination, antiretroviral therapy and MMC would likely lead to a greater decline in HIV incidence in men, with the rising prevalence of HIV in women reflecting decreased mortality rates. Wawer ended by pointing out the substantial deficit in delivery of services to all who need them in Rakai, and argued that these population-level benefits of antiretroviral therapy and MMC make increased provision of services imperative.

Justman presented data on behalf of Nkambule and colleagues on the SHIMS (Swaziland HIV Incidence Measurement Survey), conducted in 2011, which compared HIV prevalence with levels measured in 2005 (Abstract 142). HIV prevalence in 2011 was highest among men aged 35 years to 39 years (48%) and women aged 30 years to 34 years (54%). Age-specific prevalence appears to have declined for younger ages and increased at older ages in both men and women. Justman and colleagues hypothesized that this may reflect increased uptake of antiretroviral therapy, with the resulting declines in HIV incidence reflected particularly among younger persons, and increased survival rates among older persons.

Injectable Hormonal Contraception

Similar to the literature, this year's CROI presented conflicting data on the impact of injectable hormonal contraception (IHC) on the risk of HIV acquisition. McCoy and colleagues presented data on the impact of different types of hormonal contraception on the risk of HIV acquisition (Abstract 20LB). McCoy performed her secondary data analysis on the MIRA (Methods for Improving Reproductive Health in Africa) study, a randomized controlled efficacy trial of the use of a diaphragm and lubricant gel on reducing the risk of HIV-1 acquisition. In this analysis of 4866 women, the use of IHC was associated with a 37% increase in the risk of HIV-1 acquisition; oral contraceptives had no effect on HIV-1 acquisition. The mechanism for this increased risk is not clear, and the increased risk could not be attributed to a specific type of injectable hormonal contraceptive. McCoy presented data from a large number of studies analyzing the effects of contraception on HIV acquisition rates, which show a trend toward increased risk of HIV-1 acquisition associated with use of IHC. However, a number of other studies have found no such association. At the conference, Lutalo and colleagues presented data on more than 500 serodiscordant heterosexual couples in Rakai, Uganda, in 288 of which the woman was the HIV-1-uninfected partner (Abstract 563). The study found no evidence of increased HIV acquisition risk associated with use of IHC, either overall or stratified by type of injectable.

Butler and colleagues addressed the potential benefits and risks of reducing IHC use globally (Abstract 1074). The study compared the potential benefit of reduced HIV-1 infections with the increased rates of pregnancy and maternal deaths likely to result from substituting other forms of contraception. The analysis found that only southern African countries where IHC could be contributing substantial numbers of infections have any potential for public health benefit, assuming the increased relative risk among IHC users is significant. In other parts of the world, the effects of reducing IHC use could potentially be harmful, because of the potential for increased maternal mortality rates.

Modeling the Impact of Increased Testing, Treatment, and Prevention Interventions

Several investigators presented data on how best to prioritize population-level interventions to avert new infections and deaths, while remaining cost-effective. Birger and colleagues presented the relative benefit of different components of test-and-treat interventions on the HIV epidemic in Newark, New Jersey (Abstract 1075). The data model indicated that interventions aimed at retaining HIV-1-infected patients in care would have the greatest impact. However, retention was projected to lead to only a 16% reduction in new HIV-1 infections and a 19% reduction in deaths by 2050. Combining retention in care with increased testing

coverage would reduce new infections by 25%, and the model predicted the further addition of increased rates of viral suppression would lead to a 39% reduction in new infections and a 46% reduction in deaths by 2050. Kessler and colleagues presented modeled data for New York City (Abstract 1076). Their model also suggested that care coordination (efforts to retain patients in care and enhance adherence to medication) would have the largest impact on infection rates, but also incurred the most expense. The model estimated that increased testing, linkage to care, and care coordination would cost $1 billion per year for New York City, and would result in a 23% reduction in new HIV infection rates. Expanding treatment to all HIV-infected persons at the time of diagnosis would only decrease new infections by 3% in the model.

Several investigators focused on the relative impact of expanded testing with various prevention interventions on the HIV epidemic in sub-Saharan Africa. Alsallaq and colleagues presented data on the impact of home-based counseling and testing (HBCT), with linkage to prevention services in KwaZulu-Natal, South Africa (Abstract 1079). The model indicated that 90% coverage of HBCT, coupled with behavior change, MMC (for HIV-uninfected men) and antiretroviral therapy, could result in a 47% decrease in new HIV infections within 4 years of implementation. Behavior change interventions introduced short-term reductions in HIV infections, while MMC (which reduces susceptibility to infection) and antiretroviral therapy (which reduces transmissibility of infection) had long-term impacts. In the model, the expansion of treatment from those with CD4+ counts less than 200 cells/μL to all newly diagnosed persons, regardless of CD4+ cell count, could further reduce HIV incidence by 63% at year 4 and 76% at year 15. Nichols and colleagues presented data modeled for rural Zambia on the relative cost-effectiveness of increased testing and antiretroviral therapy for HIV-infected persons, compared with to providing PrEP in a targeted (high-risk groups) or non-targeted (general population) fashion (Abstract 1080). In this model, increased HIV-1 testing (assumed coverage of 70%-90%) and linkage to care (assumed coverage of 70%) could result in a 50% reduction in incidence over 10 years, at a cost of $134 for each quality-adjusted life–year (QALY) gained. In this model, targeted PrEP was somewhat less effective, with a projected 31% reduction in HIV-1 incidence at a cost of $323 per QALY. Non-targeted PrEP was the least effective (23% reduction in incidence) and most costly ($1843 per QALY) approach. Alistar and colleagues also evaluated increased rates of treatment, focused PrEP, and generalized PrEP administration for South African adults (Abstract 1081). As in the previous study, the greatest benefit comes from scaling up treatment. Increasing antiretroviral coverage to 50% of persons eligible under existing guidelines could result in 1.5 million infections averted over the next 20 years, while universal treatment could result in 3.6 million infections averted. Universal access to treatment was more cost-effective than providing treatment according to existing guidelines ($310-$340 per QALY gained vs $410-$420 per QALY gained, respectively). Targeting PrEP to those at greatest risk could actually be cost-saving if universal access were to reach fewer than 70% of the HIV-1-infected population. Generalized PrEP would be most expensive if antiretroviral therapy coverage were high ($1050-$2800 per QALY gained). Buchbinder and colleagues explored different strategies for targeting PrEP in the MSM global epidemic, based on data from the iPrEx study (Abstract 1066). In that analysis, the total number needed to treat (NNT) to prevent 1 HIV infection was 60. However, men reporting unprotected receptive anal sex, regardless of partner serostatus, accounted for two-thirds of all new HIV infections, and the NNT for this subset was only 35. All of these abstracts point to a primary need to expand coverage of antiretroviral therapy to HIV-infected populations, with a supportive role of targeted PrEP to further reduce HIV-1 infection.

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A list of all cited abstracts appears on pages 87-93.

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Neurologic Complications of HIV Infection

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The effects of HIV-1 in the nervous system are a topic of avid interest to investigators and clinicians focused on HIV, judging by the large and discriminating audience at the oral sessions and poster presentations relating to neuroscience at the 19th Conference on Retroviruses and Opportunistic Infections. Major areas of investigation at this year's conference included the use of neuropsychological testing and neuroimaging to assess the state of the central nervous system (CNS) and effects of antiretroviral therapy during HIV infection as well as basic and clinical studies of neuropathogenesis of HIV-associated neurocognitive disorder (HAND). Numerous important suggestions emerged during the meeting. Among them was the proposition that earlier initiation of therapy might benefit the CNS. Another was that the relationship between HIV and normal aging remains unclear and warrants further study. Still another was that ongoing abnormalities may persist despite treatment with antiretroviral therapy—including measurable brain microglial activation, detectable cerebrospinal fluid HIV, and progression of neurologic impairment

Introduction—Where Should Priorities Lie?

The neurologic sessions this year at the 19th Conference on Retroviruses and Opportunistic Infections (CROI) focused, as in years past, on understanding the pathogenesis of neurologic impairment in HIV, in particular on HIV-associated neurocognitive disorder (HAND), and on determining the optimal time to initiate treatment for patients with HIV infection to preserve or optimally recover neurologic function. In recent years, the mandate to investigators in Neuro-HIV has been to ascertain the best strategies to address persistent neurologic disease in patients with successful systemic viral suppression on antiretroviral therapy (ART), which assumes that most patients with access to treatment for HIV would choose therapy, resulting in undetectable plasma HIV RNA levels. Ideally, patients with HIV infection would be identified prior to advanced immunosuppression, would have full access to a broad range of ART choices, and would adhere to ART throughout the course of treatment. However, epidemiologic data indicate that it is often difficult to identify HIV infection in its early stages in most communities even in the developed world; at least 34% of patients in the United States have a CD4+ count below 200 cells/μL by the time they are diagnosed with HIV infection.[1] Furthermore, patients in the areas of the world with the highest prevalence of HIV face limited drug choices and numerous barriers to obtaining ART. Data presented at this year's CROI suggest that despite access to treatment, only 24% of HIV-infected patients in the United States have undetectable plasma HIV RNA levels (Skarbinski and colleagues, Abstract 138). These observations raise important questions relevant to the central nervous system (CNS). Is there convincing evidence that earlier diagnosis and treatment might preserve neurologic function? How much viral suppression is enough to preserve the CNS? Will ongoing plasma viremia in treated patients be associated with manifestations of active CNS infection and disorders in treated patients? Finally, investigators are faced with deciding whether we should be targeting our therapies and approaches to the majority of patients—those who are not on ART, do not adhere to ART, or who exhibit clinically consequential resistance—or address the minority of patients with persistent impairment but successful systemic suppression on ART.

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Noninvasive Tools for Investigating Neurologic Status in HIV Infection

Neuropsychological Performance

Methods for assessing neurocognitive status. One of the key challenges in diagnosing and monitoring HAND is the lack of reliable and practical methods of screening for and evaluating neurocognitive impairment. Moore and colleagues (Abstract 499) sought to identify a brief neuropsychologic testing strategy to assess patients for HAND. These investigators administered a comprehensive, 120-minute, 7-domain neuropsychologic battery to 200 HIV-infected US military personnel with few potentially confounding comorbidities, and defined impairment in these subjects as a Global Deficit Score (GDS) of greater than 0.5.[2] The investigators then compared the measurement of impairment by the complete battery with measurements of impairment detected by all possible combinations of 2, 3, and 4 neuropsychologic tests from the overall battery, limiting possible tests such that combinations required fewer than 20 minutes to administer. They identified a 16-minute battery combining 3 neuropsychologic tests with a sensitivity of 86.5% and specificity of 75.5%,

and an 18-minute battery combining 4 tests resulting in a sensitivity of 86.5% and specificity of 87.1%. These batteries may be good substitutes for comprehensive batteries in research settings in which resources and patient fatigue require brief assessments for HAND. Similarly, Smith and colleagues (Abstract 505) reported on the use of the International HIV Dementia Scale (IHDS) as a screening tool for more subtle forms of HAND. Developed as a tool for detection of HIV dementia, the IHDS is a brief bedside or office evaluation method that requires no equipment and includes a motor-speed test, a psychomotor speed test, and a memory-recall test. The investigators compared scores on the IHDS with results of a more comprehensive battery defining HAND according to 2007 Frascati criteria[3] in 106 subjects. They found that using a cutoff score of 11 points or lower, the IHDS had 72% sensitivity and 44% specificity for all forms of HAND, including asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND). Subjects with HAND had a lower IHDS-scale score than did subjects without HAND. The investigators concluded that although the IHDS was developed for detection of dementia, it may be an acceptable brief screening tool for mild categories of HAND. Meyer and colleagues (Abstract 502) examined the interpretation of a 17-neuropsychologic-test battery administered to 100 HIV-uninfected and 221 HIV-infected subjects in Kenya excluding patients with comorbidities expected to confound HAND diagnosis. The investigators found that when the interpretation was applied to test performance of HIV-uninfected subjects, 45% met Frascati criteria for ANI or MND and 6% for HIV-associated dementia (HAD) according to the most liberal definition of domain impairment (1 test per domain > 1 standard deviation [SD] below the mean), whereas these numbers were 14% and 1% when a stricter definition was used (average score for domain > 1 SD below the mean). Rates of ANI and MND were slightly higher in HIV-infected subjects according to the same criteria (68% with 1 test per domain, and 30% with abnormal score for the whole domain), but the rate of HAD was only 0.5% according to all criteria. These findings suggest that at least in the Kenyan population, neuropsychologic-test indications of impairment may be unrelated to HIV and that more rigorous standards should be applied in defining abnormality on testing to reduce false-positive results.

Neurocognitive status in early infection. It remains unresolved as to when neurologic impairment occurs during the course of HIV infection. Many individuals develop dementia after long-standing untreated HIV infection, and recent studies have demonstrated that more subtle impairment characterizes up to 50% of HIV-infected persons remains even in the ART era.[4] Peterson and colleagues (Abstract 80) reported on neurologic performance in 70 subjects recruited during primary HIV infection (median 4 months after HIV transmission) and who were longitudinally followed using an 11-test neuropsychologic battery. At baseline, 42% of subjects performed greater than 1 SD below norm means in more than 2 neuropsychologic domains, meeting Frascati definitions of ANI or MND. Before the initiation of ART, performance improved in most domains over time with repeated testing but declined in the motor domain. In subjects who initiated HIV treatment for reasons independent of the study, motor performance stabilized but did not improve during follow-up. Although these findings suggest that impairment may accrue even in the first year of HIV infection before the initiation of ART, the extent to which these changes are due to HIV rather than concomitant factors remains unknown. Vo and colleagues (Abstract 507) presented data from the Multicenter AIDS Cohort Study (MACS) following subjects who were HIV-uninfected at enrollment but who seroconverted during the course of the study. These investigators evaluated results of a brief battery of neuropsychologic tests from 5 years before seroconversion through 3 years after seroconversion, over a possible 25 years of follow-up by the MACS. They did not observe statistically significant changes in performance in the brief battery before or after seroconversion. Improvement in performance as a result of practice effect from repeated testing, effects of initiation of ART in seroconverters, and the brief nature of the battery may contribute to the differences between the findings of this study and those of Peterson and colleagues. However, the findings of Vo and colleagues also may suggest that HIV itself is not the primary cause of neurologic dysfunction in subjects with recent HIV infection.

Impact of earlier ART on neurocognitive performance. Building on the concept that injury to the CNS may occur early in the course of HIV infection, several studies investigated the effects of earlier initiation of ART on neurologic outcomes. Puthanakit and colleagues (Abstract 24) compared neuropsychological test performance outcomes in 284 Thai and Cambodian HIV-infected children (median 7 years old) in the PREDICT (Prospective Randomized Evaluation of DNA Screening in a Clinical Trial) study who were randomly assigned to immediate ART or therapy deferred until CD4+ percentage fell below 15% or Centers for Disease Control and Prevention (CDC) Category C events occurred. Although children with immediate therapy had higher CD4+ percentages and longer exposure to ART than those who deferred-therapy group at 144 weeks after enrollment, neuropsychologic test performance did not differ between the 2 groups. However, both HIV-infected groups had statistically significantly lower Wechsler Intelligence Scale (IQ) scores than did 164 age-matched HIV-uninfected Thai and Cambodian children, suggesting that either comorbid factors or effects of HIV before the initiation of therapy even in the immediate group had resulted in neurologic injury in these children by the time of evaluation.

Crum-Cianflone and colleagues (Abstract 500) evaluated the rates of neurocognitive impairment, defined as a GDS greater than 0.5, in 200 military personnel with known (within 1.2 years) dates of seroconversion and low

rates of substance use and medical or psychologic factors that might confound neuropsychologic testing. These subjects were assessed with a comprehensive neuropsychologic battery at a fairly early stage of HIV infection, with median nadir CD4+ count 319 cells/μL and median duration of infection of 5 years. A total of 65% of subjects were on ART, initiated at median 1.4 years after HIV diagnosis. The cohort overall had rates of neurocognitive impairment that were not different from those found in 50 HIV-uninfected control subjects assessed with an identical battery. This finding suggests that early intervention for HIV infection might preserve neurocognitive function, although the authors acknowledge that the minimal confounding comorbidities and stable lifestyle context for these subjects might also relate to low levels of impairment in this group. Finally, Marcotte and colleagues (Abstract 485) investigated the neurocognitive outcomes of Maharashtran subjects in Pune, India, with high baseline CD4+ counts (approximately 460 cells/μL) randomly assigned to immediate initiation of ART or to deferred treatment. Improvement from baseline to 1-year follow-up visit was statistically significantly associated with the interaction between poorer baseline neuropsychologic performance and assignment to the immediate treatment group ($P = .02$). These findings suggest that patients with relative neurocognitive impairment in the early stages of HIV might benefit from immediate initiation of ART, even while CD4+ counts are relatively preserved.

Neurocognitive decline in patients with chronic HIV. An area of controversy for clinicians and investigators is whether mild neurologic impairment—defined by reduced performance on neuropsychologic testing but no associated functional impairment—has clinical significance for patients infected with HIV. In the 1555-person CHARTER (CNS HIV Antiretroviral Therapy Effects Research) study, 33% of subjects were considered to have such a condition (defined as ANI by Frascati criteria) at study entry. Grant presented findings (Abstract 77) demonstrating that ANI conferred a risk of progression to symptomatic stages of HAND (MND or HAD) in CHARTER subjects. The researchers evaluated indices of symptoms of neurocognitive impairment, including self-report of symptoms and performance-based assessments, in 226 subjects without impairment and 121 ANI subjects every 6 months for a median time of 45 months. They found that individuals with ANI had an increased relative risk of progressing to symptomatic HAND compared with cognitively normal individuals, 2-times higher if based on self-report and more than 5-times higher if based on performance-based evaluation. These authors made efforts to correct these estimates for potentially confounding factors, including baseline education level and categorization of severity of comorbidities, such as substance abuse. Their findings suggest that mild, asymptomatic, neurologic impairment may reflect an active process that progresses to more substantial impairment in persons with HIV infection. However, since approximately 30% of subjects in the ANI group were not on ART at baseline in the study, it is unclear to what extent ANI subjects with complete systemic viral suppression might experience substantial progression of HAND during continued ART.

Another study from the CHARTER collaborative group (Abstract 474) focused on the related topic of determinants of neurocognitive decline over longitudinal follow-up in a group of 437 HIV-infected subjects mostly on ART. They found that 22.7% of subjects showed decline in performance over time, while 16.5% showed improvement. In a multivariable model, absence of ART, having a low CD4+ count, Hispanic ethnicity, and presence of severe comorbidities were associated with decline in neurocognition. These data are consistent with prior studies suggesting that detectable HIV RNA in plasma plays a continued role in neurologic impairment in the current era.[5-7] The data also suggest that comorbidities rather than HIV alone may contribute to clinical progression.

Brain Imaging Investigations of Neuropathogenesis and Assessment of Neurologic Status

Neuroimaging provides a variety of non-invasive methods to understand the pathophysiologic changes seen with HAND. A large number of presentations at CROI also focused on the use of neuroimaging as a means of investigating HIV neuropathogenesis or as a biomarker of the status of the brain in HIV-infected persons. Presentations highlighted an ever-expanding list of techniques, including morphometry, magnetic resonance spectroscopy (MRS), diffusion tensor imaging (DTI), and positron emission tomography (PET), as methods to investigate the status of the brain in HIV-infected patients, with particular focus on understanding the potential relationship between aging and HIV and the effects of ART.

Volumetrics. Both Becker and colleagues (Abstract 512) and Ortega and colleagues (Abstract 514) studied the effects of HIV and aging using volumetric measurements. Becker and associates performed neuroimaging in 84 HIV-seropositive men and 76 HIV-seronegative men. The investigators observed independent effects of HIV and aging within the gray and white matter and saw no statistically significant relationship. Cardiovascular risk factors were not associated with reductions in brain volume. Further studies that include both male and female HIV-seropositive and -seronegative participants are required. Ortega and colleagues studied 52 HIV-seropositive patients and 26 HIV-seronegative controls. The investigators assessed the effects of ART and aging on brain volumetrics. HIV-seropositive patients, whether on ART or treatment naive, had statistically significant reductions in brain volume within the amygdala, caudate, and corpus callosum compared with HIV-seronegative controls. Both HIV and aging independently caused atrophy in the caudate. These changes gradually occurred after self-reported seroconversion. Further longitudinal studies of primary infected

HIV-seropositive subjects are needed.

A complementary study by Gongvatana and colleagues (Abstract 513) investigated the relationship between observed brain volumetrics and plasma biomarkers (interferon [IFN]-γ, interleukin[IL]-β, IL-6, IL-8, IL-10, IL-16, IL-18, IP-10, monocyte-chemoattractant protein-1 [MCP-1], macrophage inflammatory protein-1-β [MIP-1-β], stromal cell-derived factor-1 [SDF1-α] tumor necrosis factor [TNF-α], and TNF-related apoptosis-inducing ligand [TRAIL]) in 74 HIV-infected participants on ART. As in the above studies, older age was associated with a reduction in brain volume even in HIV-infected subjects with well-controlled plasma viral load. The authors suggest that observed findings may reflect ART toxicity. In addition, higher IFN-γ, MCP-1, and TNF-α were related to increased volumes within the putamen, pallidum, amygdala, and corpus callosum. Higher IL-1, IL-6, IL-16, IL-18, IP-10, MIP-β, and SDF1-α were related to decreased volumes within the putamen, pallidum, thalamus, hippocampus, amygdala, and corpus callosum. Additional studies of HIV-seronegative subjects using imaging and blood biomarkers are needed.

To further study the effects of ART on brain volume, Sammet and colleagues (Abstract 511) used voxel-based morphometry (VBM) to compare gray-matter volume in treated (n = 25) and untreated (n = 25) subjects with primary HIV infection and age–matched HIV-seronegative controls (n = 20). The authors observed a statistically significant reduction in the insular cortex of HIV-seropositive patients on ART compared with HIV-seronegative controls. In addition, treated HIV-seropositive patients had a statistically significant reduction in volume within the anterior cingulate, insular cortex, precuneus, temporal gyrus, and temporal pole compared with treatment-naive HIV-seropositive patients. The authors postulate that the findings may reflect ART toxicity or injury related to immune reconstitution, or both. Further studies should investigate the effects of the degree to which ART penetrates the CNS on brain volume outcomes.

MRS. Cysique and colleagues (Abstract 492) compared metabolic ratios in chronically infected HIV-seropositive patients (n = 90) with HIV-seronegative controls (n = 25). The HIV-seropositive group had higher inflammatory marker levels in frontal white matter and reduced neural integrity in the caudate. No connection was observed between HIV and age. However, duration of HIV infection and presence of cardiovascular risk factors were associated with brain injury in HIV-infected patients. Additional analyses using standard metabolic ratios and correction for multiple comparisons might produce different results.

Young and colleagues (Abstract 79) assessed neuronal and glial changes associated with primary HIV infection. MRS data were obtained from a cohort of individuals with primary HIV infection (n = 53), a chronically HIV-infected cohort (n = 18), and HIV-seronegative controls (n = 19). At baseline, only chronically HIV-infected subjects had a statistically significant decrease in neuronal metabolites compared with individuals with primary HIV infection or HIV-seronegative controls. Within subjects with primary infection who were followed up longitudinally, ratios of choline metabolites associated with inflammation and membrane turnover increased over time before therapy and then stabilized after the initiation of ART. The authors suggested that changes associated with HIV-related injury in the CNS may develop soon after HIV infection, but early initiation of ART may ameliorate some of these changes.

Similar to Young's findings of rising choline/creatine ratios in early infection was a report by Sailasuta and colleagues (Abstract 456) that elevations in brain choline/creatine ratios were characterized in subjects with acute HIV infection compared with HIV-uninfected subjects and improved over time after very early treatment with ART. These studies suggest that both acute and progressive brain inflammation characterizes the earliest stages of HIV infection before the typical initiation of ART.

Navia and colleagues (Abstract 509) demonstrated that neuronal injury was present in chronically HIV-infected participants despite ART. Predictors of decreases in neuronal and glial metabolites included older age, longer duration of infection, and longer exposure to ART. These results suggest a possible connection between neurotoxicity and long-term exposure to ART, but additional studies are needed.

DTI and functional imaging. Wright and colleagues (Abstract 510) assessed the effects of ART on DTI measurements within the corpus callosum. Treatment-naive HIV-infected (n = 21) subjects had statistically significant reductions in DTI parameters compared with HIV-infected patients receiving ART (n = 21) and HIV-seronegative controls (n = 21). Longitudinal analysis of HIV-seropositive patients before and then 3 to 5 months after initiating ART demonstrated a normalization of DTI parameters after starting medications. These results suggest a reduction in inflammation after starting ART. Larger studies of HIV-seropositive patients receiving ART with different degrees of CNS-penetration are needed. In addition, Valcour and colleagues (Abstract 496) demonstrated that impairment evident through neuropsychologic testing correlated with changes in DTI parameters within the corpus callosum of 40 HIV-infected patients.

Thomas and colleagues (Abstract 493) used the recently developed technique of resting-state functional connectivity to map cortical networks within HIV-infected (n = 52) and HIV-infected (n = 52) subjects. Overall, HIV-seropositive subjects had a reduction in functional connections within numerous networks, including the default, salience, and control networks. A cortical signature of HIV might exist that distinguishes it from other neurodegenerative diseases (including Alzheimer's disease). Additional studies of subjects with varying degrees of HAND are required.

PET. Garvey and colleagues (Abstract 78LB) studied the role of neuroinflammation (in particular microglia) within the brains of HIV-infected subjects.

These investigators studied the role of activated microglia using the radiotracer PK 11195 in 7 HIV-infected patients and 9 HIV-seronegative controls. An increase in microglial activation was seen within the corpus callosum, anterior cingulate, and temporal lobes of neuro-asymptomatic HIV-seropositive patients on ART compared with HIV-seronegative controls. These findings warrant additional larger studies to confirm these initial findings, and longitudinal studies to determine when microglial activation is established and how it evolves in relation to ART.

Pathogenesis of HAND

Neuropathogenesis of HAND: Molecular Studies

Limitations in our understanding of the basic neuropathogenesis of HIV prompted some of the investigations presented at this year's conference, where topics included viral tropism and compartmentalization of HIV species in the CNS, potential mechanisms of neurotoxicity of HIV, and host features predisposing patients to the development of dementia.

Virologic studies. Arrildt and colleagues (Abstract 445) studied HIV species derived from cerebrospinal fluid (CSF) in patients with dementia, comparing compartmentalized HIV that was able to infect cells with high CD4 density with HIV that infected cells with low CD4 density. They observed that CD4 density varied in monocyte-derived macrophages and correlated with infectivity, and that macrophage-tropic (M-tropic) viruses appeared to use any CD4 density for entry; in contrast, T-lymphocyte tropism alone, without macrophage tropism, needed high CD4 density.

Studevant and colleagues (Abstract 447) also investigated compartmentalization of HIV-1, reporting the first evidence of compartmentalization of HIV within the CNS in HIV subtype C and in children. The investigators used single-genome amplification to compare CSF and blood samples obtained from 48 children in Malawi aged 4 months to 37 months, infected in utero or during infancy, and detected CNS compartmentalization in 37.5%. Compartmentalization was noted to be more frequent in the older children or those with higher levels of HIV RNA in CSF. The researchers also noted some preliminary evidence of the ability of viruses to use low CD4 density for entry (interpreted as M-tropic viruses) in these env variants from CSF.

Holman and colleagues (Abstract 83) reported on the development of a machine-learning approach to identifying genetic signatures in HIV *env* associated with HAD. Holman and colleagues used 1022 *env* sequences derived from brain tissue from 78 subjects identified through the HIV Brain Sequence Database (http://www.hivbrainseqdb.org/) to develop an iterative approach to recognizing certain amino acid sequences that were associated with HAD. The researchers identified sequences that were associated with HAD or non-HAD status, and they corroborated their findings with *env* sequences derived from 458 CSF samples from 36 additional clinically characterized subjects. The investigators postulated that this approach may be valuable in assessing sequence data from CNS-derived sources in association with neurologic disease and might yield insight into the neurotropism or neurovirulence of specific strains of HIV.

Choi and colleagues (Abstract 450) sequenced HIV-1 *tat* derived from CSF and blood in 60 subjects. They observed that position HXB2 5905 was associated with the CSF and that greater sequence diversity within the CSF was associated with HAND. Further studies specifically on this position and its role in neurotropism may yield insight into mechanisms of HIV compartmentalization in the CNS.

Mechanisms of neuronal injury. Several studies focused on molecular and cellular mechanisms of neuropathogenesis, specifically examining toxic or transmitter molecules that might directly induce or modulate toxic effects in the brain in the setting of HIV infection. Cantres and colleagues (Abstract 459) measured higher levels of lysosomal protease cathepsin B and its inhibitor cystatin B in monocytes in patients with HAD compared with patients with normal cognition or those with ANI, suggesting that the cathepsin B may be an important mediator of neurologic injury in HIV. Gelman and colleagues (Abstract 465) analyzed levels of type 2 dopamine receptor long isoform (DRD2L) and preproenkephalin messenger RNA (mRNA) in autopsy brain specimens from the National NeuroAIDS Tissue Consortium and found that lower levels of DRD2L were associated with better neurocognitive functioning in life. The authors concluded that downregulation of DRD2L in the setting of HIV infection is protective in HAND, and failure to reduce levels is associated with pathogenic effects of the dopamine system in the prefrontal cortex.

Host factors contributing to HAND. Levine and colleagues (Abstract 470) completed a genome-wide association study (GWAS) of 1287 subjects to investigate whether HAND might be linked to certain host genetic features in subjects enrolled in the MACS. The researchers investigated whether the rate of neurocognitive decline, the presence of HAD, or mild to severe neurocognitive impairment based on 2007 Frascati criteria could be linked to any single-nucleotide polymorphisms (SNPs) identified by either the Illumina, Inc. (San Diego, CA) or Affymetrix (Santa Clara, CA) platforms. The researchers did not identify any SNPs that were statistically significantly associated with these phenotypes. Furthermore, they did not validate previously identified candidate alleles as linked to phenotypes of HAND. The authors concluded that their study might not have had adequate subjects to find significant associations and suggest that further studies might be done that integrate their sequence data with those of other large cohort studies.

Neuropathogenesis of HAND: Clinical and Biomarker Studies

Early HIV infection. Paralleling neuroimaging studies of acute and primary

infection, several laboratory studies investigated CNS HIV pathogenesis in the early stages of infection. Morris and colleagues (Abstract 446) studied HIV coreceptor tropism in plasma in 72 subjects beginning at a mean estimated 70 days after HIV exposure and found that 4 of 72 (5.5%) harbored a CXCR4 or dual/mixed tropic (X4/DM) coreceptor phenotype at baseline, and 9 of 72 (12.5%) had an X4/DM coreceptor phenotype during at least 1 follow-up visit. In a generalized estimating equation model, X4/DM tropism was independently associated with HAND based on neuropsychologic testing criteria, though it is unclear whether this association was a causative relationship or a reflection of other differences in the patients with X4/DM coreceptor phenotype. Lee and colleagues (Abstract 457) demonstrated that although undetectable CSF HIV RNA characterizes approximately 15% of treatment-naive subjects in a primary-infection cohort at a median of 3 months after transmission, emergence of CSF HIV RNA levels not different from those in a detectable HIV RNA group occurs by 1 year in subjects remaining off treatment. Furthermore, reduced CSF inflammation associated with undetectable HIV RNA at baseline is not sustained at 1 year, suggesting that mechanisms associated with this reduced HIV burden and associated immune activation in the CNS are likely unique to the earliest stages of HIV.

Chronic HIV infection. In a study investigating neuropathogenesis and use of a laboratory biomarker for HAND during chronic HIV infection, Mellberg and colleagues (Abstract 469) found that a marker of axonal breakdown, CSF neurofilament light chain (NFL), declined in 85 asymptomatic subjects with a median CD4+ count of 190 cells/μL after initiation of ART when treatment naive or off ART for at least 6 months. This finding suggests that low-level CNS injury is ongoing in HIV-infected persons before overt symptoms of cognitive impairment, that this smoldering injury can be reduced by ART, and that NFL may be a useful marker of neurologic injury even in presymptomatic patients.

Numerous clinically oriented studies focused on mechanisms and biomarkers of HAND in the setting of stable ART. Several studies focused on ongoing abnormal activation of cells of the monocyte/macrophage or microglial lineages in the setting of effective ART. As noted above, Garvey and coworkers (Abstract 78LB) demonstrated areas of elevated uptake of a PET ligand targeted to a receptor on the surface of activated microglia in subjects on suppressive ART. Williams presented evidence (Abstract 81) that plasma soluble hemoglobin scavenger receptor (sCD163) may be a marker of persistent inflammation that, in the setting of successful ART, associates with neurologic disease. A total of 34 subjects on suppressive ART were separated into groups classified as impaired or neurocognitively normal as measured by a GDS approach, which emphasizes abnormality. Elevated levels of sCD163 characterized the subjects with a GDS greater than 0.5 and persisted in this group at a second visit on continued therapy, suggesting that processes underlying neurologic impairment in the setting of treatment are associated with immune activation of the monocyte/macrophage lineage and can be measured in the blood.

Several studies also investigated the sources and potential clinical significance of CSF HIV RNA measured in the setting of ART. Letendre and colleagues (Abstract 473) explored the correlates of CSF HIV RNA in patients on ART. They studied paired CSF and blood samples from 413 subjects in the CHARTER study, selected for their being on ART at all visits according to self-report and adherence assessments. In a multivariable model describing predictors of CSF HIV RNA levels in 2207 visits, plasma HIV RNA levels were the strongest predictor, with an odds ratio [OR] of 18.0. Protease inhibitor use was also a statistically significant predictor of detectable HIV RNA in CSF with an OR of 3.3, with CNS penetration–effectiveness (CPE) score having an overall lower effect (OR, 0.7).

Peluso and colleagues (Abstract 489) presented a report on 10 subjects on suppressive ART with either undetectable plasma HIV RNA or very low levels (median HIV RNA, 62 copies/mL) who presented with incident cognitive, balance, and motor symptoms and were found to have detectable CSF HIV RNA levels (median, 3900 copies/mL) and accompanying CSF inflammation and abnormalities on magnetic resonance imaging (MRI) scans. After their regimens were changed to address HIV genotypes associated with resistance detected in CSF and to improve CNS drug exposure based on pharmacologic properties, patients had improvement in clinical symptoms and, when data were available, in CSF parameters. The authors concluded that although the mechanisms of such symptomatic CSF escape are unknown, it is important to test for this condition in certain clinical circumstances since addressing it with treatment strategies might be beneficial for patients. However, Eden and colleagues (Abstract 488) presented evidence that although CSF HIV RNA levels above 50 copies/mL (identified by sampling in research studies in the setting of undetectable plasma HIV RNA) occurred in 25% of asymptomatic subjects during a longitudinal study, there was no evidence of progression of CNS disease or even persistence of CSF escape in longitudinal follow-up in these subjects. Thus, presence of low-level detectable CSF HIV RNA in patients without neurologic symptoms was of unclear significance.

Conclusions

This year's CROI reported substantial scientific contributions from investigators worldwide and reminded us that many important issues regarding the assessment, pathogenesis, and treatment of HIV in the CNS remain unresolved. Key challenges to the field include the lack of consensus on the definitions and significance of milder forms of impairment; the lack of biomarkers for HAND that can be considered with certainty to be specific for the effects of HIV infection; the need for more large-scale,

well-characterized cohort studies to investigate host factors related to disease; and the continued limitations in understanding the biology of HIV infection in the CNS in subjects on suppressive ART. A topic that pervaded sessions throughout this year's CROI but was not directly addressed in the neurology sessions was whether or in what circumstances the CNS compartment needs to be considered a reservoir relevant to HIV cure strategies. Future studies are required to investigate the possible role of the CNS as a viral reservoir that might elude systemic eradication efforts and to understand the potential effects of proposed cure strategies on the nervous system.

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A list of all cited abstracts appears on pages 87-93.

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Complications of HIV Disease and Antiretroviral Therapy

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Studies on the efficacy of and drug interactions with the hepatitis C virus (HCV) direct-acting antivirals (DAAs) in HCV/HIV coinfection were a highlight of the 2012 Conference on Retroviruses and Opportunistic Infections. The addition of an HCV protease inhibitor (PI) to pegylated interferon alfa/ribavirin increased HCV cure rates by 30% to 35% in HCV genotype 1 treatment-naive HIV-coinfected patients, an increase similar to that observed in HIV-uninfected HCV-infected patients. Drug interactions with antiretrovirals can be complex, and DAAs are recommended for use only with antiretroviral drugs for which pharmacokinetic data are available. Further drug interaction and clinical data are needed to ensure the safe coadminstration of DAAs with antiretroviral therapy. The conference placed continued emphasis on pathogenesis, management, and prevention of the long-term complications of HIV disease and its therapies, including cardiovascular disease, lipodystrophy, renal disease, alterations in bone metabolism, and vitamin D deficiency, along with a growing focus on biomarkers to predict development of end-organ disease. HIV has increasingly been recognized as a disease of accelerated aging, manifested by increased progression of vascular disease, cellular markers of aging, and a heightened risk of certain non–AIDS-defining malignancies. This year's conference also highlighted data on diagnosis, prevention, and complications of tuberculosis coinfection as well as the treatment and prevention of coinfections that are common with HIV, including cryptococcal meningitis, influenza, and varicella zoster.

Viral Hepatitis

DAAs in HIV/HCV Coinfection

The 2012 Conference on Retroviruses and Opportunistic Infections (CROI) provided long-awaited phase II sustained virologic response (SVR) data for the hepatitis C virus (HCV) direct-acting antivirals (DAAs) of the HCV protease inhibitor class, telaprevir and boceprevir, in HIV/HCV-coinfected individuals. In a phase II pilot study, 60 HIV/HCV-coinfected, HCV genotype 1 treatment-naive patients were randomized 2:1 to receive 12 weeks of telaprevir or placebo, each with 48 weeks of peginterferon alfa-2a plus ribavirin (Abstract 46). Antiretroviral therapy (ART) was limited to efavirenz, ritonavir-boosted (/r) atazanavir, or no ART. Those on efavirenz received telaprevir 1125 mg every 8 hours, rather than the standard 750 mg every 8 hours, due to the reduction in telaprevir levels caused by efavirenz coadministration. Overall, the SVR (HCV undetectable) rate at 12 weeks (SVR12) was 74% in the telaprevir group and 45% in the placebo group, for a difference of 29%. This is comparable to the increase in SVR rate demonstrated with telaprevir in HIV-uninfected, HCV genotype 1 treatment-naive patients (75% SVR rate with telaprevir vs 44% with placebo).[1] Similarly, in a retrospective study comparing 25 HIV/HCV-coinfected patients with 34 HCV monoinfected patients all receiving therapy with telaprevir/peginterferon alfa/ribavirin, the on-treatment responses at week 4 (rapid virologic response [RVR]) and week 12 (early virologic response [EVR]) did not differ between HIV-infected and uninfected subjects. The SVR data are forthcoming (Abstract 754). It is notable that the placebo group in the phase II study attained an SVR12 rate of 45%, which is higher than typically reported in studies of peginterferon alfa/ribavirin treatment for HIV/HCV coinfection; this may in part reflect the limited fibrosis of the participants. The 24-week SVR (SVR24) data will be forthcoming, but SVR12 has an excellent predictive value for SVR24[2] and was accepted as an endpoint by the US Food and Drug Administration (FDA) in 2010. SVR12 rate in the atazanavir/r group was higher (80%) than in the efavirenz group (69%) and in the no–ART group (71%). The numbers in each group are too small to draw conclusions about differential efficacy of telaprevir in terms of concomitant ART. Telaprevir is associated with rash, which was more common in the group assigned to that drug (34%) than in the placebo group (23%). However, no cases of severe rash were reported. Pruritus, nausea, fever, and headache were more common in the telaprevir group, and, overall, more serious adverse events occurred with telaprevir (18%) than with placebo (9%). No virologic breakthrough of HIV occurred in any of the treatment groups. Of note, all study participants received 48 weeks of therapy. Data are not yet available on the feasibility of response-guided treatment to shorten treatment with telaprevir in HIV/HCV coinfection.

SVR12 data were also presented from a phase II trial of 100 HIV/HCV coinfected, HCV genotype 1 treatment-naive patients who were randomized 2:1 to receive boceprevir or placebo, each with 48 weeks of peginterferon

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alfa-2b plus weight-based ribavirin (Abstract 47). Boceprevir 800 mg was administered 3 times a day for 44 weeks after a 4-week lead-in period with peginterferon alfa/ribavirin alone. Permissible ART included raltegravir, maraviroc, nucleos(t)ide analogue reverse transcriptase inhibitors (nRTIs) (with the exception of didanosine or zidovudine), and HIV protease inhibitors (PIs) boosted with ritonavir (PI/r), with the majority of participants on a PI/r. Nonnucleoside reverse transcriptase inhibitors (NNRTIs) were not permitted. The SVR12 rate was 60.7% in the boceprevir group and 26.5% in the placebo group, for a difference of 34%, a difference similar to that observed with telaprevir in HIV/HCV coinfection, as well as with boceprevir in HCV monoinfection (66% SVR rate with boceprevir vs 38% with placebo).[3] Three participants in the boceprevir group have not yet reached the SVR12 time point. Adverse events leading to discontinuation were more frequent in the boceprevir group than in the placebo group (20% vs 9%, respectively), and adverse effects occurred more often with boceprevir than with placebo. These adverse effects included dysgeusia, fever, vomiting, anemia, and neutropenia. At week 48, virologic breakthrough of HIV occurred in 3 individuals in the boceprevir group and 4 in the control group. HCV resistance data are forthcoming from both phase II studies.

Drug-drug interactions with HCV PIs have been of particular interest since a 2012 FDA warning cautioned against coadminstering boceprevir with HIV PIs, which substantially reduced HIV PI levels.[4] The supporting data from non-HIV-infected volunteers were more fully presented in Abstract 771LB. Coadministering boceprevir led to reductions in atazanavir/r, lopinavir/r, and darunavir/r areas under the concentration-time curve (AUC) by 35%, 34%, and 44%, respectively, and minimum concentration (C_{min}) levels by 49%, 57%, and 59%, respectively. Conversely, boceprevir AUC and C_{min} were lowered by 45% and 57% in the presence of lopinavir/r, 32% and 35% by darunavir/r, and 5% and 18% by atazanavir/r. Boceprevir does not appear to affect raltegravir AUC (Abstract 772LB). Pharmacokinetic data from non-HIV-infected volunteers for the investigational HCV PI TMC435, which is a substrate of CY3A4, demonstrated that efavirenz greatly reduces TMC435 AUC by 71% and C_{min} by 91% and these drugs should therefore not be coadministered (Abstract 49). However, neither rilpivirine, tenofovir, nor raltegravir substantially affected TMC435 concentrations and were not in turn affected substantively by TMC435. They are therefore attractive ART options to pair with this HCV PI. Because TMC435 is a CYP3A4 substrate, data on coadminstration with HIV PIs will be needed. Pharmacokinetic data for the investigational nonstructural protein 5A (NS5A) inhibitor daclatasvir were also presented (Abstract 618). Efavirenz decreased daclatasvir concentrations, and atazanavir/r increased daclatasvir levels. The recommended increase in daclatasvir dosage to 90 mg with efavirenz and decrease to 30 mg with atazanavir were each estimated to lead to therapeutic drug levels in an extrapolated dose model. Daclatasvir did not have a clinically relevant impact on tenofovir, efavirenz, or atazanavir concentrations.

Overall, these data serve as a reminder to proceed with caution when using HCV PIs and other DAA agents in HIV coinfection. HCV PIs may improve HCV cure rates by 30% to 35% but come with increased toxicity, and drug-drug interactions with ART may be complex and unpredictable. This was demonstrated by pharmacokinetic data on telaprevir, indicating that telaprevir increases atazanavir and lopinavir levels and decreases darunavir levels.[5] Although the rates of virologic breakthrough on HIV in the phase II study of boceprevir (Abstract 47) were similar to the rates in the largely HIV PI-treated boceprevir and placebo groups, prescribing HIV PIs or NNRTIs with boceprevir is not recommended until the clinical significance of the drug-drug interactions is better understood. Boceprevir is expected to have minimal drug interactions with raltegravir. However, clinical data for coadministration are limited. Telaprevir can be coadministered with atazanavir/r, efavirenz (with appropriate adjustment of the telaprevir dose), and likely raltegravir, but coadministration with antiretroviral drug classes other than nRTIs is not yet recommended.

Additional DAA data from HCV-monoinfected patients were presented. The investigational nRTI GS7977 (formerly PSI 7977) generated excitement earlier this year with pilot data for the interferon alfa-free combination of GS7977/ribavirin for 12 weeks that resulted in a 100% SVR12 rate in 10 HCV genotype 2/3, treatment-naive, non-cirrhotic patients.[6] At this year's CROI, data were presented from a subsequent pilot study in which 10 HCV genotype 1 (90% genotype 1a), previous null responders received 12 weeks of GS7977/ribavirin (Abstract 54LB). The initial virologic response was robust, with all participants' HCV RNA undetectable by week 4, but 9 of the 10 participants relapsed by week 4 off treatment, demonstrating that in this harder-to-treat population, 12 weeks of this dual therapy was not sufficient. Findings on the efficacy of 12 weeks of GS7977/ribavirin in treatment-naive genotype 1 patients are expected to be presented this year; preliminary data from the 2012 EASL (European Association for the Study of the Liver) annual meeting demonstrated an 88% SVR4 (SVR after 4 weeks) rate in treatment-naive genotype 1 patients, the majority of whom (22/25) had genotype 1a.[7] The data illustrate that RVR, which is a positive predictor of attainment of SVR with interferon alfa-based regimens, does not appear to predict reliably SVR with interferon alfa-sparing treatments. The combination of GS7997 with ribavirin has not yet been evaluated in HIV-coinfected subjects.

Acute HCV, HCV Reinfection, and Sexual Transmission

The European AIDS Treatment Network (NEAT) cohort presented observational data on outcomes associated with the treatment of acute HCV (Abstract 50). In a sobering reminder of the importance of screening for HCV

in at-risk populations of men who have sex with men (MSM), 95% of acute HCV infections were attributed to MSM sexual transmission, and only 25% of those were symptomatic. When diagnosed and treated during the first year of infection, 69.7% of the subjects were cured, far exceeding SVR rates typically seen with interferon alfa/ribavirin in chronic HIV/HCV coinfection. Of interest, the cure rates in patients with HCV genotype 2/3 improved from 60% to 94% (P = .007) with the addition of ribavirin. There did not appear to be a significant difference in sustained virologic response rates between peginterferon alfa monotherapy and peginterferon alfa/ribavirin in patients with genotype 1 HCV (66.5% vs 70%, respectively; P = ns). However, the administration of ribavirin was not randomly assigned, and the duration of therapy was variable, which may confound the interpretation of the apparent effect of ribavirin in genotype 2/3 HCV.

Once HCV has cleared spontaneously or with treatment, HCV reinfection can occur. A retrospective German cohort study reported that 45 HIV-infected MSM who had cleared a first episode of HCV, either spontaneously or with treatment, went on to develop second, third, and in one case fourth reinfections with HCV (Abstract 752). All reinfections were attributed to sexual acquisition. This report reinforces the need to counsel patients successfully treated for HCV about the risk of reinfection and patients with sexual risk factors about the possibility of HCV transmission through MSM sexual contact. The role of sexual transmission of HCV was highlighted in data from the SHCS (Swiss HIV Cohort Study), which showed that the epidemiology of HCV has shifted from a disease of injection drug users (incidence rate [IR] declined from 13.5/100 person-years of observation in 1998 to 1 incident case during 2008-2011) to a disease predominantly of MSM (IR of 0.2/100 person-years in 1998 increased to 7.4/100 person-years in 2011) (Abstract 743). Heterosexual transmission was rare, with an IR of 0.7/100 person-years.

Predicting Progression of Liver Disease and Cure with Peginterferon Alfa

Understanding the risk of liver fibrosis progression is an important component of deciding on initiation of HCV treatment. In HIV/HCV-coinfected patients with limited fibrosis (transient elastography scores of ≤ 9.5 kPa, corresponding to Metavir fibrosis score of F0-F2), the Ariadne Index found the major determinants of progression to transient elastography scores greater than 9.5 kPa (approximate fibrosis score, F3-F4) included age (odds ratio [OR], 1.10 per year), extent of baseline fibrosis (OR, 1.98 per kPa), HCV genotypes 1/4 (OR, 5.02), and alanine aminotransferase (OR, 1.23 per 10 IU/L). The logistic regression model had a positive predictive value of 0.88 and a negative predictive value of 0.71 for progression to a fibrosis score of F3 or F4 over 5 years. Relying on elastography, which is not FDA approved, limits its usefulness in the United States for the Ariadne and Prometheus (see below) models.

Insulin resistance is also a risk factor for fibrosis progression, occurring in 56% of an HIV/HCV cohort and associated with an adjusted hazard ratio (aHR) of 5.79 (95% confidence interval [CI], 2.08-16.10) for progression to substantial fibrosis (defined as an aspartate aminotransferase to platelet ratio index [APRI] score > 1.5) in those without frank diabetes (Abstract 782). Weight loss or therapies to improve insulin resistance prior to HCV treatment have been suggested. However, in a pilot study of HIV-coinfected patients with HCV genotype 1 and baseline insulin resistance while undergoing HCV retreatment, administering the insulin sensitizer pioglitazone for 24 weeks prior to as well as during peginterferon alfa/ribavirin treatment appears not to substantially improve week-24 HCV RNA virologic response compared with historical controls (15.8% vs 10%, respectively) and was associated with SVR in only 1 of 19 (5.3%) subjects (Abstract 783). Hepatic steatosis frequently occurs in HIV/HCV-coinfected patients. In a Spanish cohort, hepatic steatosis occurred in 60% of HIV/HCV-coinfected patients who underwent 2 or more biopsies (Abstract 781). Fibrosis progression of stage 1 or higher was independently associated with persistence or progression of steatosis (adjusted OR, 2.4). Elevated fasting plasma glucose levels and the use of dideoxynucleoside RTIs (stavudine or didanosine) were also associated with a trend toward steatosis, although these are modifiable risk factors.

Considerable progress has been made in understanding the factors that predict a favorable response to peginterferon alfa-based HCV treatment. The Prometheus score, which incorporated IL28B genotype, liver stiffness by elastometry, HCV genotype, and baseline HCV RNA level, had a favorable area under the receiver operator curve (AUROC) of 0.87 (Abstract 761). Given that the prediction score was derived from an HIV/HCV-coinfected cohort, it is not surprising that the model performed less well in HCV monoinfection (AUROC, 0.77). A free, easy-to-use Internet application for this prediction tool is available at http://www.fundacionies.com/prometheusindex.php?lang=ing.[8] A large German cohort demonstrated that older age predicts a lower rate of SVR in HCV monoinfection and does so more markedly in HIV/HCV coinfection, in which the SVR for those aged 50 years to 60 years declined by more than half to 23.5%, compared with 50% in those aged 18 years to 30 years, with an adjusted OR for SVR at age 50 years to 60 years of 0.17 (P = .006). Favorable IL28B genotype and low-density lipoprotein (LDL) receptor genotype have both been associated with SVR and, when evaluated together, may improve predictive value. The favorable LDL receptor allele C/C was correlated with a faster HCV RNA decline in patients on peginterferon alfa/ribavirin with an already favorable IL28B C/C allele (Abstract 765), suggesting a synergistic effect. A lack of the favorable IL28B C/C allele and of the LDL receptor C/C allele was associated with a 10-fold lower rate of RVR than was the presence of both favorable alleles in a small study (Abstract 765) and with an odds ratio of

0.13 for SVR ($P < .001$) (Abstract 764). The importance of IL28B and LDL receptor genotype status with the newer DAA agents in HIV/HCV coinfection is not yet established.

Impact of HCV on ART Hepatoxicity and Efficacy

HCV coinfection has been associated with increased hepatoxicity on ART. Although hepatoxicity has declined somewhat with current ART in HCV-coinfected patients (37.5/100 person years in 2004-2009 vs 24.6/100 person-years in 1997-1999), HCV-coinfected patients in the most recent time period still had up to a 12-times-higher relative risk of developing hepatoxicity on ART than patients without HCV infection (Abstract 778). Similarly, in an analysis of several randomized AIDS Clinical Trials Group (ACTG) trials, the hazard ratio (HR) for developing earlier hepatotoxicity on ART was 1.53 for patients with HCV coinfection compared with those without HCV (Abstract 779). HCV-coinfected patients had statistically significantly earlier virologic failure of ART (72 weeks vs 182 weeks; $P < .01$) than their HCV-infected counterparts, an aHR of virologic failure of 1.42, and a blunted CD4+ cell response to ART initiation.

Low Rates of HCV Testing and Treatment in the HIV Population

Despite the importance of HCV as a growing driver of morbidity and mortality in the HIV population, HCV coinfection is underdiagnosed and undertreated. In a Florida cohort of more than 14,000 HIV-infected patients evaluated over 10 years, only 51% were ever tested for HCV. Of the 17.6% diagnosed with HCV infection, 44% were referred for hepatitis care, 12% were treated for HCV, and only 10% attained an SVR (Abstract 751). Improved diagnosis of HCV coinfection and access to HCV treatment will be crucial for HIV/HCV-coinfected patients to benefit from the HCV DAAs' tremendous promise of improved efficacy and shortened treatment.

Hepatitis B Virus

Decline in quantitative hepatitis B surface antigen (HbsAg) levels has emerged as an important predictor of patient response to hepatitis B virus (HBV) treatment. In HIV-coinfected patients positive for hepatitis B e antigen (HbeAg) treated with up to 8 years of tenofovir, a decline in HbsAg of 2 $\log_{10}$ or more at month 6 was correlated with HbeAg loss by year 6. Patients with HbsAg less than 100 IU/mL at 6 months of treatment had a 71% probability of HbsAg loss, and none of the patients with HbsAg greater than 100 IU/mL attained HbsAg loss during a median follow-up of 56 months (Abstract 53). However, overall HbsAg loss was infrequent, occurring in 18% (8% HbeAg+ and 8% HbeAg-), indicating the long-term nature of HBV treatment in most HIV/HBV-coinfected patients. Suppression of HBV DNA alone with tenofovir can take years; only 56% had HBV DNA below the limit of detection after 1 year of tenofovir therapy (Abstract 796). Where available, tenofovir is the mainstay of HIV/HBV treatment, because lamivudine monotherapy for HIV is associated with high rates of HBV resistance in HIV/HBV coinfection.[9] A Malawi cohort of HIV/HBV-coinfected patients treated for HBV with only lamivudine as part of ART demonstrated that 85% of those with detectable HBV DNA at 48 weeks had HBV-resistance mutations, reinforcing the need for access to tenofovir-based regimens for managing HBV coinfection in resource-limited settings (Abstract 797).

CVD and Ischemic Stroke

Identifying the mechanisms that underlie cardiovascular disease (CVD) risk in the setting of HIV infection continues to be an active area of investigation. Studies of treatment-naive patients may provide some insights into the role of HIV infection. A cross-sectional study of relatively young (median age, 36 years) treatment-naive patients found that traditional risk factors (ie, age, weight, small LDL) were independently associated with carotid intima-media thickness (IMT), whereas HIV RNA, CD4+ T-cell counts, and markers of immune activation (CD38 expression on CD8+ and CD4+ T cells) were not (Abstract 801). A prospective study of carotid IMT progression in a group of untreated HIV patients matched to an HIV-uninfected group followed for 1 year demonstrated a higher rate of progression of carotid IMT in the HIV-uninfected group (Abstract 802). Independent predictors of a greater change in common carotid artery IMT in this study were higher body mass index and family history of CVD, whereas predictors of greater change in bulb IMT were higher soluble tumor necrosis factor receptor I (sTNF1) and higher diastolic blood pressure, and not other markers of inflammation. Together, these studies underscore the importance of traditional risk factors as a driving force for CVD in untreated HIV infection.

The D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study, a prospective cohort, has yielded many important observations about risk factors for CVD in patients with HIV. Now with more than 223,242 person-years of follow-up, a larger number of events has been recorded, including 716 myocardial infarctions (MIs), 1056 coronary heart disease (CHD) events (MI or invasive procedure), 303 strokes, and 1374 CVD events, with overall rates of 3.21, 4.75, 1.35, and 6.21 events/1000 person-years, respectively (Abstract 822). Sabin and D:A:D colleagues examined the relationships between nadir CD4+ cell count and latest CD4+ cell and CVD events. The associations between immunodeficiency and the CVD events varied. The investigators found no evidence of a higher risk of MI or CHD (MI plus invasive procedures) in those with lower latest or nadir CD4+ cell counts. However, stroke and CVD (stroke plus CHD) rates were substantially higher in those with a latest CD4+ cell count less than 100/μL. Of note, prior cytomegalovirus disease was significantly associated with CVD risk but not with stroke and did not modify the relationship between latest CD4+ cell count and the risk of stroke or CVD. These findings underscore the

potential importance of preventing CD4+ cell count decline with earlier treatment of HIV infection as a means of reducing CVD.

Hypertension, an important risk factor for CVD, is receiving more attention in HIV-infected patients. Armah and colleagues from the VACS (Veterans Aging Cohort Study) Project Team, using data from the VACS database that includes more than 80,000 veterans free of CVD at baseline, examined whether the association between systolic blood pressure and risk for acute MI differed by HIV serostatus (Abstract 120). The risks of MI by JNC-7 (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) blood pressure categories were compared in the HIV-seropositive and -seronegative groups after controlling for other known CVD risk factors. The association between blood pressure category and the risk of acute MI was greater in the HIV-infected group at all levels, including the prehypertension group (systolic blood pressure 120 mmHg-139 mmHg on no medications). These findings have important implications for how we screen and manage CVD risk factors in patients with HIV.

The relationship between renal dysfunction and CVD risk received further attention this year at CROI. Investigators from the SUN (Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy) identified an association between declining kidney function and progression of carotid IMT (Abstract 804). The greatest impact of this association was found in those with the most impairment in renal function and among persons of older age or black race. An association between impaired renal function and CVD events was also noted in an Italian cohort with a small number of clinical events (Abstract 868).

Data from a large health care database that included an HIV-uninfected control group indicated an association between HIV infection and the risk for ischemic stroke (Abstract 820). The incidence rate of ischemic stroke in the HIV-seropositive cohort was 5.27/1000 person-years, compared with 3.75/1000 person-years in the HIV-seronegative cohort. After adjustment for several important confounders, the excess risk in the HIV group was attenuated but remained significant (HR, 1.21; 95% CI, 1.01-1.46; P = .043). The excess risk associated with HIV was most notable in younger patients, a finding that was previously observed for CVD in a similar database analysis.[10] Within the HIV-infected cohort, higher viral load was associated with increased stroke risk, and the use of NNRTIs was associated with decreased stroke risk. The issue of sensitivity of ICD-9 (International Statistical Classification of Diseases and Related Health Problems, ninth edition) codes for the diagnosis of secondary MIs, was raised by a study from the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) (Abstract 821). Using data from an ongoing cohort that includes laboratory and electrocardiography (ECG) data from all inpatient and outpatient encounters, a group of reviewers adjudicated potential MI events and found that only 35% of the definite or probable MI events would have been captured by ICD-9 codes and that this was due to a high rate of secondary MIs (in the setting of sepsis or cocaine use). The results of this study underscore the importance of secondary MI events in the setting of patients with HIV infection and highlight the limitations of the reliance on ICD-9 codes for epidemiologic research.

Rates of sudden cardiac death (SCD) for patients with HIV infection have not been well studied. Tseng and colleagues examined such SCD rates by studying the records of 2860 patients who died between 2000 and 2009 (Abstract 824). SCD events were determined using standard criteria, and deaths in hospice or due to overdose, violence, suicide, cancer, or opportunistic infections were excluded. SCD accounted for 13% of all deaths and 86% of the cardiac deaths. Patients who died from SCD tended to have higher CD4+ cell counts and lower HIV RNA levels. The risk factors for SCD in patients with HIV warrant closer study.

Endothelial Dysfunction

Asymmetric dimethylarginine (ADMA), a marker of NO_2-mediated endothelial dysfunction that predicts the risk of CVD in the HIV-uninfected population, received a lot of attention at the conference (Abstracts 831-833, 841). In a cross-sectional study comparing HIV-seropositive patients to controls, ADMA levels were higher in the HIV-infected group. Lower CD4+ cell count and higher HIV RNA level were associated with higher ADMA level (Abstract 833). ADMA level was also associated with pulmonary hypertension in another study (Abstract 841). Previous studies have demonstrated that endothelial function, as measured by flow-mediated dilatation of the brachial artery, improves when ART is initiated. It was therefore reassuring to see improvements in ADMA in patients started on ART (Abstracts 831, 832). Baker and colleagues from the INSIGHT/SMART (International Network for Strategic Initiatives in Global HIV Trials/Strategies for Management of Antiretroviral Therapy) Study Groups reported a decline in ADMA among patients starting ART compared with those who deferred therapy (Abstract 831). The decline in ADMA was greater among those with higher baseline levels of high-sensitivity C-reactive protein (hsCRP) and D-dimer but did not differ according to HIV RNA level or CD4+ cell count. More long-term studies are needed to determine whether declines in ADMA on ART predict reduced risk for future CVD events.

Questions remain about the association between specific antiretroviral agents and changes in endothelial function and markers of inflammation. Wohl and colleagues reported the results of the NICE (Nucleoside Inflammation, Coagulation, and Endothelial Function) Study (Abstract 838), a cross-sectional study in which flow-mediated dilation (FMD) of the brachial artery and markers of inflammation were compared among patients who had originally been randomly assigned to receive ART including either abacavir or tenofovir. Individuals who had been receiving ART regimens containing

zidovudine served as the control group. Lower (more impaired) FMD was observed in the abacavir group (3.9%) and the tenofovir group (4.5%) than in the zidovudine group (6.1%). However, lower levels of hsCRP and D-dimer were observed in the abacavir and tenofovir groups. Prospective randomized studies will be required to lay this issue to rest.

Novel Imaging Methods and CVD

New data from novel imaging modalities were employed to investigate the prevalence and mechanisms of CVD in HIV patients. Subramanian and colleagues used fludeoxyglucose positron emission tomography (^{18}FDG-PET) to evaluate arterial-wall inflammation in HIV-infected patients in relation to traditional and non-traditional risk markers, including coronary calcium and a marker of macrophage activation, soluble hemoglobin scavenger receptor (sCD163) (Abstract 121). HIV-infected participants with low Framingham Risk Scores (FRS) were compared with a matched HIV-seronegative group. A third group with known atherosclerotic disease served as positive controls. Arterial inflammation was higher in the HIV-seropositive subjects than in the FRS-matched control subjects but was similar to that of the atherosclerotic controls. When the analysis was restricted to the group with zero coronary calcium detected by computed tomography (CT) scan, the intensity of arterial inflammation remained greater in the HIV-seropositive group. Arterial inflammation as measured by ^{18}FDG-PET was associated with the macrophage activation marker sCD163 but not with hsCRP. These findings suggest that macrophage activation may contribute to atherosclerosis in HIV; they also uncover a substantial amount of disease in patients deemed to be at low risk according to traditional measures. Cardiac magnetic resonance imaging and magnetic resonance spectroscopy were used to assess myocardial fibrosis, cardiac systolic and diastolic function, cardiac torsion, and intramyocardial lipids in a descriptive study of myocardial disease in an observational study of 104 HIV-infected patients and 39 age-matched controls without a history of CVD (Abstract 810). In addition, transthoracic echocardiography was used to measure cardiac diastolic function. The prevalence of midwall and epicardial myocardial fibrosis of the left ventricle was significantly higher in the HIV-infected group. Myocardial lipid content was 43% higher in the treated HIV-infected patients than in the controls. The prevalence of systolic and diastolic dysfunction was higher in the HIV-infected group and most notable among the smaller group of ART-naive participants. Longitudinal assessments of HIV-infected patients initiating therapy are needed to determine the time course and relationship between the development of myocardial fibrosis and steatosis and ART and to determine the clinical significance of these findings.

The MACS (Multicenter AIDS Cohort Study) group investigated the relationship between fat depots, markers of inflammation, and other factors associated with coronary plaque in a large cohort of HIV-seropositive and -seronegative men. Using CT angiography, the group was able to examine the prevalence of coronary plaque and to distinguish calcified plaque from the earlier-stage, noncalcified plaque. This distinction is important, as non-calcified plaque may be more prone to rupture. Plaque composition was graded in coronary segments to generate scores for total, noncalcified, mixed, and calcified plaque (Abstracts 807-809). The prevalence of coronary plaque did not differ between the HIV-seropositive and seronegative men, but non calcified plaque was more common in those with HIV and appeared to be associated with nadir CD4+ cell counts. Higher plasma levels of interleukin 6 (IL-6) and tumor necrosis factor-alpha receptor 1 (TNFα-R1) were associated with measures of advanced HIV disease and increased subclinical coronary atherosclerotic plaque (Abstract 808). In both HIV-seropositive and -seronegative men, larger amounts of visceral fat were associated with higher plaque scores. However, the relationship between subcutaneous fat, liver fat, and plaque varied by HIV serostatus. Lower amounts of subcutaneous fat correlated with greater amounts of mixed plaque only in the HIV-seropositive group. These findings support the idea that inflammation contributes to atherosclerosis in HIV-infected patients and might shed light on the importance of noncalcified plaque in patients with HIV infection.

Interventions to Reduce Cardiovascular Risk

There are limited data from randomized controlled trials on outcomes of interventions aimed at reducing cardiovascular risk. Fitch and colleagues reported the results of a small, double-blind, placebo-controlled, 12-month study of 50 HIV-infected patients with metabolic syndrome that compared the effect of lifestyle modification (LSM; 60 minutes of exercise 3 times per week, with weekly nutrition counseling) with metformin (500 mg twice daily for 3 months, followed by 850 mg twice daily) on the progression of coronary artery calcification (CAC) as measured by CT scan (Abstract 119). After 48 weeks of follow-up, 72% of the participants remained in the study. Progression of CAC was statistically significantly reduced in the metformin-treated group compared with the LSM group. These results were driven by a high rate of CAC progression in the placebo groups (these groups also had a higher prevalence of CAC at baseline) compared with minimal change in the metformin group. The finding of a 56% change in CAC over 1 year in the placebo groups was noted as a striking rate of progression, much greater than what has been reported in the general population. The authors also noted that the sample size may have been too small to demonstrate an effect of LSM. This is the first study to show a potential benefit of metformin for reducing CAC progression in general and, in particular, in patients with HIV infection with metabolic syndrome. The findings warrant further research in a larger study and more investigation to determine whether metformin will reduce cardiovascular events.

Statin drugs have been demonstrated to reduce mortality in patients with prior cardiovascular disease, and there is great interest in other properties of the drugs in its class due to their potential to reduce inflammation. By examining the outcomes of patients who initiated statin therapy during long-term follow-up in ACTG studies, Overton and colleagues explored whether statins reduce the risk for serious non-AIDS events and all-cause mortality (Abstract 124). Statin use was not associated with a reduction in mortality in the group overall; however, among the subgroup over the age of 50 years, the risk of mortality was lower among the statin users. In exploratory analyses, statins appeared to have a protective effect in reducing malignancy events (see Malignancies, below). Although limited by the observational nature of this cohort, these pilot findings should help to guide future efforts to explore the potential benefits of statin drugs for patients with HIV.

Finally, a pilot study examined the impact of pravastatin and lisinopril in virologically suppressed patients with a modest level of CVD risk. The researchers found a statistically significant reduction in biomarkers of inflammation (hsCRP and TNFα-R1) in the lisinopril-treated patients but saw no improvement in lipids or inflammatory markers in the group receiving 20 mg of pravastatin (Abstract 825). Future studies of statin therapy, targeting patients at highest risk of long-term complications, appear to be warranted.

Biomarkers of Inflammation and Risk of End-Organ Disease

There continues to be tremendous interest in identifying biomarkers that predict the risk of end-organ disease (eg, CVD and hepatic and renal events) in HIV-infected patients. Previous studies have found strong associations between markers of inflammation (hsCRP and IL-6), altered coagulation (D-dimers) and microbial translocation, and morbidity and mortality in treated and un-treated HIV infection. Investigators from VACS examined levels of these biomarkers in HIV-infected veterans and a matched group of HIV-uninfected veterans with a similar burden of comorbid diseases and found that higher levels of the biomarkers IL-6 and D-dimer (> 75th percentile) were most notable in the HIV-seropositive veterans with an unsuppressed HIV viral load or a low CD4+ cell count. Higher levels of soluble CD14 (sCD14) were only seen in the HIV group with CD4+ counts lower than 200 cells/μL (Abstract 829).

Microbial Translocation and Clinical Outcomes

It has been postulated that the loss of gut lymphoid tissue early in the course of HIV infection can lead to microbial translocation. However, the direct relationship between markers of microbial translocation and the progression of clinical disease and mortality remains incompletely understood. Hunt and colleagues examined the relationship between plasma markers of inflammation, monocyte activation, coagulation, indoleamine 2,3-dioxygenase (IDO)-induced tryptophan catabolism, and gut epithelial barrier dysfunction (intestinal fatty acid binding protein [I-FABP] and zonulin, a protein involved in tight junctions between gut cells), and mortality in a case-controlled study of treated virally suppressed patients with a history of AIDS (Abstract 278). Strong associations between markers of inflammation (OR for IL-6, 119), gut epithelial barrier dysfunction (independent associations for both I-FABP and zonulin after controlling for the other markers were noted), IDO-induced tryptophan catabolism and coagulation (OR for D-dimer, 29) were observed. Other studies investigating relationships between sCD14, a measure of monocyte activation, and clinical outcomes found associations between higher plasma levels of sCD14 and progression of atherosclerosis (as measured by carotid IMT) in adults (Abstract 122) but not in children (Abstract 976), as a predictor of the development of hypertension (Abstract 814), and as a marker for the risk for mother-to-child transmission (Abstract 1039). In addition, several studies examined the associations between cerebrospinal fluid (CSF) levels of sCD14 and neurologic outcomes (see Spudich et al in this issue). These findings confirmed the important relationship between markers of gut permeability and outcomes in treated HIV infection and open the door for interventions aimed at reducing the impact of microbial translocation in treated HIV infection. Further support for such studies came from the results of Pandrea and colleagues, showing that administration of rifaximin and sulfasalazine during acute simian immunodeficiency virus (SIV) infection reduced markers of microbial translocation and coagulation and had an impact on SIV replication in pigtail macaques (Abstract 162). Results from ongoing studies of similar interventions in patients with HIV infection are eagerly awaited.

Interesting new insights into how different ART regimens might contribute to changes in biomarkers of microbial translocation emerged at the conference. Small studies using stored samples from randomized clinical trials examined changes in these biomarkers (Abstracts 277, 338, 836). Barqasho found that sCD14 declined during 72 weeks of ART with either lopinavir/r or efavirenz; however, a greater decline in antiflagellin antibiodies and I-FABP was noted among those who received lopinavir/r than in those who received efavirenz (Abstract 836). In the SPIRAL (Switching from Protease Inhibitor to Raltegravir in HIV Stable Patients) study, patients who were virologically suppressed on a lopinavir/r-based regimen were randomly assigned to switch to raltegravir or remain on lopinavir/r. A greater decline in sCD14 was observed in the raltegravir-treated group than in those remaining on lopinavir/r. A study of raltegravir intensification failed to document a greater decline in sCD14 (Abstract 338). Further work is needed to determine whether specific ART regimens have varied effects on gut healing.

Lipids

Metabolomic profiling is a novel method for investigating associations between

specific circulating metabolites and clinical conditions. Cassol and colleagues reported one of the first in-depth studies of the metabolome in HIV-infected patients on suppressive ART with risk factors for hepatic dysfunction to investigate the relationship between hepatic dysfunction and metabolic abnormalities (Abstract 118). Studies were conducted in an initial and a validation cohort that included noninfected controls in both cohorts. More than 300 metabolites were detected by mass spectroscopy in each cohort, and a distinct signature of metabolite levels was observed in the HIV-infected patients in both cohorts. The majority of abnormal metabolites in the HIV group were lipids, followed by amino acids. Summarizing an enormous amount of data, the investigators concluded that the patterns of metabolites observed indicated decreased lipolysis associated with mitochondrial dysfunction and altered regulation of nuclear receptors controlling lipid metabolism and inflammation. In addition, there appeared to be an association between processes involved in hepatic steatosis, microbial translocation, and dyslipidemia in HIV patients.

Nuclear magnetic resonance (NMR) spectroscopy was used to further define lipid changes that occur in treatment-naive patients randomly assigned to efavirenz or atazanavir/r. In both groups, ART promoted a restoration of high-density lipoprotein (HDL) and an increase in the large HDL subclass. However, 16% of the participants did not reach normal levels after 48 weeks of treatment. Patients on efavirenz had greater increases in HDL, but these were in the large HDL particles that are believed to be protective (Abstract 850).

Lipoatrophy

Discontinuation of thymidine analogue nRTIs is the only proven beneficial strategy for recovery from lipoatrophy. An open-label, 96-week study of lopinavir/r twice daily plus abacavir and lamivudine versus lopinavir/r twice daily monotherapy was conducted in patients with moderate to severe lipoatrophy while they received zidovudine/lamivudine/abacavir (Abstract 846). The primary endpoint was change in limb fat at 48 weeks; the secondary, at 96 weeks, was limb-fat change; HIV RNA level, lipid level, and adverse events were also measured. Switching either to lopinavir/r plus abacavir and lamivudine or to lopinavir/r monotherapy led to non-statistically significant limb-fat increases at 2 years that were lower than those previously reported. There were no differences in limb-fat gain between both strategies.

Calculating the fat mass ratio using dual-energy x-ray absorptiometry scanning (DEXA) data (percentage of trunk fat/percentage of limb fat) has been reported as a useful metric for assessing the prevalence of lipodystrophy.[11] Martinez and colleagues reported an improvement in limb fat as well as a normalizing of the fat mass ratio among patients who switched from a zidovudine-based regimen to tenofovir in the RECOMB (Peripheral Body Fat Distribution After Switching Zidovudine and Lamivudine to Truvada) study (Abstract 845).

The pathogenesis of dorsocervical fat depots in patients with HIV infection remains poorly defined, and it has been postulated that this fat may have some characteristics of brown fat. In an intensive study involving ^{18}FDG-PET and fat biopsies to measure gene expression in patients with HIV lipodystrophy and in non-HIV-infected adults, Torriani and colleagues reported that the adipose tissue in the dorsocervical area did not appear to be classical brown fat (Abstract 849). However, the study did demonstrate an increase in deiodinase 2 expression, which may be related to increased energy expenditure.

Gerschenson and colleagues reported that lower baseline measures of mitochondrial function (mitochondrial oxidative phosphorylation protein levels) measured in peripheral blood mononuclear cells predicted greater amounts of fat loss in Thai patients starting ART. These results further support the notion that mitochondrial dysfunction underlies fat loss related to thymidine nRTIs (Abstract 848). Finally, it is important to note that lipodystrophy remains an important clinical problem in areas in which stavudine continues to be used as first-line ART. Shiau and colleagues, using a standardized exam, reported that nearly 20% of children treated with ART prior to the age of 2 years had definite or probable lipodystrophy (Abstract 973). The long-term consequences of these early fat changes require further study as efforts to obtain alternative initial ART regimens continue.

Vitamin D

Significant interest continues in the relationship between vitamin D deficiency and a variety of outcomes in HIV infection, specifically metabolic complications and HIV-disease progression. A previous study in adults demonstrated a relationship between specific vitamin D receptor mutations and rapid progression of HIV disease. Moodley and colleagues demonstrated this same finding among children, suggesting a possible role of vitamin D in HIV pathogenesis (Abstract 996). Vitamin D insufficiency (defined as < 32 ng/mL) before the start of ART was associated with HIV-disease progression and mortality among participants from resource-limited settings enrolled in the PEARLS (Prospective Evaluation of Antiretrovirals in Resource-Limited Settings) study confirming the results of earlier reports from cohort studies (Abstract 886). Low levels of vitamin D have been correlated with carotid IMT in adults, but these findings were not replicated in a small study of children (Abstract 977). In an observational study, replacing vitamin D reduced glucose and (unexpectedly) adiponectin levels but had no effect on insulin levels (Abstract 884). In a large group of patients in a French cohort ANRS COPANA (Agence Nationale de Recherches sur le SIDA Cohorte de Patients Non traités par Antirétroviraux à l'inclusion), low 25-hydroxyvitamin D (25[OH]D) levels were associated with lower CD4+ cell counts and higher levels of inflammation markers in black and white patients. However, the associations between low vitamin

D and body mass index, visceral adipose tissue, and leptin levels were only observed among white patients. In contrast to findings in HCV monoinfection, baseline 25(OH)D levels did not predict early virologic response in patients with HIV/HCV coinfection (Abstract 767).

The efficacy of different vitamin D replacement strategies has not been well studied in patients with HIV infection. Pacanowski and colleagues reported the results of a large prospective study (n = 483) in which cholecalciferol (D3) supplementation 100,000 IU/month was prescribed in escalating doses to patients according to the degree of vitamin D deficiency. Uvedose 100,000 IU/ampoule was prescribed for patients according to baseline 25(OH)D: for participants with baseline 25(OH)D levels of 10 ng/mL to 30 ng/mL, 100,000 IU/month for 4 months, and for those with 25(OH)D levels below 10 ng/mL, 100,000 IU every 2 weeks for 2 months and then 100,000 IU/month for 2 additional months. Not surprisingly, the follow-up levels of 25(OH)D correlated with the number of doses received. No cases of hyperkalemia were reported, but overall efficacy was difficult to ascertain.

Bone Disease

Low bone mineral density (BMD) is common in patients with HIV infection, and screening guidelines recommend considering DEXA scans for those over the age of 50 years with 1 or more risk factors for osteopenia. Chu and colleagues from the Houston Veterans Administration Medical Center reviewed compliance with these screening recommendations in a large HIV practice (Abstract 876). Among the 476 men over the age of 50 years, 84% had 1 or more risk factors for osteopenia (> 95% if use of tenofovir was considered a risk factor), yet only 15% had undergone DEXA screening, and few who were found to have osteopenia when screened had complete work-ups.

The relationship between HIV infection, specific ART drugs, immune reconstitution, and bone loss continues to be explored. Brown and ACTG colleagues found a low prevalence of low BMD among treatment-naive patients enrolling in an ART clinical trial and no associations between parameters reflective of HIV-disease status or immune activation and low BMD (Abstract 875). On the other hand, Gazzola reported an association between the level of CD4+ and CD8+ T-cell activation and lower BMD in a small group of ART-treated patients (Abstract 879). Ofotokun and colleagues previously demonstrated a relationship between early bone loss after starting ART and immune reconstitution. They further explored the contributions of ART to bone loss by examining markers of bone resorption and formation in a cohort of patients with suppressed HIV-1 RNA who were switched from nRTI-based ART to lopinavir/r and raltegravir (Abstract 877). Over 48 weeks following the change in ART, markers of bone resorption (C-terminal telopeptide [CTx]) were stable. However, a statistically significant drop in osteocalcin, a marker of bone formation, was noted. The mechanism explaining this drop in bone formation requires further study to determine whether this might represent a late effect of ART or the sequelae of immune restoration. Finally, 2 studies examined the association between tenofovir exposure and bone loss in switch studies. Cotter and colleagues examined bone turnover markers and DEXA results in a randomized trial comparing continued therapy with ART containing zidovudine/lamivudine with a switch to ART containing tenofovir among patients who were virologically suppressed (Abstract 125LB). After 48 weeks of follow-up, BMD declined (-2% in lumbar BMD) in the tenofovir group, corresponding to increases in markers of bone turnover. Bloch and colleagues examined bone markers in a study of patients switching from tenofovir to raltegravir while continuing a PI/r (Abstract 878). The participants in this open-label study had been aviremic and on ART containing tenofovir for an average of 3 years. BMD increased after the change in regimen, and markers of bone turnover declined statistically significantly, suggesting that in this setting, tenofovir was probably contributing to bone loss prior to the change to raltegravir. Together, these switch studies provide further support for the likely contribution of tenofovir exposure to bone loss. However, the clinical significance of these changes remains unclear and warrants further follow-up.

Renal Complications

Understanding and predicting the renal toxicity of ART agents, particularly tenofovir, was highlighted at this year's CROI. In patients with normal baseline estimated clearance (by Cockcroft-Gault) the D:A:D study reported a statistically significant association of estimated glomerular filtration rate (eGFR) decline to less than 70 with tenofovir, and eGFR decline to less than 70 as well as to chronic kidney disease (eGFR < 60) with atazanavir/r and lopinavir/r. However, overall rates of renal toxicity in this cohort of more than 22,000 subjects were low, with 2.1% developing eGFR below 70 mL/min/1.73m^2 and 0.6% developing eGFR below 60 over a median 4.5 years of follow-up (Abstract 865). Renal function appeared to normalize when these drugs were discontinued, suggesting reversibility. By contrast, in a Spanish cohort, although 60% of tenofovir-associated nephrotoxicity rapidly reversed after tenofovir was discontinued, 31% of patients had persistently abnormal kidney function after a median period of 22 months (Abstract 870). Suggesting a value for predicting tenofovir toxicity, higher tenofovir plasma levels were associated with renal toxicity in a Dutch cohort, but a clear threshold for tenofovir levels that identified the risk for renal toxicity with acceptable sensitivity and specificity could not be identified (Abstract 603). Elevated tenofovir trough levels were linked to accompanying ART; both boosted and unboosted PIs were associated with higher tenofovir troughs compared with NNRTIs and integrase inhibitors, suggesting that the association of PIs with renal dysfunction may in part be mediated by increased tenofovir levels.

Aging and HIV

Many of the common problems observed in long-term treated HIV infection resemble those seen in normal aging. Factors that contribute to the phenotype of premature aging in HIV infection continue to be explored. One hypothesis is that mitochondrial dysfunction may contribute to loss of muscle volume and function. Payne and colleagues examined mitochondrial function by studying phosphorus magnetic resonance spectroscopy (^{31}P-MRS) of the gastrocnemius/soleus muscle at rest and during recovery from brief exercise in a group of older HIV patients and age-matched controls (Abstract 856). The study also included data on muscle biopsies. The findings of higher levels of basal adenosine triphosphate (ATP) metabolite levels combined with preserved function during exercise in the HIV group were thought to be consistent with functional compensation for an acquired mitochondrial DNA defect. In addition, the authors concluded that the disordered muscle pH handling noted in the HIV group may contribute to fatigue. Another potential contributor to the aging phenotype in HIV is immune activation and immune senescence. Hearps compared the phenotypes of monocytes in young HIV-seropositive men with those in matched controls and in older patients and found that HIV infection was associated with changes in monocyte phenotype and function that resemble those observed in elderly uninfected individuals (Abstract 324). Specifically, elevated plasma levels of innate immune activation markers (sCD163, neopterin, and interferon gamma-induced protein 10 [IP-10]) correlated with the phenotypes observed in the HIV-infected patients. In addition, monocytes from HIV-seropositive patients have shorter telomeres than do healthy controls. These findings suggest that chronic HIV infection may be associated with the aging of monocytes, which in turn may contribute to the development of complications observed with long-term HIV infection.

Malignancies

There has been increasing recognition of the elevated risk in the HIV-infected population of non–AIDS-defining malignancies (NADM), both infectious in etiology, such as anal and hepatocellular carcinoma, and noninfectious cancers, such as colon and lung cancer. In the D:A:D cohort, immunosuppression and low nadir CD4 + cell count emerged again as risk factors for NADM (Abstract 130). Lung cancer was associated with a nadir CD4 + cell count, Hodgkin's lymphoma with lower recent CD4+ cell count and HIV viremia, and anal cancer with lower recent CD4+ cell count and duration of immunosuppression. HIV-infected patients generally had a younger age at the time of diagnosis with NADM, with a trend toward more advanced stages of lung and anal cancers at the time of diagnoses, than HIV-uninfected counterparts in the Kaiser database (Abstract 903). HIV-infected patients with prostate cancer (84% vs 91%; $P = .038$) and lung cancer (8% vs 22%; $P < .001$), had reduced 5-year survival rates compared with HIV-uninfected subjects. The NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) found higher incidence of oral-cavity and pharynx cancer in HIV-infected patients compared with an HIV-uninfected cohort, and this risk increased with age over 50 years and baseline CD4+ count less than 350 cells/μL (Abstract 133).

Given accumulating data for the use of CT scan for lung cancer screening in HIV-infected patients[12] and elevated rates of lung cancer in HIV infection, it was encouraging to note that HIV-seropositive patients undergoing chest CTs in prospective evaluations of HIV-associated lung disease did not have higher rates of incidental pulmonary nodules than did HIV-uninfected patients (Abstract 907). Further data are needed to define the role of screening chest CTs for lung-cancer detection in HIV infection.

In an analysis of several ACTG randomized trials, statin use (prescribed as indicated by the practitioner) was associated with a statistically significant decrease in malignancy of 55% compared with those not on a statin (Abstract 124). Prior studies[13-15] of HIV-uninfected populations have also suggested an association of statin use with a decrease in malignancies. This association to date has not been borne out in subsequent meta-analyses.[16,17] Whether statins are indeed driving the reduction in malignancy in HIV infection or the results are due to confounding given the observational nature of the study will require further study.

Tuberculosis

Prevention

Whether to provide at least 36 months (vs 6 months) of isoniazid (INH) preventive therapy (IPT) for HIV-infected persons living in high tuberculosis (TB)-incident regions is still debated, despite evidence from several randomized controlled trials. Samandari contributed to this debate by analyzing TB rates in an IPT trial in Botswana after all study participants were randomly assigned to 6 or 36 months of INH discontinued IPT (Abstract 147). During the evaluation of 1995 HIV-seropositive subjects within the 36-month study period, TB rates were 1.26% versus 0.72% ($P = .047$) in the 6- versus 36-month IPT groups, respectively. After the study period, when no participants were taking IPT, rates of TB among tuberculin skin test-positive persons who had been randomly assigned to 36 months of IPT increased by 70%. These data suggest that HIV-infected persons living in high TB-incident areas are susceptible to repeat TB infection and benefit from prolonged IPT.

TB infection rates are extraordinarily elevated in certain settings, such as mines, due to poor ventilation and silicosis. In South African gold mines, up to 30% of workers are HIV infected, making this work environment a high priority for TB-prevention efforts. Churchyard presented the first glimpse into results from the eagerly awaited Thibela study in TB (Abstract 150aLB). Using a cluster randomized study design in South African gold mines,

investigators tested the hypothesis that providing IPT to all gold-mine workers, regardless of their HIV serostatus, would reduce the incidence of TB. There were 41,387 miners in the intervention cluster and 37,209 in the control cluster. HIV infection was reported in 12% of the study participants, though actual HIV testing of study participants was prohibited by organized labor. Within the intervention group, 67% of miners participated in the study, and 87% of these started IPT. Uptake of IPT as measured by medication pick-up varied in the range of 35% to 79%. In the analysis of the primary endpoint of TB incidence, there was no difference between the treatment groups: 3.04 TB cases/100 person-years in the intervention group versus 2.96/100 person-years in the control group (incidence rate ratio [IRR], 1.02; 95% CI, 0.77-1.31).

In part 2 of the Thibela trial results, investigators presented the individual-level benefit of IPT in the gold mines (Abstract 150bLB). For this analysis, the investigators included only patients in the intervention group who started IPT. During the first 9 months of observation when patients were receiving IPT, rates of TB were 63% lower in the intervention group, with 0.95 cases/100 person-years, than in the control group, with 2.53 cases/100 person years. After 9 months, rates in the 2 groups were similar in the range of 2.1/100 person-years to 2.6/100 person-years. Thus in the Thibela study, widespread IPT was not successful in reducing TB rates at the community level but showed evidence of individual-level benefit. The most obvious explanation for these findings is that the uptake of the intervention by individuals was insufficient to confer a benefit detectable at the community level. Failing to start IPT and nonadherence to IPT both contributed. In addition, the analysis of the individual-level benefit underscored the importance of lifelong IPT because the beneficial effect of IPT was lost after its discontinuation. The authors concluded that their study supports targeted (eg, for HIV-seropositive subjects) versus community-wide IPT. However, some would argue that abandoning evaluation of a community-level approach could be premature because community uptake in this trial was limited.

Further insights into TB prevention efforts were gained in the ZAMSTAR (Zambia/South Africa TB and AIDS Reduction) trial conducted in Zambia and South Africa (Abstract 149bLB). This study evaluated both enhanced case finding at the community level and household TB case prevention and detection strategy using a community cluster randomized design that covered nearly a million persons. TB prevalence and transmission were both lower in the household-intervention populations than in the control, although the reported data showed confidence intervals that crossed 1. There was no difference between the enhanced case finding using community-based intervention and the control communities. The authors posited that the trend for reduction in TB prevalence and transmission to favor household intervention was promising. Upon questioning, Ayers stated that the cost of intervention was around US $1 per person but added that detailed costing studies were under way.

Diagnosis

Identifying active TB prior to the start of ART remains a challenge. Swindells reported 13% prevalence of TB among HIV-seropositive patients who were waiting to start ART and were screened for TB using clinical symptoms and culture at sites in sub-Saharan Africa (Abstract 927). As expected, clinical-symptom screens were sensitive for TB, although notably 5 of 52 patients with TB reported no cardinal symptoms. The positive predictive value of symptoms was only 24%. This study underscores the need for more sensitive and specific diagnostic algorithms. The Xpert® MTB/RIF molecular diagnostic technology holds promise for rapid detection of TB in HIV-infected patients and is more sensitive than routine acid-fast bacillus smear. However, there are still a substantial number of persons with TB who screen negative using this technology. In South Africa, where the Xpert® technology is the first line for TB diagnosis, TB suspects who have a negative Xpert (X) had a follow-up culture (C) for screening. Because a second Xpert test can increase detection of TB, investigators performed a cost-assessment model of an algorithm comparing 2 sequential Xperts (X/X) with an Xpert followed by culture (X/C) (Abstract 923). In this model, the X/X was superior to X/C because the former detected cases faster, simplified logistics, and saved costs.

In another study examining potential benefits of the line-probe assay GenoType® MTBDRplus to identify multi-drug-resistant TB (MDR-TB) cases in South Africa, the detection of MDR-TB increased and the time to start MDR-TB treatment decreased after the introduction of MTBDRplus. However, median time to start MDR-TB treatment from the initial clinic visit was still unacceptably high, at 2 months (Abstract 925). Finally, Dorman reported that the point-of-care test Determine™ TB-LAM, which detects urinary mycobacterial lipoarabinomannan (LAM), reported a sensitivity of 44.8% and a specificity of 90.1% (Abstract 149aLB). The test had a higher sensitivity in patients with lower CD4+ cell count and could be an adjunctive test for clinicians. However, more work is needed to determine the relative contribution of this assay in view of limitations arising from its sensitivity and positive predictive value.

ART and TB Treatment

Global guidelines now recommend that ART start in TB patients at 2 weeks after the initiation of TB treatment, based on randomized controlled trials. Does starting ART even earlier, at 1 week after initiation of TB treatment confer any further benefit? In a study of 474 patients with TB starting ART in Ethiopia, Degu reported that starting ART at 1 versus 2 weeks did not confer additional benefit or harm in terms of mortality (Abstract 144). Starting ART at 2 weeks after initiation of TB treatment means that programs will need to be prepared to diagnose and manage TB-associated immune

reconstitution inflammatory syndrome (TB-IRIS), a known complication of early ART. Luetkemeyer reported that in STRIDE (Strategy Study of Immediate Versus Deferred Initiation of Antiretroviral Therapy), the overall incidence was 7.6%, and most cases were mild to moderate in severity (Abstract 145). Nevertheless, 31% of TB-IRIS cases were diagnosed while the patient was hospitalized; 34% required at least 1 invasive procedure, such as a fine needle aspirate; 54% required steroids for treatment; and the median duration of the TB-IRIS event was approximately 3 months. Compatibility of new ART agents and rifampin (which induces hepatic enzymes that lower levels of many ART drugs) is a key issue for optimal comanagement of these diseases. Dooley's drug-interaction study between the investigational ART dolutegravir and rifampin showed that doubling the dose of dolutegravir to 50 mg twice daily achieved dolutegravir levels similar to those in standard dosing in the absence of rifampin (Abstract 148).

Cryptococcal Disease

Rolfes and colleagues evaluated a new lateral flow point-of-care assay (LFA) for cryptococcal disease in stored CSF and serum from Uganda with cryptococcal meningitis (Abstract 953). There was high sensitivity for the LFA and high concordance between the standard serum cryptococcal antigen (CrAg) assay and the LFA. Of note, titers of the LFA were 3-fold higher than CrAg; expanded evaluation of the LFA assay is under way. Asymptomatic cryptococcemia, defined as detectable serum CrAg without symptoms, is known to occur among patients with AIDS who have low CD4+ cell counts. Kwan examined banked plasma from Thai women and found 11% prevalent CrAg in 84 women with less than 100 CD4+ cells/μL and none in women with greater than 125 CD4+ cells/μL (Abstract 954). These women were not evaluated for cryptococcal meningitis; approximately half received fluconazole prophylaxis. Not surprisingly, women with CrAg in plasma at baseline were at highest risk to develop cryptococcal meningitis. Among the women who had positive CrAg, decreased titers were observed in 8 of 9 women after 48 weeks of antiretroviral therapy. Restoration of immunity provides protection against cryptococcal disease, but all patients with CrAg should have evaluation of CSF to determine whether treatment with amphotericin is indicated for meningitis.

Malaria

HIV PIs are active against *Plasmodium falciparum* in vitro. Achan and colleagues tested the hypothesis that an ART regimen containing lopinavir/r versus an ART regimen based on an NNRTI would decrease malaria among HIV-infected Ugandan children living in a high malaria-endemic region (Abstract 26). The study enrolled 176 children and randomly assigned them to an NNRTI or a lopinavir/r combination ART regimen; malaria cases were treated with artemether-lumefantrine. Malaria incidence was 2.25 episodes/year versus 1.32 episodes/year in the NNRTI group versus the lopinavir/r group, respectively (IRR, 0.59; 95% CI, 0.36-0.97). The 41% reduction in risk for malaria conferred by the lopinavir/r group compared with the NNRTI group was primarily driven by a reduction in the rate of recurrent malaria, confirmed by genotypic analysis. The authors proposed that this effect was mediated by elevated levels of lumefantrine as a result of a pharmacokinetic interaction with ritonavir. No added toxicity was observed in the children with the elevated lumefantrine levels. Ritonavir thus may be valuable as a pharmacoenhancer for malaria drugs as well as for HIV agents. This trial is continuing to follow participants to evaluate the HIV outcomes.

Vaccination for Influenza and Herpes Zoster

HIV infection is an established risk factor for herpes zoster reactivation and severe clinical disease. However, little is known about the safety and efficacy of the zoster vaccine in HIV-infected adults. In a US ACTG study, HIV-infected adults with CD4+ counts greater than 200 cells/μL on suppressive ART were randomly assigned 3:1 to receive 2 zoster vaccinations or placebo (Abstract 96). Zoster vaccination appeared safe in HIV infection, meeting the protocol's safety definition. Injection-site reaction and rash were more common with the active zoster vaccine; however, there were no confirmed vaccine-related zoster cases, and 2 cases of clinical zoster occurred in each group. The vaccine appeared immunogenic, with an increase in geometric-mean zoster-antibody titer that was higher in vaccine recipients than in placebo at week 12 (6.4 vs 5.15; $P = .017$). These data suggest that zoster vaccination may be a safe option for virologically suppressed patients with CD4+ counts greater than 200 cells/μL. Larger studies will be needed to evaluate the vaccine's ability to prevent zoster reactivation in HIV disease. The second administration of zoster vaccine did not appear to lead to increased antibody response and may not be required to generate a protective antibody.

The higher dose trivalent influenza vaccine (60 μg/strain) resulted in a modest increase of 4% to 12% in geometric-mean influenza titers for the 3 vaccine strains at week 3 post vaccination, compared with standard influenza vaccination (15 μg/strain) (Abstract 97). In this study, median current CD4+ count was 452 cells/μL (IQR 293-629), and a nadir CD4+ count was 180 cells/μL (IQR 53-318). It is unclear whether this increase would confer a clinical benefit, but high-dose influenza vaccination may be a consideration for HIV-infected patients considered to be at higher risk for complications from influenza or less likely to respond to standard-dose vaccination.

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Advances in Antiretroviral Therapy

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The 19th Conference on Retroviruses and Opportunistic Infections (CROI) highlighted new information and provided in-depth discussion on advances in antiretroviral therapy (ART). Data regarding investigational drugs, including integrase strand transfer inhibitors (InSTIs) and zinc-finger nucleases disrupting CC chemokine receptor 5 (CCR5), were presented. Treatment trials in treatment-naive and treatment-experienced patients added to the knowledge base of which antiretroviral agents to initiate and when. Data from trials and observational cohorts suggested that, for patients on successful ART in resource-rich settings, mortality from non-HIV-related diseases may surpass that from HIV-related diseases, and overall lifespan may be nearing that of people without HIV infection. In resource-limited settings (RLS), prevention of mother-to-child transmission (PMTCT) and ART scale-up remained priorities. New data on antiretroviral resistance in RLS and on the implications of low-frequency mutations were presented.

New Antiretroviral Agents

GS-7340

GS-7340 is a prodrug of tenofovir and results in the same active compound as tenofovir disoproxil fumarate: tenofovir-diphosphate. At the 2012 Conference on Retroviruses and Opportunistic Infections (CROI), Ruane and colleagues presented results from a partially blinded, controlled, dose-escalation study comparing GS-7340 (8 mg, 25 mg, and 40 mg once daily), tenofovir 300 mg once daily, and placebo given as monotherapy for 10 days (Abstract 103). This trial enrolled 38 HIV-infected participants, of whom 97% were men; mean HIV-1 RNA level was 4.5 $\log_{10}$ copies/mL; mean CD4+ count, 478 cells/μL. As expected, plasma tenofovir exposures were 80% to 97% lower in the GS-7340 arms than in the tenofovir arm, and the intracellular tenofovir-diphosphate levels were higher in the GS-7340 arms than in the tenofovir arm. The time-averaged change in plasma HIV-1 RNA levels through 10 days was greater in the GS-7340 25 mg and 40 mg arms (-0.94 $\log_{10}$ copies/mL and -1.13 $\log_{10}$ copies/mL, respectively) than in the tenofovir arm (-0.48 $\log_{10}$ copies/mL, $P = .01$ and $P = .001$, respectively). The investigators assert that GS-7340 has the potential to be more efficacious with less systemic toxicity than tenofovir. This will be investigated further in phase II trials.

CCR5 Disruption by Zinc-Finger Nucleases

Tebas and colleagues presented data from 2 phase I, single-arm, single-dose clinical trials of zinc-finger nuclease–modified autologous CD4+ T cells (SB-728-T) (Abstract 155). This strategy uses apheresis to collect large numbers of CD4+ cells, which are then exposed ex vivo to zinc-finger nucleases that target and disrupt the CC chemokine receptor 5 (CCR5). The genetically modified CD4+ cells are expanded, cryopreserved, and infused back into the participant. The studies enrolled 6 immune responders with CD4+ counts at least 450 cells/μL (median count 974 cells/μL) and 15 immune non-responders with CD4+ counts below 450 cells/μL (median count 357 cells/μL). All participants had virologic suppression on combination antiretroviral therapy (ART).

The infusions were generally well tolerated. One serious adverse event, a transfusion reaction of arthritis, was reported. In the immune-responder group, the mean CD4+ count increased at day 7 postinfusion by 1533 cells/μL, including 83 cells/μL of genetically modified CD4+ cells. Increases of 820 CD4+ cells/μL and 19 genetically modified CD4+ cells/μL were observed after infusion in the immune–non-responder group. Genetically modified CD4+ cells were detected at 1 year of follow-up in approximately 2% of circulating CD4+ cells. In participants undergoing a treatment interruption, plasma HIV-1 RNA levels rebounded. The frequency of genetically modified CD4+ cells correlated with control of viremia during the treatment interruption. Future studies will focus on increasing the efficiency of engrafting modified CD4+ cells to enhance virologic control.

Inhibitors of Integrase Complexes

Current integrase strand transfer inhibitors (InSTIs) target enzymatic activity of HIV integrase. Gros and colleagues described a short 11-mer cyclic peptide that binds integrase and causes dissociation of integrase–DNA, integrase–lens epithelium-derived growth factor (LEDGF), and reverse transcriptase (RT)–integrase complexes (Abstract 576). The compound exhibited low nanomolar activity against a broad range of HIV isolates, and the investigators were unable to generate resistance to the peptide after a 12-month evaluation.

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Nanoformulations of Atazanavir/Ritonavir

Gendelmen and colleagues presented data on the pharmacokinetics on nanoparticle formulations of ritonavir-boosted (/r) atazanavir in a mouse model (Abstract 582). They tested increasing doses of atazanavir/r and were able to achieve atazanavir concentrations of 287 ng/mL with weekly injections. The nanoparticles resulted in partial virologic suppression (HIV RNA 2 $\log_{10}$ copies/mL) in a humanized mouse model of HIV infection.

Clinical Trials of Antiretroviral Therapy of Treatment-Naive Individuals

Elvitegravir/Cobicistat/Tenofovir/Emtricitabine

Sax and colleagues presented data from a phase III, randomized, double-blind, placebo-controlled trial of a fixed-dose combination of elvitegravir/cobicistat/tenofovir/emtricitabine (elvitegravir/cobicistat arm) versus fixed-dose efavirenz/tenofovir/emtricitabine (efavirenz arm) (Abstract 101). Elvitegravir is an investigational InSTI, and cobicistat is an investigational pharmacoenhancer. The trial enrolled antiretroviral-naive adults with plasma HIV-1 RNA levels greater than 5,000 copies/mL, calculated creatinine clearance greater than 70 mL/min, and no resistance to efavirenz/tenofovir/emtricitabine. Seven hundred participants (89% male; 37% nonwhite) were randomly assigned to the 2 treatment groups. The mean CD4+ counts were 382 cells/μL and 391 cells/μL in the 2 arms, respectively, and 33% of participants had plasma HIV-1 RNA levels greater than 100,000 copies/mL.

Viral suppression by the US Food and Drug Administration (FDA) snapshot algorithm at week 48 was 88% and 84% (difference, 3.6%; 95% confidence interval [CI], -1.6%-8.8%) in the elvitegravir/cobicistat and efavirenz arms respectively. The elvitegravir/cobicistat arm was found to be noninferior to the efavirenz arm. The mean CD4+ count increases were 239 cells/μL and 206 cells/μL (P = .009), respectively. Drug discontinuations due to adverse events occurred in 4% and 5% of the treatment groups, respectively. Nausea was more common in the elvitegravir/cobicistat arm (21% vs 14%); central nervous system effects (CNS) and rash were more common in the efavirenz group. Calculated creatinine clearance decreased by 14.3 mL/min after 2 weeks in the elvitegravir/cobicistat group due to the known inhibition of tubular secretions of creatinine by cobicistat. The creatinine increased 0.14 mg/dL in the elvitegravir/cobicistat arm and 0.01 mg/dL in the efavirenz arm at 48 weeks. Drug resistance emerged in 8 participants in each arm. In the elvitegravir/cobicistat arm, integrase resistance emerged in 7 participants and nucleoside analogue reverse transcriptase inhibitor (nRTI) resistance in 8 participants. In the efavirenz arm, nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) resistance emerged in 8 participants and nRTI resistance in 2 participants.

DeJesus and colleagues presented data on a clinical trial of similar design and enrollment criteria comparing elvitegravir/cobicistat/tenofovir/emtricitabine with atazanavir/r plus tenofovir/emtricitabine (Abstract 627). This study enrolled 708 participants (90% male; 26% nonwhite). Viral suppression by the FDA snapshot algorithm at week 48 was 90% and 87%, respectively (difference, 3.0%; 95% CI, -1.9-+7.8). Elvitegravir/cobicistat/tenofovir/emtricitabine was found to be noninferior to the atazanavir/r-containing regimen. The mean CD4+ count increases were similar in the 2 arms (207 cells/μL and 211 cells/μL, respectively). Drug discontinuations due to adverse events occurred in 4% and 5% of participants, respectively.

Dolutegravir

Dolutegravir is an investigational InSTI with activity against most isolates resistant to raltegravir or elvitegravir. Investigators presented data on the 96-week outcomes from the SPRING-1 trial: a randomized, partially blinded, dose-finding study of dolutegravir versus efavirenz, each paired with 2 nRTIs (Abstract 102LB). Participants were required to have a plasma HIV-1 RNA level greater than 1000 copies/mL and CD4+ count greater than 200 cells/μL. The 205 participants were randomized to receive either dolutegravir (10 mg, 25 mg, or 50 mg) or efavirenz. The participants were 86% male and 20% nonwhite, with a mean CD4+ count of 343 cells/μL, and mean plasma HIV-1 RNA level of 4.46 $\log_{10}$ copies/mL. At week 96, the plasma HIV-1 RNA level was below 50 copies/mL in 79%, 78%, and 88% of participants for the dolutegravir groups, respectively, compared with 72% for the efavirenz group. No InSTI or NNRTI resistance was detected in any participant. Drug-related grade-2 to -4 adverse events occurred less frequently in the dolutegravir arms than in the efavirenz arm (11% vs 24%), and fewer participants discontinued dolutegravir than discontinued efavirenz for adverse events (3% vs 10%). It is important to note that randomization to dolutegravir versus efavirenz was open-label, and only the dosage of dolutegravir was blinded. The dolutegravir groups overall had an increase in serum creatinine of 0.1 mg/dL to 0.15 mg/dL, which did not progress over time. The investigators noted that this is consistent with a small inhibition of creatinine secretion in the proximal renal tubules. Ongoing clinical trials in ART-naive individuals are using a dosage of dolutegravir 50 mg once daily.

Antiretroviral Therapy Strategies

Lopinavir/r Monotherapy

Du Pasquier and colleagues examined cerebrospinal fluid from participants in the MOST (Monotherapy Switzerland/Thailand) trial, which randomized participants to continued therapy with lopinavir/r and 2 nRTIs or lopinavir/r monotherapy (Abstract 480). The study was stopped early because of viral breakthrough in the monotherapy arm. The researchers examined 5 markers of CNS inflammation from 52 participants who maintained virologic suppression throughout trial participation and

found that 2 of these markers (S100-beta and neopterin) were higher in the monotherapy group (P = .002 and P = .058, respectively). The authors concluded that lopinavir/r leads to CNS inflammation despite virologic control in the plasma.

Adherence Interventions

Two clinical trials evaluated adherence interventions. Lucas and colleagues enrolled 107 participants attending a methadone maintenance program who were either not receiving ART or receiving ART but had ongoing viremia (Abstract 628). Participants were randomized to directly observed ART for one dose per day on weekdays (other doses self-administered) or self-administered ART. The proportion achieving virologic suppression was marginally higher in the direct-observation group: 51% versus 40% at month 12 (difference, 11%; 95% CI, -2%-24%; P = .09).

Investigators from the University of Pennsylvania evaluated a behavioral intervention called managed problem solving (MAPS), a five-step behavioral intervention (Abstract 629). Eligible participants were either ART-naive or restarting ART. The researchers randomized 180 participants, of whom 61% were male, 85% black, and 58% treatment-experienced. The primary endpoint was adherence as measured by a microelectronic monitoring system (MEMS). Adherence was greater in the MAPS group (69% of doses taken compared with 39% for non-MAPS, P = .023). The odds of having an undetectable plasma HIV-1 RNA level were significantly higher for the MAPS group in the as-treated analysis (missing = ignored), and marginally higher in the intent-to-treat analysis (missing = failure).

Clinical Trials to Decrease the Latent Reservoir of HIV-1 Infection

A major obstacle to eradication of HIV-1 is the proviral latency of HIV-1 in resting CD4+ T cells. Histone deacetylase inhibitors have the potential to disrupt this latency to allow clearance of HIV-1 from this reservoir. Margolis and colleagues investigated the effects of vorinostat ex vivo and in vivo (Abstract 157LB). They presented data on 5 men with sustained suppression of plasma HIV-1 RNA on ART. The researchers obtained peripheral blood mononuclear cells (PBMCs) by leukapheresis and confirmed ex vivo that the addition of vorinostat resulted in an increase in HIV-1 RNA expression. Participants received a 400 mg infusion of vorinostat at a subsequent visit. Pharmacokinetic parameters of vorinostat observed in this trial were similar to those obtained in oncology trials. Leukapheresis was performed a second time. HIV-1 RNA levels increased significantly in resting CD4+ T cells with a mean 5-fold change (range, 3-9 fold). This provides proof of concept that HIV proviral latency can be disrupted in vivo and suggests a trial design for evaluating such an approach.

Disulfiram has been shown to induce HIV-1 expression in resting memory T cells in vitro. Spivak and colleagues investigated whether disulfiram would lead to increased plasma HIV-1 RNA levels as measured by the single-copy assay in HIV-1-infected participants with sustained viral suppression (Abstract 369). The researchers enrolled 14 participants who received disulfiram for 2 weeks. The drug was well tolerated with no substantial adverse effects. The researchers observed a nonsignificant increase in plasma HIV-1 RNA levels (difference, 55%; 95% CI, –28%-225%) during disulfiram treatment and afterward (difference, 88%; 95% CI, -23%-355%). This study is ongoing.

Pharmacokinetic Interactions of ART Agents

Drugs and ART Agents

Dooley and colleagues presented data on 11 healthy, HIV-uninfected participants receiving dolutegravir and rifampin (Abstract 148). Dolutegravir is metabolized primarily by UDP-glucuronosyltransferase 1A1 (UGT1A1) and, to a lesser extent, by cytochrome P450 3A4 (CYP3A4). Both of these enzymes are induced by rifampin. The investigators hypothesized that the expected drug-drug interaction could be overcome by increasing the dolutegravir to 50 mg twice daily. Participants received 7 days of dolutegravir dosage 50 mg once daily, followed by 7 days of dolutegravir 50 mg twice daily, followed by 14 days of dolutegravir 50 mg twice daily and rifampin 600 mg once daily. Dolutegravir twice daily with rifampin resulted in dolutegravir concentrations that were 22% to 33% higher than those achieved by once-daily dolutegravir. This strategy effectively overcame the drug-drug interaction, suggesting that dolutegravir-based regimens should be investigated further for HIV-infected patients with active tuberculosis (TB).

ART Pharmacokinetics in Participants with Liver Disease

Dolutegravir pharmacokinetics were investigated in 8 participants with moderate hepatic dysfunction (Child-Pugh score, 7-9) and 8 healthy matched controls (Abstract 608). The study found that the pharmacokinetic parameters were generally similar between groups, with no appreciable difference except for a small increase in the concentrations of non-protein-bound dolutegravir in participants with moderate hepatic impairment.

Other investigators evaluated the pharmacokinetics of raltegravir in 5 hepatitis C-virus (HCV)/HIV-coinfected participants with advanced cirrhosis and 5 with no histologic damage on liver biopsy (Abstract 609). Participants were virologically suppressed for at least 6 months on a regimen containing lopinavir/r, fosamprenavir/r, or darunavir/r. Raltegravir 400 mg was added twice daily for 5 days. Raltegravir concentrations were higher in the group with cirrhosis: the 12-hour area under the curve (AUC) was 1.72 times higher (90% CI, 1.02-2.92), and the trough concentration was 6.58 times higher (90% CI, 2.92-14.85). Despite the higher concentrations, no safety concerns were identified, and raltegravir was well tolerated by all participants.

Inhaled Beclomethasone

Boyd and colleagues investigated the drug interactions with inhaled beclomethasone in 30 HIV-uninfected participants (Abstracts 610 and 611). All participants received inhaled beclomethasone twice daily for 14 days. On day 15, participants were randomized to 1 of 3 groups: inhaled beclomethasone alone twice daily; inhaled beclomethasone and ritonavir 100 mg twice daily; or inhaled beclamethasone, darunavir 600 mg, and ritonavir 100 mg twice daily. Each regimen was administered for 14 additional days. The concentrations of basal morning cortisol and response to adrenocorticotropic hormone stimulation testing did not differ among the groups. The pharmacokinetics of the active beclomethasone metabolite were not altered by darunavir/r. Interestingly, the concentrations of the beclomethasone metabolite were statistically significantly increased by ritonavir alone ($P = .006$), suggesting that ritonavir alone cannot be used to assess the drug-drug interactions for ritonavir-boosted protease inhibitors (PIs).

Antimalarial Drugs

Two abstracts reported on the interaction between malaria treatments and commonly used antiretroviral drugs in HIV-1-infected adults with malaria coinfection. Kredo and colleagues compared lumefantrine and dihydroartemisinin exposure over 72 hours of twice-daily dosing in 18 HIV-infected adults not on ART with 16 HIV-infected adults on lopinavir/r (Abstract 613). The study found that the drug concentrations of dihydroartemisinin were not altered by lopinavir/r. The concentrations of lumefantrine were statistically significantly higher in the lopinavir/r group. However, the increased concentrations were not associated with adverse clinical events or QT prolongation.

Byakika-Kibwika and colleagues assessed the pharmacokinetic interaction of nevirapine and artemether/lumefantrine in HIV-infected adults (Abstract 614). Participants received 6 doses of artemether/lumefantrine and underwent intensive pharmacokinetic sampling. The dosing and sampling process was repeated after dosing nevirapine to steady state. The study found statistically significant reductions in artemether and dihydroartemsinin concentrations with nevirapine coadministration. The levels of lumefantrine were not affected. Concentrations of nevirapine were statistically significantly lower with artemether/lumefantrine coadministration. This study suggested that alternative malaria treatments should be pursued for participants receiving nevirapine.

HCV NS5A Inhibitor

BMS-790052 is an HCV nonstructural protein 5A (NS5A) inhibitor that is entering clinical investigation in HIV/HCV-coinfected individuals. Bifano and colleagues reported on 3 separate clinical trials examining potential interactions of BMS-790052 with tenofovir, efavirenz, and atazanavir/r (Abstract 618). The concentrations of the ART agents did not appear to be changed by coadministration with BMS-790052. Efavirenz decreased the concentrations of BMS-790052, atazanavir/r increased the concentrations of BMS-790052, and tenofovir had no substantial effect. The authors estimated that higher doses of BMS-790052 were necessary when coadministering with efavirenz (90 mg vs 60 mg), and lower doses were necessary when coadministering with atazanavir/r (30 mg vs 60 mg).

Treatment Outcomes and Mortality Data from Secondary Analyses and Observational Cohorts

The conference showcased many interesting presentations using data from large, observational cohorts. See Table 1 for a review of notabel findings. One of the highlights was a presentation by Skarbinski and colleagues (Abstract 138) of data from the US Centers for Disease Control and Prevention (CDC) Medical Monitoring Project (MMP). The MMP collects data from individual HIV-infected adults receiving care at a sample of outpatient HIV-care facilities within 17 states or territories that contain 76% of all persons diagnosed with HIV in the United States. Interview and medical-record data are collected and linked to the National HIV Surveillance system, and population-size estimates are calculated using weighting for design and nonresponse adjustments.

The researchers collected data from 4217 patients receiving care at 461 facilities between January and April of 2009. Patient and facility response rates were 53% and 76%, respectively. Using a weighted analysis, the researchers estimated that 421,186 HIV-seropositive adults received at least 1 visit in an HIV clinic during the observation period. This represented 44% of the estimated 941,950 adults living with HIV. Of the patients in care, 89% (95% CI, 87%-91%) were prescribed ART, and 71% (95% CI, 68%-75%) had an HIV-1 plasma RNA level of 200 copies/mL or below. Adjusted, multivariate logistic regression models were developed to predict ART prescription and virologic suppression. Non-Hispanic blacks were less likely to achieve both than were non-Hispanic whites. The authors concluded that, because fewer than half of HIV-seropositive individuals were estimated as being in care, expanding ART coverage for those with CD4+ counts greater than 500 cells/μL would have a minor impact. Increasing the number of HIV-infected persons in care is essential to reduce mortality and impact transmission.

Four presentations addressed issues of mortality in HIV-infected cohorts in western and northern settings (see Table 1). Hogg and colleagues (Abstract 137) used data from 18 clinical and interval cohort studies in the United States and Canada that participate in NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design). The analysis estimated changes in life expectancy between 1996 and 2007 for HIV-infected individuals 20 years of age or older who were ART naive and initiating ART. Death ascertainment occurred through direct linkage to vital-statistic registries and clinic reports, and death and person-time were partitioned into 5-year groups. Life expectancy from age 20 years

increased steadily, from 34.4 years in the 1996-to-1999 period to 47.1 years in the 2006-to-2007 period. The life expectancy of injection drug users (IDUs) was lower (28.1 years) than it was for either men who have sex with men (MSM) (51.6 years) or those who acquired HIV through heterosexual sex (47.7 years). The gap between average national life expectancy at age 20 years in the general US population and that in the cohort was largest for African Americans at 54.7 years versus 41.0 years, respectively, compared with 59 years versus 50 years for whites. Finally, life expectancy by pre-ART CD4+ count was lower for those with a count below 100 cells/μL (18.7 years; standard error [SE], 0.7 years) than for those with a count of more than 350 cells/μL (42.2 years; SE, 0.5 years). The authors concluded that life expectancy of an HIV-infected person on ART would be only slightly lower than that of one in the general population, with notable differences by race and HIV risk factor.

Rodger and colleagues undertook a similar analysis (Abstract 638) to compare mortality rates in adults with well-controlled HIV with those of adults in the general population. The researchers used data from the SMART (Strategies for Management of Antiretroviral Therapy) and ESPRIT (Evaluation of Subcutaneous Proleukin in a Randomized International Trial) studies to examine mortality in 3280 participants who met inclusion criteria of being from 20 years to 70 years old, receiving continuous ART, not being IDUs, and having HIV-1 plasma RNA levels below 500 copies/mL and CD4+ counts of 350 cells/μL or higher at any time in the previous 6 months. Standardized mortality ratios (SMRs) were calculated by comparing death rates with those in the Human Mortality Database (HMD), after stratification by country, sex, and age. For participants with a CD4+ count between 350 cells/μL and 499 cells/μL, the SMR was 1.79 (95% CI, 1.19-2.59), reflecting an increased mortality rate compared with the general population. However, for participants with CD4+ counts of 500 cells/μL or higher, there was not a statistically significant increase in mortality compared with the general population. The most common cause of death overall was cardiovascular disease (CVD) or sudden death (19 deaths, 31%), followed by non–AIDS-related malignancy (12 deaths, 19%). These results were robust to 2 separate sensitivity analyses, but the authors cautioned that a selection bias of healthier individuals may have been present in these 2 clinical trials.

Morlat and colleagues compared causes of death in a cross-sectional, nationally representative 2010 survey of 90 HIV treatment sites in France (representing approximately 82,000 patients) with causes of death found in similar surveys in 2000 and 2005 (Abstract 1130). The proportion of deaths due to AIDS-defining events decreased from 47% in 2000 to 36% in 2005 and to 25% in 2010, but AIDS-defining events remained the most frequent cause of death overall. Conversely, the proportion of non–AIDS-defining and non–hepatitis-related malignancies increased from 11% in 2000 to 22% in 2010. Cardiovascular deaths were similar in proportion in the 3 time periods at 7% in 2000, 8% in 2005, and 10% in 2010. The authors emphasized the need for integrated care, with prevention, screening, and treatment for malignancies and viral hepatitis, as well as continued improvements in HIV control.

In the last presentation addressing mortality in ART cohorts, Ingle and colleagues from ART-CC (Antiretroviral Therapy Cohort Collaboration) examined cause-specific mortality in 16 cohorts containing 65,121 HIV-infected people from Europe and North America (Abstract 640). The overall mortality rate was 12.9 per 1000 person-years, and a specific cause could be determined for 84% of the deaths. Of the overall mortality, AIDS-related deaths accounted for 42%, and non-AIDS-related deaths accounted for 58%. By using Poisson regression to estimate crude and adjusted mortality rates by ART duration, AIDS-related deaths were found to decrease significantly with each year on ART (adjusted rate ratio [aRR], 0.81/year; 95% CI, 0.79-0.83). Rates of death from both non–AIDS-related malignancy and stroke increased significantly (aRRs, 1.05; 95% CI, 1.01-1.09, and 1.13; 95% CI, 1.02-1.26, respectively). Similar to what was seen in prior presentations, non–AIDS-related mortality surpassed that from AIDS after 2 years on ART, led by non-AIDS-related malignancies and CVD risks. This again highlighted the need for HIV-specific care to integrate longitudinal prevention and treatment for malignancies of all types and CVD.

Two other cohort studies found health disparities by race, one examining CD4+ cell count at ART start (Abstract 139) and one determining AIDS as a cause of death (Abstract 1045). The first presentation, by Troung and colleagues, assessed CD4+ cell count at ART initiation in the San Francisco HIV/AIDS case registry for individuals older than 12 years diagnosed with HIV infection between 2004 and 2010 (Abstract 139). In 2010, public health clinics in San Francisco began recommending ART at any CD4+ cell count. The investigators found consistent increases in CD4+ cell count at ART initiation from 2004 to 2010. Early initiation of ART, at CD4+ counts greater than 500 cells/μL, was seen starting in 2007. However, after adjustment for the number of people presenting in each substratum, people initiating ART at CD4+ counts greater than 500 cells/μL were more likely to be white, MSM, non-poor, and diagnosed by a private practitioner ($P < .01$ for each association, compared with all others in group). The authors speculated that these disparities, if carried forward, could partition the benefits of initiating ART at CD4+ counts greater than 350 cells/μL or 500 cells/μL into less marginalized populations.

A second presentation, by Murphy and colleagues, examined the association between black race and death from AIDS in the WIHS (Women's Interagency HIV Study) cohort (Abstract 1045). Inclusion criteria were enrollment in the WIHS cohort and continuous ART, primary exposure was self-reported race, and the primary outcome was AIDS-related death. In the univariate

Table **1**. Selected Studies on Treatment Outcomes and Mortality in People Receiving Antiretroviral Therapy in Resource-Rich Settings

Study Description	Cohort Description	Key Findings
Abstract 138 US-based, nationally-representative estimate of HIV+ adults in care, on ART, and virologically suppressed	Structured sample of 4217 patients at 461 facilities in 17 states or territories Observation period: Jan–April 2009 Using weighted analysis, this was representative of 421,186 HIV+ adults in care	• 44% of an estimated 941,940 adults living with HIV were in care (had 1 clinic visit during observation period). Of those in care: - 89% were prescribed ART - 71% had HIV-1 plasma RNA level ≤200 copies/mL • Non-Hispanic blacks were less likely to be prescribed ART and be virologically suppressed in adjusted MVA *Conclusion:* Because < half of HIV+ individuals were in care, expanding ART coverage to those with CD4+ cell counts >500 cells/μL will have minor impact. Increasing numbers in care is important.
Abstract 137 NA-ACCORD analysis to estimate temporal changes in life expectancy between 1996 and 2007	18 clinical and interval cohorts in U.S. and Canada Observation period: 1996–2007	• Life expectancy at age 20 increased: - 1996-1999: 34.4 years - 2006-2007: 47.1 years • Life expectancy at age 20 was lower for IDU (28.1 years) than for MSM (51.6 years) or heterosexuals (47.7 years) • Gap between life expectancy at age 20 in HIV+ vs general population: - Blacks: 41 years (HIV+) vs. 54.7 years (general population) - Whites: 50 years (HIV+) vs. 59 years (general population) *Conclusion*: Life expectancy at 20 years of an HIV+ person on ART is only slightly lower than that of the general population, but notable differences exist by race and HIV risk factor.
Abstract 638 Mortality in patients with well-controlled HIV and high CD4+ cell counts in 2 randomized controlled trials, compared with the general population	3280 non-IDU participants in the ESPRIT or SMART studies with CD4+ ≥350 cells/μL and HIV-1 plasma RNA <500 copies/mL were randomized to the continuous ART arms Observation period: 2000–2008 [ESPRIT], 2002–2006 [SMART] SMRs calculated comparing death rates in the combined cohort with those in the Human Mortality Database, stratifying by country, sex, and age	• SMR for participants with CD4+ count between 350 and 499 cells/μL: - 1.77; 95% CI, 1.17-2.55 • Standardized mortality ratio for participants with CD4+ count >500 cells/μL: - 1.00; 95% CI, 0.69-1.40 • Most common causes of death: - Cardiovascular disease or sudden death (n=19 or 31%) - Non–AIDS-defining malignancy (n=12, 19%) *Conclusion:* Risk of mortality in healthy HIV+ patients on ART enrolled in 2 clinical trials was not statistically significantly higher than that for the general population, though a selection bias toward healthier trial participants may be present.
Abstract 1130 Causes of death among HIV+ patients in France from 2000 to 2010	Cross-sectional, nationally representative survey of 90 HIV treatment sites in France, ~82,000 patients [ANRS Cohort] Observation period: cross-sectional surveys conducted in 2000, 2005, 2010	• Proportion of deaths from AIDS-defining events decreased from 47% in 2000 to 25% in 2010 • Proportion of non–AIDS-defining and non–hepatitis-related malignancies rose from 11% in 2000 to 22% in 2010 • Proportion of cardiovascular deaths not statistically significantly different: 7% in 2000, 10% in 2010 *Conclusion:* AIDS-defining events have decreased, but still account for 1/4 of all mortality. Integrated care with prevention, screening, and treatment for malignancies, hepatitis, and cardiovascular disease will be increasingly important.
Abstract 640 Cause-specific mortality in European and North American cohorts	Longitudinal data from the ART Cohort Collaboration assessed mortality for 65,121 HIV+ people in 16 cohorts Observation period: 1996–2009	• Overall mortality rate was 12.9 per 1000 person-years • Specific cause of death determined for 84% of individuals: - 42% were AIDS-related - 58% were non–AIDS-related • AIDS-related deaths decreased each year on ART: - Adjusted rate ratio 0.81/year; 95% CI, 0.79-0.83 • Non–AIDS-related mortality surpassed that from AIDS after 2 years on ART: - Non–AIDS-related malignancy increased aRR/year on ART: 1.05; 95% CI, 1.01-1.09 - Stroke increased aRR/year on ART: 1.13; 95% CI, 1.02-1.26 *Conclusion:* Integrated HIV care should address HIV-specific factors, eg, malignancies and cardiovascular risk.

HIV+ indicates HIV seropositive; ART, antiretroviral therapy; MVA, multivariable analysis; IDU, injection drug users; CI, confidence interval; MSM, men who have sex with men; NA-ACCORD, North American AIDS Cohort on Research and Design; ESPRIT, Evaluation of Subcutaneous Proleukin in a Randomized International Trial; SMART, Strategies for Management of Antiretroviral Therapy Study Group; SMR, standard mortality ratio; ANRS, French National Agency for Research on AIDS and Viral Hepatitis; aRR, adjusted rate ratio

model, the hazard ratio (HR) for death from AIDS was 2.11 for black women compared with white women (P = .002); the difference remained statistically significant after adjustment for HCV, IDU, depression, and virologic control. Black women were also less likely than white women to adhere to ART (adjusted HR [aHR], 0.65; P = .0001), but race remained a predictor of death from AIDS after adjustment for adherence. The authors suggested that further studies are needed to determine the role of genetic polymorphisms that vary by race in lower adherence and response to treatment among black women.

Acute HIV Infection

Several studies were dedicated to understanding the effect of ART on acute HIV infection. To further elucidate the possible benefits of ART during acute or early HIV infection, Margolick and colleagues reported on the effect of ART on rates of viral suppression at 24 months off therapy for patients with acute or early HIV infection enrolled from 2005 to 2009 (Abstract 356). Patients with acute or early HIV infection and CD4+ count of 350 cells/µL or higher were randomized to 12 months of immediate ART (n = 57) or deferred treatment (n = 56), and both groups were followed for 24 months off therapy. The plasma HIV RNA set point at 24 months in those who had not (re)initiated ART was below 10,000 copies/mL in 17.5% of patients in the immediate-treatment arm and 5.4% of the patients in the deferred-treatment arm (P = .07). Similarly, Lafeuillade and colleagues reported on the long-term control of HIV after a 2-year ART course for acute HIV infection in 45 patients (Abstract 358). Of patients who had received a 2-year ART course initiated at the time of acute infection, 17% were still off therapy 12 years after completing the course. The majority of those patients demonstrated stable plasma viral levels of less than 3500 copies/mL.

Perelson explored the impact of ART during acute infection on the level of resting CD4+ cell infection and decay of latent infection (Abstract 152). Investigators developed a mathematical model of the initial frequency of resting-cell infection and decay of latent infection and compared the model with T-cell and HIV RNA-level data from 27 study participants who elected to start ART during acute HIV infection. The model predicted a strong relationship between containment of viremia and the level of resting-cell infection (r = 0.65, P = .0003). The authors suggested that there may be 2 pools of infected resting CD4+ T cells: a less stable pool of cells observed in patients with high levels of resting-cell infection and an extremely stable pool of cells that are established despite ART. The less stable pool may be easily activated and eliminated, but the stable pool may have an extremely long half-life and be highly resistant to elimination, even by long-term ART.

Buzon and colleagues presented findings on patients who initiated ART during early HIV infection and continued on ART for more than 10 years, compared the effect on the viral reservoir with elite controllers (Abstract 151). Investigators compared CD4+ cell counts and levels of total, integrated, and 2-long terminal repeat (LTR) HIV-1 DNA by quantitative polymerase chain reaction (PCR) in 9 individuals treated during acute HIV infection, 26 individuals with established HIV on treatment, and 37 elite controllers. Levels of integrated and total HIV-1 DNA were statistically significantly lower in elite controllers and in patients who began treatment during acute infection (P = .06 and P = .001, respectively). The ratio between total and integrated HIV-DNA was statistically significantly lower in patients treated early than in chronically treated patients (P = .04) and elite controllers (P = .04). The authors suggested that this difference in ratio is evidence that prolonged ART initiated during acute infection may allow for a clinically significant depletion of HIV-1 reservoirs.

Hamlyn and colleagues explored factors associated with progression after primary HIV in participants of the SPARTAC (Short Pulse Anti Retroviral Therapy at HIV Seroconversion) Trial (Abstract 553). SPARTAC participants were randomized to 1 of 3 arms: no treatment, 12 weeks of ART, or 48 weeks of ART. The primary study endpoint was either CD4+ count less than 350 cells/µL or initiation of ART. The authors explored associations between interleukin-6 (IL-6) and D-dimer levels at HIV seroconversion as predictors of HIV disease progression. Data on IL-6 and D-dimer were available for 200 patients. There was no association between D-dimer level and progression; however, IL-6 levels at HIV seroconversion were independently associated with HIV disease progression even after controlling for HIV RNA levels and CD4+ cell counts (HR, 1.38; 95% CI, 1.09-1.75; P = .007). The authors urged further exploration of the IL-6 marker.

Vinikoor and colleagues analyzed immunologic outcomes of acutely infected HIV patients who started ART within 30 days of diagnosis in a prospective clinical trial with a primary outcome of T-cell activation as measured by percent of circulating CD8 + HLA-DR + CD38 + T cells at 96 weeks (Abstract 554). Thirty-one patients were included in the 96-week analysis. In multivariable analysis, adjusted for age, nadir CD4+ cell count, and peak HIV RNA level, there was no association between the length of time from infection to ART initiation and immune activation at 96 weeks (P = .8).

To understand the impact of ART regimens on the viral load in the anogenital compartment, Phanuphak and colleagues compared 3-drug (tenofovir/emtricitabine/efavirenz) with 5-drug (tenofovir/emtricitabine/efavirenz/raltegravir/maraviroc) ART regimens in 24 men with acute HIV infection (Abstract 555). Investigators collected blood, anal lavage, and seminal plasma to measure HIV RNA levels from baseline to 24 weeks on treatment. For anal lavage, median time to HIV RNA levels less than 3 $\log_{10}$ copies/mL and less than 1.7 $\log_{10}$ copies/mL was 4 days (3 days-13 days) and 3 days (3 days-7 days), respectively. For seminal plasma, the median times to these levels were 7 days (3 days-26 days) and 12 days (6 days-26 days),

respectively. There was no difference between the ART regimens in time to achieve HIV RNA level less than 3 $\log_{10}$ copies/mL and less than 1.7 $\log_{10}$ copies/mL in anal lavage (P = .33 and P = .92, respectively) or in seminal plasma (P = .90 and P = .08, respectively). The 5-drug regimen and a high baseline HIV RNA level on anal lavage were both statistically significantly associated with a greater likelihood of a serum HIV RNA level lower than 1.7 $\log_{10}$ copies/mL at 24 weeks. The authors encouraged uptake of early treatment to decrease the risk of transmission.

Ananworanich and colleagues described the effect of 5-drug and 3-drug highly active antiretroviral therapy (HAART) regimens during acute HIV infection on restoration of immunity and HIV reservoir size in 35 patients (Abstract 363). Twenty-two patients were treated with a 5-drug combination (tenofovir/emtricitabine/efavirenz/raltegravir/maraviroc) and 13 were treated with a 3-drug combination (tenofovir/emtricitabine/efavirenz). HIV RNA and DNA levels were measured in the blood and sigmoid colon at baseline and at 24 weeks, and PBMCs were analyzed by flow cytometry. After 24 weeks of treatment, HIV RNA and total and integrated DNA in the PBMCs all declined significantly, whereas in the sigmoid colon, a statistically significant decline was seen only for HIV DNA levels after 5-drug therapy. Similar results were seen when HIV DNA levels were adjusted for CD4+ cell count. At week 24, overall total DNA was undetectable in blood in 8 of 27 patients and integrated DNA was undetectable in blood in 18 of 24 patients. In the sigmoid colon, total DNA was undetectable in 5 of 14 patients and integrated DNA in 7 of 10 patients. Predictors for higher total DNA level in blood at week 24 were higher baseline total DNA and use of 5-drug regimen. Authors concluded that both 5-drug and 3-drug antiretroviral regimens during acute HIV reconstitute CD4+CCR5+ T cells in the gut and reduced HIV reservoir in the blood and gut. Additionally, the 5-drug regimen may have a greater impact on the HIV reservoir in the gut than the 3-drug therapy.

Pérez-Santiago and colleagues reported a study aimed at understanding perturbations and recovery of gut flora during acute HIV infection and the effect of ART on these processes (Abstract 546). Investigators found statistically significant associations between CD4+ count and specific gut bacterial flora during HIV acute infection. Seven subjects with acute infection underwent anal swab, lymphocyte subset profiles, and viral HIV RNA testing at baseline and at weeks 24 to 36. Six patients were treated with ART, and 1 was not. Researchers employed pyrosequencing of the 16s ribosomal DNA (rDNA) to evaluate the gut flora and to characterize associations of bacterial populations with immune status and treatment. Proportions of bacterial populations did not differ significantly between time points among treated subjects. Five orders of bacteria were positively correlated with CD4+ cell count, and 2 orders were negatively correlated. Bacterial population changes were greatest in the single ART-naive individual. The researchers concluded that proportions of gastrointestinal populations shift during acute HIV infection, but ART appears to stabilize gut flora, and untreated acute infection results in the greatest perturbation.

Detection of acute HIV infection is crucial but often overlooked in clinical settings. O'Connell and colleagues presented data from a prospective screening study that showed particularly subtle clinical features of acute HIV. The ECHO (Early Capture HIV Cohort) study enrolled individuals in East Africa and Thailand at high risk for HIV infection for prospective observation (Abstract 60LB). Study participants underwent a baseline history and physical followed by routine clinical follow-up and twice-weekly nucleic-acid testing (NAT). Individuals who became infected with HIV were evaluated over 9 subsequent visits for symptoms, physical-exam findings, and immunologic or virologic parameters. This analysis included 32 volunteers with evidence of acute HIV infection. Investigators reported that clinical symptoms were mild and occurred just before and during the peak of viremia. The most common symptoms were subjective fever (in 50% of participants) and headache (in 38%). Physical examination detected abnormalities in 84% of participants, and lymphadenopathy was the most common finding. Interestingly, fever was documented in only 1 participant at 1 visit. Hospitalization was also notably rare, having occurred in only 2 pregnant women. The authors emphasized the limitations of using clinical manifestations to identify acute HIV infection.

Lodi and colleagues categorized patients in the CASCADE (Concerted Action on Seroconversion to AIDS and Death in Europe) cohort using 3 different definitions of severe primary HIV infection (PHI) and compared rates of survival based on each definition (Abstract 550). Acutely infected patients were considered to have severe or non-severe PHI based on the following 3 definitions: (1) clinical: symptomatic seroconversion illnesses with brain and neurological involvement; (2) immunologic: at least 1 CD4+ count less than 350 cells/µL in the first 6 months; or (3) virologic: at least 1 HIV-1 RNA level over 1,000,000 copies/mL in the first 6 months. For each definition, Kaplan-Meier curves and log-rank tests were used to compare survival (all-cause mortality) for severe and non-severe PHI during follow-up without ART ending at the earliest of 3 events: death, last clinic visit, or January 1, 1997. Of 3878 individuals with acute HIV infection and a recorded CD4+ count, 919 (24%) had severe PHI based on the immunologic definition. There was strong evidence of difference in survival by severity of PHI (P < .001) with median interquartile range (IQR) survival times of 7 years (5 years to 10 years) and 13 years (7 years to -) for severe and non-severe PHI, respectively. There was no statistically significant difference in survival between patients with and without reported severe clinical illness (P = .667) or based on the virologic definition (P = .338). The authors concluded that a low initial CD4+ count may be a useful indicator for identifying patients who are likely to experience rapid disease progression.

Yue and colleagues explored the cumulative impact of host and viral factors on HIV-1 RNA control after HIV-1 transmission (Abstract 551). A heterosexual Zambian transmission cohort provided 195 phylogenetically linked HIV-1 transmission pairs. HLA class I (HLA-I) and HIV-1 viral set point analysis was performed for both partners and associations were determined based on univariate and multivariate analyses. Viral load set point in the source partner was significantly correlated with the viral load set point in the seroconverter (Pearson Correlation R2 = 0.020; P = .046). However, this effect was significantly modulated by sex, HLA-I marker, and HLA-B allele. Multivariable general linear regression analysis accounting for these factors continued to reveal a strong association between transmitting partner viral load and seroconverter viral load (beta = 0.28 $\log_{10}$ viral load; P < .001).

Session 102 was dedicated to diagnostic tools for detecting acute HIV. Peel and colleagues shared an evaluation of the APTIMA® HIV-1 Qualitative RNA Assay (Gen-Probe) for identification of acute HIV infection as a screening assay in high-risk populations in East Africa and Southeast Asia (Abstract 556). A total of 48,229 results were analyzed from 1045 participants. Of these, 127 patients tested reactive by the APTIMA®, with 18 incident cases detected. Prevalence among the high-risk populations examined was 15.6% (Thailand), 12.4% (Tanzania), and 10.1% (Kenya). Infection status over time was used to calculate the sensitivity, which was 99.2%, and specificity, which was 99.3%. Karris and colleagues assessed the cost of missed acute HIV diagnoses in a comparative analysis of an HIV NAT and a fourth-generation antigen/antibody combination assay (ARCHITECT® HIV Combo) for detection of acute HIV performed retrospectively in blinded, banked samples (Abstract 557). A negative rapid test and a positive NAT detected 14 cases of acute infection. Of these, the fourth-generation combo assay detected 9 cases, suggesting that the fourth-generation combo assay had 5 false-negative results. The investigators predicted these 5 missed diagnoses would result in 4.55 new transmissions over 12 months, compared with fewer transmissions when HIV serostatus is known. Cost-savings analysis was performed, and the authors concluded that the NAT should be used in populations with a high incidence of acute HIV infection.

High viral loads associated with acute HIV infection raise the risk of transmission. Kuruc and colleagues found that acute HIV infections detected through the North Carolina Screening and Tracing Active Transmission (STAT) program showed an increasing proportion of infections in African Americans, MSM, and individuals less than 30 years (Abstract 566). The researchers encouraged rapid assessment of acute HIV infection cases so that patients could enter care and begin treatment immediately to avoid transmitting the virus. Frange and colleagues reported on the increasing role of primary HIV-1 infection in the spread of HIV in the ANRS (French National Agency for Research on AIDS and Viral Hepatitis) PRIMO (Primary Infection) cohort in France (Abstract 1107). Investigators analyzed the HIV *pol* sequence using a phylogenetic approach to characterize HIV transmission dynamics in 987 patients. An increasing frequency of primary HIV cosegregated transmission chains was identified, with 10.2% before 2006 and 15.2% from 2006 to 2010. Compared with unique primary HIV, clusters of primary HIV were more often MSM, of younger age, and having reported more casual partnerships. With this in mind, the authors urged reconsideration of current HIV prevention methods and testing programs.

Advances in ART in RLS

This year's CROI featured many outstanding presentations describing advances in ART in resource-limited settings (RLS). The conference began its coverage of issues in RLS with the 6th Annual N'galy-Mann Lectureship, awarded to Quarraisha Abdool Karim and Salim Abdool Karim, who gave a combined lecture on their experience conducting HIV research in South Africa over the past 3 decades (Abstract 17). The awardees attributed their continued success to a dedication to collaborating with and training researchers and medical students, a willingness to conduct research within the community, and outstanding mentorship.

Scale-up of ART and Response to Treatment in RLS

Bendavid described the impact of HIV development assistance on adult mortality in sub-Saharan Africa as "one of the greatest global health achievements in recent memory" (Abstract 85). He noted the correlation between the rise in HIV assistance to sub-Saharan Africa, from US $75 million annually before 2001 to more than US $5 billion annually by 2004, and the stabilization of and decrease in numbers of deaths from HIV in South Africa. To examine the possible linkage between these 2 trends, Bendavid and colleagues conducted 2 analyses: one to determine if assistance from the President's Emergency Plan for AIDS Relief (PEPFAR) was associated with reductions in all-cause adult mortality, and one to compare changes in all-cause adult mortality associated with PEPFAR with changes in HIV-related deaths associated with PEPFAR. This strategy allowed for the assessment of unintended harms that could be caused by PEPFAR's focus on the HIV epidemic crowding out other health priorities, which could result in a less dramatic reduction in all-cause mortality than what would be expected as HIV-related mortality declines.

Data from the Demographic and Health Surveys (DHSs), cross-sectional, nationally representative surveys conducted annually in many African countries from 1998 to 2008, were pooled from 27 countries, 9 of which were PEPFAR focus countries. Focus countries were statistically significantly more populous than non-PEPFAR focus countries but did not have statistically significant differences in gross domestic product (GDP) per capita or HIV prevalence. In the first analysis, the authors found an unadjusted odds

ratio (OR) for adult death of 0.80 (95% CI, 0.68-0.95) in PEPFAR focus countries compared with nonfocus countries. This association remained statistically significant after adjustment for country-specific factors of HIV prevalence, non-PEPFAR health assistance, GDP per capita, government effectiveness, and individual-level covariates of age, residence in an urban area, and level of education (adjusted OR [aOR], 0.84; 95% CI, 0.72-0.99).

For the second analysis, the authors compared the number of all-cause deaths averted in the 9 PEPFAR focus countries from 2004 to 2008, an estimated 740,800 deaths (95% CI, 443,300-1,808,500), with the number of HIV-specific deaths averted over the same time frame in the same countries, an estimated 631,338 deaths (95% CI, 249,026-1,060,253). The wide range in CIs prevents conclusions about the likelihood of unintended harms. Bendavid and colleagues argued that, despite the uncertainty, the overall effect of PEPFAR intervention on mortality outcomes was beneficial.

Two presentations offered different views of the change in CD4+ cell count at the initiation of ART. Egger and colleagues examined data from patients participating in IeDEA (International Epidemiologic Databases to Evaluate AIDS) and ART-CC who had a CD4+ cell count measured 6 months prior to or 1 month after ART initiation (Abstract 100). The researchers used 2 random-effects linear regression model analyses to examine trends in CD4+ cell count at ART initiation in low-, middle-, and high-income countries. A univariate analysis determined median CD4+ cell count at ART start in 2009 for 36 countries with a collective 244,953 ART patients, and change in CD4+ cell count from 2002 to 2009 or 2010. A multivariable analysis used data from 240,515 patients in 22 countries with more than 500 ART patients each and more than 1 treatment site, and to explore the influences of age, sex, country income, country-level ART coverage, and calendar year on CD4+ cell count at ART start.

The analyses found large discrepancies in median CD4+ cell count at ART initiation in 2009, varying from 89 cells/μL (95% CI, 69-110) in Indonesia to 307 cells/μL (95% CI, 301-314) in the United States. However, trends in median CD4+ cell counts at ART start from 2002 to 2010 were similar in low-income and upper-middle-income countries, with annual changes being largest (20-25 cells/μL/year) in low-income countries. Men and subjects over 40 years of age had lower CD4+ cell counts at ART initiation than other groups. For low-income countries only, national ART coverage for 80% or more of people qualifying for ART by the WHO 2010 guidelines was statistically significantly associated with an annual increase in CD4+ cell count at start of ART, but countries with ART coverage for less than 80% of people diagnosed with HIV did not demonstrate statistically significant changes in CD4+ cell count at ART start. The authors noted limitations in the analyses, including the exclusion of 25% of patients in the cohort because of missing CD4+ cell count data, limited or unrepresentative data from some countries, and the observational nature of the study. The researchers observed that, although median CD4+ count at ART start increased in most countries over time, it remained below 200 cells/μL and 350 cells/μL in low- and high-income countries, respectively. The authors also noted that higher national ART coverage led to statistically significant increases in CD4+ cell counts over time.

Lahuerta and colleagues used data from 151 sites supported by ICAP (International Center for AIDS Care and Treatment Programs) in sub-Saharan Africa with 262,638 eligible patients over 14 years of age to study late enrollment into care and late ART initiation, defined as CD4+ count less than 100 cells/μL or World Health Organization (WHO) stage IV disease (Abstract 650). The researchers found that the proportion of patients enrolling in care late decreased statistically significantly from 20% in 2005 to 16% in 2010 (*P* value for trend < .001). Late ART initiation also decreased from 43% to 31% over the same period (*P* value for trend < .001), and men had higher risk than women of both enrolling late (relative risk [RR], 1.7; 95% CI, 1.6-1.8) and initiating ART late (RR, 1.4; 95% CI, 1.3-1.5) in 2010; there were similar discrepancies in 2005. Median CD4+ count within the cohort rose from 125 cells/μL in 2005 to 178 cells/μL in 2010 (P value for trend < .001), approaching prior WHO thresholds for ART initiation of 200 cells/μL. The authors suggested that targeted efforts are needed to reach HIV-infected men.

To address the lack of information on ART outcomes in women in RLS, Firnhaber and colleagues used data from the AIDS Clinical Trial Group (ACTG) PEARLS (Prospective Evaluation of Antiretrovirals in Resource Limited Settings) trial to examine sex differences in ART efficacy outcomes (Abstract 89). The study randomly assigned 1571 ART-naive participants (47% of whom were women) with CD4+ counts less than 300 cells/μL to receive (A) lamivudine/zidovudine plus efavirenz, (B) didanosine, emtricitabine, and atazanavir, or (C) emtricitabine/tenofovir plus efavirenz. The study ran from May 2005 to 2010, and the primary endpoint was time to treatment failure, defined as confirmed HIV-1 plasma RNA greater than or equal to 1000 copies/mL at week 16 or later, a new AIDS-defining condition (ADC) at week 12 or later, or death due to any cause. A Data Safety and Monitoring Board (DSMB) review in 2008 led to the discontinuation of arm B because of inferior efficacy. The authors used a Kaplan-Meier analysis to examine time to treatment failure by sex and treatment arm, and they used a Cox proportional hazard model to examine the association of sex with outcome in both univariate and adjusted analyses. At baseline, women had a statistically significantly higher body mass index (BMI) and CD4+ cell count than men had, and lower plasma HIV-1 RNA levels (*P* < .001 for all data). In the primary analysis, there was no difference in time to treatment failure between men and women. Interestingly, there was no difference between efficacy of treatment arms in the women in the Kaplan-Meier analysis, but men reached treatment failure more quickly

in the atazanavir-based arm (arm B) than women, and this difference was due to virologic failure. Men were found to report any nonadherence more frequently than women did (42% vs 38%, respectively; $P < .0011$). The data are currently being analyzed to explore these adherence differences as well as possible sex-based pharmacokinetic differences that could explain the poor treatment outcome for men in arm B.

Treatment outcomes in women were also examined by Sawe and colleagues (Abstract 642) using posttrial follow-up data from the ACTG A5208 OCTANE (Optimal Combination Therapy After Nevirapine) study in Africa. In OCTANE, 214 women who had received single-dose nevirapine (sdNVP) for prevention of mother-to-child transmission (PMTCT) and 500 women who had not been exposed to sdNVP initiated ART with tenofovir/emtricitabine plus either lopinavir/r or nevirapine. Of 513 women in follow-up at completion of the study, 77% consented to extended follow-up and transitioned to standard care at local clinics. Of those, 489 (95%) completed 72 weeks of follow-up. No statistically significant increase in grade 3 or 4 adverse events, new HIV-related diagnoses, or WHO clinical stage was seen after transfer to local ART care, compared with such developments while the women were under the care of the study team. These are encouraging results for patients transitioning from care under clinical trials to standard care in RLS, although data are limited because 33% of the patients did not enroll in long-term follow-up.

Clumeck and colleagues presented data from a prospective, randomized clinical trial taking place in the Democratic Republic of Congo (Abstract 88LB). The trial examined differences in treatment outcomes in 425 participants randomized to either lopinavir/r-based or nevirapine-based regimens, with a second tier of randomization to determine nRTI allocation of either tenofovir/emtricitabine or zidovudine/lamivudine. Inclusion criteria included being at least 18 years of age and ART naive (except for sdNVP if given more than 1 year prior to enrollment) and meeting national guidelines for ART initiation (WHO clinical stage IV, WHO clinical stage III with CD4+ count < 350 cells/μL or CD4+ count < 200 cells/μL). Patients with active TB, pregnancy, or substantial laboratory abnormalities were excluded, and there were no statistically significant differences in baseline characteristics among the groups. The primary outcome was therapeutic failure, defined as new categorization of WHO stage III or IV, plasma HIV-1 RNA level greater than 1000 copies/mL, or treatment change because of toxicity. Therapeutic failure was seen in 36 (17%) of the nevirapine-based regimen arm and 23 (11%) of the lopinavir/r-based arm at 96 weeks ($P = .014$). The difference was driven by increased virologic failure in the nevirapine arm. Of those in whom nevirapine failed, 86% had drug resistance mutations, compared with 20% in the lopinavir/r arm, but the statistical significance of this difference was not reported. There was no statistically significant difference in glomerular filtration rate or anemia based on nRTI regimen component. The authors concluded that the increased incidence of virologic failure and resistance seen in the nevirapine-based regimen was of concern and should be taken into account in rollout program planning.

Two other groups presented concordant results regarding the use of regimens containing nevirapine and tenofovir. Wandeler and colleagues (Abstract 635) examined data from the IeDEA Southern Africa Collaboration and found that patients on first-line regimens containing nevirapine and tenofovir were more likely to die (aHR 1.24; 95% CI, 1.15-1.34) but less likely to be lost to follow-up (aHR, 0.86; 95% CI, 0.83-0.90) than those receiving ART containing efavirenz and tenofovir. Scarsi and colleagues (Abstract 636) found a higher initial and persistent rate of virologic failure in Nigerians initiating ART with tenofovir, emtricitabine, and nevirapine (10.6%) than in those initiating with zidovudine, lamivudine, and nevirapine (7.1%, $P < .001$). These results add to the growing call for an evaluation of initial regimens containing nevirapine and tenofovir.

Linkage to Care and Loss to Follow-Up in Adults in RLS

A themed discussion included several presentations on novel approaches to linkage to care. See Table 2 for some of the major findings. McNairy moderated the session, which began with a brief overview, highlighting data from RLS showing that 59% of HIV-infected people link to care, but the range in studies is from 33% to 88%.[1] As linkage to care is not a PEPFAR indicator or routinely reported, data are often limited. McNairy discussed several novel approaches to linkage to care, including point-of-care CD4+ cell count measurements, case management, and financial incentives for care entry. Chamie and colleagues explored the first of these strategies by offering community-based voluntary counseling and testing along with point-of-care CD4+ cell count testing and rapid TB testing during a 5-day multi-disease community health campaign in Uganda (Abstract 1134). Participants who were tested were stratified into active referral (CD4+ count > 100 cells/μL or enhanced referral (CD4+ count ≤ 100 cells/μL). Active referral cases were given a follow-up appointment within 3 months; enhanced referral cases were given an appointment within 2 weeks and initiated ART at the first clinic visit. The community population was 6300, and approximately 75% were tested. The adult HIV prevalence was 7.8%. Of 139 adults accepting referral to care, only 8 met criteria for enhanced referral. Of these, 6 (75%) linked to care successfully, all within 10 days, and initiated ART at their first clinic visit. Of the 131 participants who were classified as active referral, only 58% linked to care within 3 months; the lower the CD4+ cell count, the more likely the person would link to care. The authors concluded that the active-referral strategy was insufficient to achieve high levels of linkage to care.

Van Rooyen and colleagues presented a study on the efficacy of home-based HIV counseling in achieving linkage to care in KwaZulu-Natal, South Africa (Abstract 1135). The study enrolled 282 households with 743 adults,

91% of whom consented to HIV testing and point-of-care CD4+ cell count measurement. Only 33% of participants were male. Of all participants, 203 were newly identified as HIV-infected. By 3 months after HIV testing, 88% of those found to be seropositive had linked to care, and 11 of 13 eligible for ART were receiving it. The authors concluded that home-based testing was effective in reaching undiagnosed individuals with high CD4+ cell counts and achieved high rates of linkage to care.

The IeDEA cohort also presented a meta-analysis and review of linkage to care from diagnosis to ART initiation (Abstract 1143). The analysis used published data to determine the completion of 4 key steps in linkage to care: (1) HIV testing, (2) CD4+ cell testing with ART eligibility assessment, (3) ART eligibility, and (4) ART initiation. The data were drawn from 29 studies involving 148,912 ART-naive patients, and the researchers found that, of ART-eligible patients, only 62% initiated treatment (95% CI, 55.2%-70.7%). Mortality among those patients eligible for ART who did not initiate was 10.8% (95% CI, 4.6%-17.0%). Loss to follow-up occurred in 24.6% (95% CI, 10.8%-30.3%) of patients eligible for ART and 54.2% (95% CI, 42.8%-72.0%) of patients who were not eligible for ART. Based on these data, mortality and loss to follow-up prior to ART initiation are substantial barriers to ART coverage in RLS.

Geng and colleagues examined the issue of loss to follow-up in 4318 Ugandan patients entering HIV care with CD4+ cell counts greater than 350 cells/μL, making them ineligible for ART (Abstract 1151). A random sample of patients lost to follow-up was tracked in the community to determine vital status and clinical-care information. Over 2.5 years of follow-up, 1101 (35%) of patients initiated ART. Of the 858 patients (30%) lost to follow-up, 67 were tracked in the community, and outcomes were ascertained for 56 (84%) of them. Cumulative mortality at 2.5 years after last clinic visit for those lost to follow-up was 13.6% (95% CI, 5.5%-31.6%), and 56% of those thought to be lost to follow-up were found to be alive and in care at a new site. Although it is encouraging that many of those considered lost to follow-up were actually in care at a different site, the high mortality seen in this study corroborates the concern generated by the previously discussed presentations on linkage to care and follow-up.

Several groups explored retention in care and loss to follow-up after ART initiation. Elul and colleagues used data from 656 ICAP-sponsored treatment sites in sub-Saharan Africa to determine whether the proportion of nonretention in care at 6 and 12 months was changing over time and what factors were associated with nonretention trends (Abstract 86). The study aggregated program data from more than 316,762 patients older than 6 years in 5690 successive cohorts initiating ART quarterly from 2005 to 2010 were analyzed. Poisson regression with generalized estimating equations was used to show that there was no statistically significant change in nonretention at 6 or 12 months after ART initiation, with 27% to 29% of patients not being retained in care at 12 months throughout the observation period. When the investigators stratified nonretention at 12 months by country, they found statistically significant heterogeneity, with the lowest nonretention rates in Rwanda and the highest nonretention rates in Lesotho and Cote d'Ivoire. Nonretention was also examined by clinic maturity, and no statistically significant change in nonretention was found from 1 year to 5 years of clinic operation. Urban location, smaller clinic sizes, and lower CD4+ cell testing coverage at ART initiation were factors statistically significantly associated with nonretention at 12 months. One limitation to this analysis was that undocumented transfers of care were counted as nonretention events, but the authors noted that the lack of deterioration in retention rates over time during scale-up was encouraging.

Lamb and colleagues also used data from ICAP-sponsored sites to examine nonretention of loss to follow-up among 51,880 HIV-infected individuals 15 to 24 years of age (Abstract 1149). Loss to follow-up was defined as not returning to clinic for 6 months for those receiving ART and 12 months for those not receiving ART. Compared with adults from 25 to 54 years of age, HIV-infected youth had a relative risk of loss to follow-up of 1.30 (95% CI, 1.27-1.34) prior to ART initiation, and 1.64 (95% CI, 1.55-1.73) after ART initiation, after adjustment for country, facility type, location, point of HIV care entry, year of ART initiation, sex, pregnancy status, TB status, and CD4+ cell count at ART initiation. Risk factors for loss to follow-up before ART initiation included TB treatment (which was protective), earlier enrollment, and higher enrollment CD4+ cell count. Risk for loss to follow-up after ART initiation was associated with male sex, pregnancy, and CD4+ count at initiation either less than 100 cells/μL or 350 cells/μL or above. Youth between the ages of 15 years and 24 years appeared to be particularly at risk for loss to follow-up before and after ART initiation.

Finally, 2 investigator groups presented data on the efficacy of community-based adherence support, one in the form of one-on-one home visits (Abstract 1146) and the second using nonclinical adherence clubs run by health workers (Abstract 1150). Both studies showed increased rates of retention in care in the adherence support groups.

ART Outcomes in Children in RLS

The consequences of early versus deferred ART in children were examined in 3 presentations. Ananworanich and colleagues (Abstract 24) conducted a substudy on neurodevelopmental outcomes within PREDICT (Prospective Randomized Evaluation of DNA Screening in a Clinical Trial), which randomized 299 HIV-infected Thai and Cambodian children from 1 to 12 years of age with CD4+ percentage from 15% to 24% to either immediate ART or deferral of treatment until CD4+ percentage was less than 15%. The primary results of this study were presented by Puthanakit and colleagues at the 2011 International AIDS Society (IAS) conference; investigators

Table 2. Selected Presentations Regarding Linkage to Care and Retention in Care in Resource-Limited Settings

Study Description	Cohort Description	Key Findings
Abstract 1143 Meta-analysis of linkage to care from diagnosis to ART initiation	Sample: data published from 29 studies on 148,912 ART-naive patients Examined completion of 4 steps: 1) HIV testing, 2) CD4+ cell testing and ART eligibility assessment, 3)ART eligibility, and 4) ART initiation	• Of ART-eligible patients, 62% (95% CI, 55.2-70.7) initiated ART • Mortality among those patients eligible for ART who did not initiate was 10.8% (95% CI, 4.6-17.0) • Loss to follow-up occurred for: - 24.6% of those eligible for ART (95% CI, 10.8-30.3) - 54.2% of those not eligible for ART (95% CI, 42.8-72.0) *Conclusion:* Mortality and loss to follow-up prior to ART initiation are barriers to ART coverage in RLS, particularly for those who are not eligible for ART at diagnosis.
Abstract 1151 Examining loss to follow-up for those ineligible for ART at diagnosis in Uganda	Sample: 4,318 Ugandan patients entering care with CD4+ count >350 cells/μL Tracked a random sample of those who were lost to follow-up to determine status and clinical care information	• Over 2.5 years of follow-up, 1101 (35%) of patients with initial CD4+ count >350 cells/μL initiated ART • Cumulative mortality at 2.5 years for those lost to follow-up was 13.6% (95% CI, 5.5-31.6) • 56% of those lost to follow-up were found to be alive and in care at a new site *Conclusion:* More than half of those lost to follow-up were in care at a new clinical site, but those lost to follow-up had high mortality rates.
Abstract 86 Assessing changes over time in the proportion of nonretention in care at 6 and 12 months after ART initiation	Sample: Aggregate ICAP program data from over 316,762 patients >6 years of age in 5,690 successive cohorts initiating ART quarterly from 2005 to 2010 Poisson regression with generalized estimating equations used to assess changes in nonretention at 6 and 12 months	• No significant change in nonretention over time at 6 or 12 months • 27%-29% of patients were not retained at 12 months throughout the observation period • Urban location, smaller clinic sizes, and lower CD4+ cell testing coverage at ART initiation were associated with nonretention at 12 months *Conclusion:* Lack of deterioration in retention rates over time in a setting of rapid scale-up of treatment capacity across various sites is encouraging.
Abstract 1149 Determining loss to follow-up in 15-to 24-year-olds in RLS	Sample: 51,880 HIV+ individuals 15 to 24 years of age receiving care at an ICAP-sponsored site Determined predictors of loss to follow-up, defined as not returning to clinic for 6 months if receiving ART and 12 months if not	• HIV+ youth had a relative risk of loss to follow-up compared with adults 20-54 years of age: - Prior to ART initiation: 1.30 (95% CI, 1.27-1.34); associated with: tuberculosis treatment, which was protective; earlier enrollment; and higher enrollment CD4+ count - After ART initiation: 1.64 (95% CI, 1.55-1.73); associated with male sex, pregnancy, and CD4+ count at initiation either <100 or ≥350 cells/μL *Conclusion:* Youth aged 15 to 24 years appear to be particularly at risk for loss to follow-up both before and after ART initiation

ART indicates antiretroviral therapy; CI, confidence interval; ICAP, International Center for AIDS Care and Treatment Programs; HIV+, HIV seropositive; RLS, resource-limited settings

found AIDS-free survival rates of 98% in both arms at 144 weeks.[2] The neurodevelopmental substudy's primary objective was to test the hypothesis that neurodevelopmental outcomes at week 144 would be superior in the immediate ART group compared with the deferred ART group. Investigators enrolled 284 children from PREDICT using criteria described above. Control groups included 155 HIV-uninfected exposed children and 164 HIV-uninfected unexposed children. The researchers found that intelligence test scores did not differ between immediate and deferred ART groups, but both were statistically significantly lower than the HIV-uninfected control groups. Statistically significantly poorer outcomes were also seen in fine motor skills, memory scores, and behavioral scores for HIV-infected children than in HIV-uninfected controls. The authors compared their results to the CHER (Children with HIV Early Antiretroviral Therapy) study, which found that early ART was associated with improved neurodevelopmental outcomes for infants when it was initiated prior to 12 weeks of age. This suggests that a crucial window for early ART impact on neurocognitive development may have been missed in children who did not initiate ART until at least 12 months of age.

Wamalwa and colleagues presented

a different treatment strategy for infants, treatment interruption after early ART initiation. This approach was tested in Kenya in the OPHO3 (Optimizing Pediatric HIV-1 Therapy 03) Study (Abstract 27). The study included 42 infants who initiated ART aged 13 months or younger and who were on ART for more than 24 months, had CD4+ percentage of 25% or higher, and had normalized their growth. Participants were randomized in a nonblinded fashion to continued versus interrupted ART and monitored over 18 months for the endpoints of weight-for-height *z*-scores and serious adverse events. Treatment was reinitiated in the interruption arm if CD4+ percentage dropped below 25%, or participants experienced poor growth or a new opportunistic infection. There were no statistically significant differences between the 2 arms. Of the 21 children in the treatment interruption arm, 18 (86%) reinitiated ART; 14 of these reinitiated at 3 months because CD4+ percentage fell below 25%. The study's DSMB recommended that randomization be discontinued because too few participants remained in treatment interruption beyond 3 months, rather than for safety concerns. There were no statistically significant differences in growth or serious adverse events (SAEs) between the treatment interruption and continuation arms, but children who interrupted treatment had statistically significantly lower CD4+ percentages 15 months after randomization. Reinitiation of ART in the interruption group was associated with lower CD4+ percentage at randomization, with a median CD4+ percentage of 33% in the group reinitiating at or before 3 months, compared with a median CD4+ percentage of 39% in the group reinitiating at or after 6 months (P = .04). The investigators concluded that treatment interruption was not feasible for this patient population.

Cotton and colleagues presented the final data from 6 years of follow-up in the CHER trial (Abstract 28LB). The trial tested the utility of early, limited ART initiated at or before 12 weeks of age, followed by treatment interruption. The study randomized 375 children diagnosed with HIV infection before 12 weeks of age who had a CD4+ percentage of 25% or higher to 1 of 3 arms: (1) deferred ART; (2) early ART to 40 weeks followed by treatment interruption; or (3) early ART to 96 weeks. ART was (re)initiated in all 3 arms when CD4+ percentage dropped below 20% or participants experienced a clinical event. The primary study endpoint was time to failure of initial ART (lopinavir/r plus zidovudine and lamivudine); failure was defined as CDC category B or C clinical events, CD4+ percentage below 20%, or regimen-limiting toxicity. Within the first year of the study, a DSMB review found that the deferred ART arm had 16% mortality, and the other 2 arms had 4% in each. The deferred ART arm (arm 1) was stopped, 34 additional infants were enrolled in the study to maintain power, and early ART became standard of care for infants.[3] Baseline characteristics were not statistically significantly different among the 3 study arms, and 91% of participants completed the study. The HR for death or failure of the initial ART for the interruption after 96 weeks arm (arm 3) was 0.58 (95% CI, 0.35-0.96) compared with the ART deferred arm (arm 1), but was not statistically significantly different for the ART interruption after 40 weeks arm (arm 2). Comparing the 40- and 96-week arms (arms 2 and 3), there was no statistically significant difference in achievement of the primary endpoint. Only 7 participants switched to second-line ART in any of the arms. The authors concluded that early treatment initiation and continuation for 96 weeks versus 40 weeks prior to interruption resulted in similar ART exposure and longer subsequent treatment interruption, with no statistically significant differences seen in treatment failure or clinical events. Resistance data and other analyses from the 6-year follow-up data are forthcoming.

Lindsey and colleagues (Abstract 25) presented data from the P1060 trial, which compared the safety and efficacy of lopinavir/r-based regimens with nevirapine-based regimens for children 6 months to 3 years of age, 164 of whom had been exposed to sdNVP for PMTCT (exposed group) and 228 of whom had not been exposed to nevirapine (unexposed group). The primary outcome was permanent discontinuation of nevirapine or lopinavir/r or failure to achieve virologic control after 24 weeks on ART. The exposed group was statistically significantly younger, more likely to have HIV subtype C, and less likely to be breastfed than the unexposed group. The exposed group also had statistically significantly higher median CD4+ percentage, plasma HIV-1 RNA levels, and WHO weight *z*-score at baseline than the unexposed group. The DSMB for the study recommended early closure of accrual to the nevirapine-exposed group because the lopinavir/r arm showed superiority to the nevirapine arm for the primary endpoint. Cox proportional hazard models showed no statistically significant interaction between prior exposure to nevirapine and treatment effect. In the adjusted model, no statistically significant difference was seen between treatment response in the sdNVP-exposed and unexposed groups, but lower CD4+ percentage and higher plasma HIV-1 RNA levels predicted shorter time to the primary outcome. Interestingly, children in the nevirapine-based treatment arm had a statistically significantly greater increase in CD4+ percentage and weight-for-height *z*-score than those treated with lopinavir/r-based regimens. The dominant limitation of the analysis was that exposure to sdNVP was not randomized and the 2 cohorts had significant differences at entry. The investigators concluded that these data do not support the use of sdNVP as a reason to avoid nevirapine-based regimens for children between 6 months and 3 years of age, and speculated that the high HIV-1 plasma RNA levels at ART start and nevirapine initiation at half-dose may have led to the poor performance of nevirapine-based regimens in this investigation.

Prendergast placed the treatment strategy data reviewed above in context in a symposium on early ART initiation strategies in infants (Abstract

113). He explored data regarding 3 major strategic questions: (1) when to start ART, (2) what regimen to start, and (3) whether to switch or stop ART. A webcast of this symposium, which also discussed results from published trials relevant to these strategic questions, is available on the CROI web site (http://www.retroconference.org).

ART for Pregnant and Postpartum Women

An interesting addition to this year's CROI was a focus on the complexities of implementing ART in pregnant women in RLS and in non-RLS, highlighted in a themed discussion (Abstracts 1015-1019) and several other presentations (Abstracts 1005, 1006, 1020-1023). Anderson began the themed discussion with an emphasis on the current convergence between guidelines for ART in pregnancy in RLS and resource-rich settings, with the 2010 WHO guidelines for RLS recommending lifelong ART for those with CD4+ counts less than 350 cells/μL and encouraging triple ART prophylaxis for PMTCT if possible. The remaining discrepancy in RLS is predominantly because of the lack of virologic monitoring in such settings and the 2 options for discontinuation of ART in the setting of PMTCT: option A, 1 week postpartum, or option B, at delivery if formula feeding or 1 week after completion of breastfeeding. Recently, an "option B+" of lifelong ART for pregnant women regardless of disease status has been proposed, but concerns remain regarding the feasibility of ensuring lifelong adherence and retention in care, as well as the potential for toxicity or adverse pregnancy outcomes.[4] Further data on option B+ will be discussed in the PMTCT section in this review.

Fowler and colleagues explored a similar question in HIV-infected women in sub-Saharan Africa enrolled in the HPTN (HIV Prevention Trials Network) 046 study by examining disease progression in the first 12 months postpartum in women not meeting regional guidelines for ART initiation (Abstract 1015). Of 2025 HIV-infected women, 71% had a CD4+ count 350 cells/μL or higher at delivery. By 12 months postpartum, 26 (2%) of 1154 women with CD4+ counts 350 cells/μL or higher at delivery had dropped to CD4+ below 200 cells/μL. Of the 350 women with baseline CD4+ counts from 400 cells/μL to 549 cells/μL, 37% had CD4+ counts below 350 cells/μL at 12 months postpartum. Only 4.3% of all women progressed to AIDS based on immunologic or clinical criteria during the observation period. The authors concluded that, although progression to AIDS was relatively uncommon, the dramatic decreases in CD4+ cell counts over the 12 postpartum months could support an option B+ of initiating lifelong therapy for HIV-infected women during their first pregnancy.

Data on the difficulties of adherence during continuous ART in pregnancy and postpartum in RLS was presented by Kreitchmann and colleagues (Abstract 1016). The LILAC (Longitudinal Study in Latin American Countries) is a prospective cohort of HIV-infected women and their infants at 10 sites in Brazil, 1 in Argentina, and 2 in Peru. The study observes women from 22 weeks of pregnancy to 2.5 years after delivery and examines self-reported adherence to ART by 3-day recall. Of this cohort, 53% were using ART for PMTCT alone, and 47% met criteria for treatment. The study found a statistically significant decline in adherence rates from pre-delivery (mean percent adherence, 96.2%) to 6 months postpartum (mean percent adherence, 90.7%; $P < .005$), but no difference in adherence between those on ART for prophylaxis and those on ART for treatment. Multivariate models were developed to predict nonadherence at 3 time points: predelivery, 6 to 12 weeks postpartum, and 6 months postpartum. The final adjusted models showed that nonadherence was statistically significantly associated with current tobacco use predelivery (aOR, 2.9; 95% CI, 1.46-6.14), older age 6 to 12 weeks postpartum (aOR, 1.06/year; 95% CI, 1.00-1.12), and current alcohol use 6 months postpartum (aOR, 3.04; 95% CI, 1.34-6.90). The researchers concluded that adherence support is needed throughout the entire postpartum period, particularly in women using alcohol or tobacco.

Strategies for Laboratory Monitoring in RLS

Saag and colleagues presented data from a cluster randomized trial of HIV-infected individuals initiating ART in Zambia (Abstract 87). The trial compared routine plasma HIV-1 RNA testing (every 3 months for the first 6 months and every 6 months thereafter) with discretionary testing (available for anyone meeting criteria for clinical or immunologic failure at each visit and standard of care for the country). The primary endpoint of the study was all-cause mortality, with secondary endpoints of switch to second-line regimen and genotypic testing for resistance. The investigators highlighted that the plasma HIV-1 RNA level data from the discretionary testing arm was only 65% complete at the time of the presentation. The study found that overall mortality and virologic suppression rates were not statistically significantly different between the 2 arms. As anticipated, the switch to second-line regimen was higher (3.1 switches per 100 patient/years; HR for switch, 1.94; 95% CI, 1.22-3.10) in the routine monitoring arm than in the discretionary testing arm (1.6 per 100 patient/years) because the latter used changes in a patient's clinical or immunologic condition to trigger consideration of switch. Although the time to virologic failure was similar in both arms, the median time to switch was 168 days in the routine testing arm and 560 days in the discretionary testing arm ($P < .0001$). Limitations to this investigation included that it was underpowered to detect a mortality difference and unable to fully assess reasons for switch to second-line regimens. Additionally, constraints on formulary options for second- and third-line ART in Zambia may have influenced the willingness of providers to change regimens. The researchers concluded that routine virologic monitoring led to higher rates of change to second-line

regimens and less time on failing ART, and highlighted that it was feasible to successfully embed this operational research project into routine care at PEPFAR clinics. HIV genotype analyses, cost effectiveness analyses, and detailed examinations of adherence interventions are forthcoming.

Egger and colleagues addressed the problem of lack of virologic monitoring in RLS by using data from the IeDEA cohort to develop a chart of risk for virologic failure based on CD4+ cell count over time (Abstract 634). The researchers incorporated data from all IeDEA cohorts in South Africa where routine virologic monitoring was available, and included patients with baseline CD4+ cell count, age, sex, and more than 1 plasma HIV-1 RNA level and CD4+ cell count cell count at least 6 months after ART initiation. CD4+ cell count trajectories were analyzed in patients with virologic suppression using mixed models and fractional polynomials, stratified by pre-ART CD4+ cell count. The converse analysis, predicting virologic failure for the same CD4+ categories, was conducted using Poisson models. These data were combined to create overlapping charts of CD4+ cell count trajectories over time and risk of virologic failure, with separate charts for men and women in each of the 4 baseline CD4+ cell count strata. These risk charts were then validated with data from the TREAT Asia (Therapeutics Research, Education, and AIDS Training in Asia) HIV Observational Database (TAHOD). CD4+ cell count trajectories with suppressed viral replication were somewhat more favorable in women than in men, and the charts were most accurate in predicting virologic failure in patients initiating ART at lower CD4+ cell counts. The investigators suggested that these risk charts could be used to support decision-making with respect to switching to second-line therapy in programs without access to plasma HIV-1 RNA level monitoring.

A highlight of the laboratory monitoring in RLS discussion was Sherman's presentation on the challenges of HIV diagnosis in infants in RLS (Abstract 112). In 2004, when ART became available for the first time for infants in RLS, the WHO guidelines recommended a single PCR test at 6 weeks of age, with the timepoint chosen because it coincided with scheduled immunization visits. From 2004 to 2010, there was an impressive scale-up of PCR diagnostic testing in South Africa. However, access to this technology remains limited, not all HIV-exposed infants are tested, and some infants who test positive for early infection with HIV are not accessing ART. Despite these caveats, the increased availability of PCR testing for infant diagnosis has enabled South Africa to use PCR test results to monitor the success of PMTCT programs by region. Using estimated numbers of infants who should be tested by area, early infant diagnosis coverage and early transmission rates among those infants who were tested can be determined. Sherman cited this as a success in allowing a transition from national to local control and accountability for PMTCT efforts.

Current testing available for early infant diagnosis is increasingly automated, leading to decreased technologist time, increased sensitivity, and improved specificity, all of which may enable earlier diagnosis, even in the setting of ART for PMTCT. Point-of-care testing platforms for early infant diagnosis are also being evaluated, but none have been launched. Sherman discussed the underutilization of rapid HIV antibody detection assays, which can identify HIV-exposed infants and can exclude infection in older HIV-exposed infants. For children younger than 18 months, rapid test performance is less uniform than in adults and tests must be chosen based on specific clinical application, whether that be testing for exposure or seroreversion because of the passive transfer of maternal antibody to the infant.

Sherman presented unpublished data from her own laboratory of infant diagnosis algorithm testing in 838 mother/infant pairs using 2 plasma HIV-1 RNA measurement assays, 1 at birth and the other 6 weeks later. Of those, tests showed 43 infants were infected: 29 in utero (positive PCR for HIV infection at birth), 9 intrapartum (negative PCR at birth and positive PCR at 6 weeks), and 5 postpartum (positive HIV test after 6 months of age). At the 6-week PCR test for this same cohort, 18 of the intrauterine infections and 8 intrapartum infections were detected. Thus, 76% of all early infections within the cohort would have been detected at birth. Using the standard of care 6-week test meant that 11 (32%) of the infants diagnosed retrospectively with early HIV infection were lost to follow-up. Sherman also discussed the mounting evidence that prolonged PMTCT prophylaxis may delay infant diagnosis, including her own laboratory's data, which showed that a single dose of nevirapine and zidovudine led to 4 of 18 HIV-infected infants having negative plasma HIV-1 RNA levels. Sherman stated that research priorities should focus on data collection directed at a revision to the testing algorithm, perhaps with at-birth testing using a point-of-care test.

PMTCT

Two oral presentations on PMTCT efforts placed particular emphasis on the advent of the 2010 WHO Guidelines and the Joint United Nations Programme on HIV/AIDS (UNAIDS) Global Plan to reduce mother-to-child transmission (MTCT) to less than 5% of the current rate by 2015.

As part of the CROI Workshops for New Investigators and Trainees, Flynn reviewed the successes in, barriers to, and consequences of PMTCT (Abstract 5). She reflected on the evolution of the understanding of risk of HIV transmission to infants in utero, during labor and delivery, and during the breastfeeding period, and she reviewed how such understanding has led to effective new PMTCT strategies. She highlighted exciting innovations in the field and areas of growth such as promising immune therapies, enhanced testing initiatives, programs to optimize engagement in care, outcomes data on children with HIV or ART exposure, and novel point-of-care technology.

Mbori-Ngacha echoed many of these themes in her plenary session that opened the third day of the conference,

dedicated to the elimination of MTCT of HIV (Abstract 75). She provided an overview of PMTCT strategies with emphasis on the scope of MTCT, scientific advances, and opportunities for global elimination, describing the Global Plan for the elimination of MTCT. Staggering statistics from 2010 regarding ongoing MTCT of HIV were cited, with 390,000 children infected with HIV globally and 92% of these infections having occurred in sub-Saharan Africa. The Global Plan, which focuses on 22 countries (located primarily in sub-Saharan Africa) that bear 91% of the global burden of MTCT of HIV, has 2 main targets: to reduce MTCT to less than 5% in HIV-infected breastfeeding mothers and to reduce the number of AIDS-related maternal deaths by 50% by 2015. UNAIDS is proposing a multi-pronged approach for PMTCT in RLS, including prevention of HIV in young women, prevention of unintended pregnancies in HIV-infected women, prevention of transmission from HIV-infected women their infants, and support for infected mothers and their families.

Mbori-Ngacha reviewed the benefits and drawbacks of options for PMTCT at higher CD4+ cell counts. Although option A (maternal zidovudine and 6 weeks of infant prophylaxis with nevirapine or zidovudine) is associated with lower rates of infant adverse events, costs less, and requires less monitoring, this option requires a known CD4+ cell count, may be more complex to deliver, and is associated with a substantial risk of NNRTI resistance. On the other hand, option B (triple drug ART prophylaxis) offers uniformity in treatment for pregnant women, prevents transmission to uninfected partners, and may provide additional health benefits to the mother during pregnancy, but there are concerns about increased cost, more necessary safety monitoring, and more adverse effect than option A, as well as the potential for drug resistance.

Application of PMTCT Guidelines

Rundare and colleagues presented data on the effect of the uptake of the South African National Department of Health PMTCT Guidelines in South Africa (Abstract 1003). Investigators compared outcomes in women observed between June 2009 and June 2011. A cohort of 1995 mother-infant pairs was included, with 1147 mothers attending prior to these guidelines being released and 848 attending after the guidelines' release. Transmission rate prior to the guideline change was 3.4% (95% CI, 2.6%-5.0%) and dropped to 1.5% (95% CI, 0.9%-2.9%; $P = .2$) after the implementation of the guidelines. The authors concluded that the South African guidelines were effective and associated with decreased MTCT of HIV at 6 weeks.

French and colleagues reported on rates of repeat pregnancies among HIV-infected women, stratified by immunologic status and virologic outcomes for women not on ART at conception (Abstract 1019). Based on analysis from the United Kingdom/Ireland National Study of HIV in Pregnancy and Childhood, 1177 second pregnancies were identified from 2000 to 2010 in women not on ART at conception. At the time of the second pregnancy, the median CD4+ count was 392 cells/μL, with 40% of women having CD4+ counts less than 350 cells/μL and 24% with a CD4+ count less than 200 cells/μL. Investigators found that two-fifths of women had an immunologic indication for ART at the start of their second pregnancy. Nearly half of these women had had CD4+ counts of 350 cells/μL or higher at their first pregnancy. There were high rates of antenatal ART (97%); however, most started during or after the second trimester and 27% of women not on ART at conception had detectable plasma HIV RNA levels at delivery. The risk of a detectable plasma HIV RNA levels at delivery was associated with timing of ART initiation. The authors urged consideration of lifelong ART at first pregnancy for all women (option B+).

Availability of PMTCT Services

The effort to reduce MTCT rates to less than 5% of the current number by 2015 is hindered by many factors: inadequate coverage of PTMCT treatment in many settings, cost considerations, and political commitment.

Chi presented on field effectiveness of universal ART for PMTCT in rural Zambia (Abstract 23LB). In a prospective cohort study, 9 rural facilities in Zambia were analyzed. Four sites offered universal ART regardless of CD4+ cell count, and 5 sites provided standard-of-care treatment: short-course zidovudine starting at 28 weeks of pregnancy and through the intrapartum period and sdNVP intrapartum with a zidovudine/lamivudine tail. Infants received sdNVP followed by a week of zidovudine. From April 2009 to December 2010, 284 women were enrolled; 143 received universal ART and 141 received short-course therapy. At 12-month follow-up, rates of HIV infection or death were higher in the short-course therapy arm (19.8% compared with 5.8% in the universal ART arm; RR, 3.44; 95% CI, 1.56-7.59). The rate of loss to follow-up was higher in the universal ART arm. The authors offered this as evidence in support of 2010 WHO guidelines recommending option B over option A and urged tailored interventions to improve adherence and retention in care for pregnant and postpartum women.

Assessments of PMTCT program outcomes in the United States were presented by Taylor and colleagues (Abstract 1000). Using published national estimates of rates of perinatal ART exposure, cases prevented, and infected infants in the era of ART prophylaxis, the authors reported 124,280 HIV-exposed infants, 25,659 cases of MTCT prevented, and 102,543 infants exposed to ART from 1994 to 2010. Nationally, there were 183 and 151 cases of MTCT in 2006 and 2009, respectively. The authors pointed out that the incidence of perinatal HIV infection continues to exceed the goal of 1 infection per 100,000 live births.

Diagnostics and MTCT

Given that women with low CD4+ cell counts are more likely to transmit HIV to their infants perinatally and have high mortality rates, identification and treatment of pregnant women with

low CD4+ counts is a top priority. Delays in CD4+ cell count testing can hinder care. Furthermore, awareness of a low CD4+ cell count can motivate women to engage more fully in care. Mnyani and colleagues presented data on the role of point-of-care CD4+ testing in a PMTCT setting (Abstract 1007). The investigators compared the performance of the Pima™ analyzer, a point-of-care CD4+ count machine, with laboratory-based CD4+ cell testing in a high-volume PMTCT clinic in South Africa. Parallel CD4+ cell testing was performed on 232 consecutive HIV-infected pregnant women. The median Pima™ CD4+ count was 350 cells/μL (IQR, 231-488) and for the laboratory-based assay the median count was 362 cells/μL (IQR, 246-522). The mean difference in laboratory minus Pima™ CD4+ count was 13.9 cells/μL (95% CI, 5.1-22.7) and no difference was found in the level of agreement related to participant age or time of gestation.

Acute HIV Infection in Pregnancy and Postpartum

Several studies have suggested an increased risk of HIV transmission to women during pregnancy, higher rates of MTCT for women with primary HIV during the perinatal period than those with chronic HIV, and high rates of unintended pregnancies among HIV-infected women in RLS. Marum and colleagues presented modeling data from Zambia suggesting that incident acute infection during pregnancy and lactation among women testing HIV-seronegative early on in pregnancy results in more infant infections in Zambia than regimen failure and lack of coverage combined, and urged joint couples testing and treatment of HIV-serodiscordant couples to advance prevention of MTCT (Abstract 1001).

Family Planning

Availability of effective contraception for HIV-infected women was an important theme at the conference. Sutton and colleagues reported on unplanned pregnancies among women in care for HIV infection and followed up as part of the MMP in sites in the United States and Puerto Rico (Abstract 1044). Of 1407 women in the study, 370 (26.3%) reported 1 or more pregnancy after HIV diagnosis, and 316 of these pregnancies (85.6%) were unplanned. The authors called for strengthened contraception awareness and access for women. Heffron and colleagues reported no association between HIV disease progression and hormonal contraceptive use in a prospective cohort of 2236 HIV-infected women in Africa ($P = .03$) (Abstract 21).

Novel Immune Methods for Treating Women During Pregnancy

Although ART has been the mainstay of PMTCT during all periods of potential perinatal transmission, novel methods that incorporate vaccines or neutralizing antibodies may be part of future regimens. Session 183 was dedicated to research on the role of neutralizing antibodies during MTCT. Mabuka and colleagues found no evidence for an association between HIV neutralizing antibody levels in breast milk and infant HIV infection in a small study of 10 women who transmitted to their children during breastfeeding compared with 7 women who did not (Abstract 1035). Omenda and colleagues found that maternal neutralizing antibodies correlated with infant passive antibodies but not with the risk of MTCT in a study of 22 transmitting and 51 nontransmitting mother/infant pairs (Abstract 1036). These early studies, among others, provide contextual background for the potential use of broadly cross-active neutralizing antibodies as passive therapy to reduce MTCT rate.

Breastfeeding

Although avoidance of breastfeeding where safe formula is attainable may reduce MTCT, in some RLS this benefit has been neutralized by higher infant mortality rates as the result of the absence of nutritional and immunologic benefits provided by breast milk.[5] Such findings have resulted in a multitude of studies to identify methods to lower the risk of transmission during the breastfeeding period, including studies aimed at understanding risks associated with patterns of breastfeeding and weaning and options for either maternal or infant ART to prevent transmission. Postnatal MTCT rates are comparably low across studies that have included maternal triple ART during the breastfeeding period. Additionally, there have been important studies showing that infant prophylaxis is also effective during the breastfeeding period. The BAN (Breastfeeding, Antiretrovirals and Nutrition) Study of infant nevirapine or maternal triple ART in nursing mothers found that both active strategies statistically significantly reduced transmission compared with no intervention. However, due to inadequate statistical power, it remains unclear which active method is more effective.

Adherence and Retention in Care for PMTCT

The ambitious goal of a 90% reduction in MTCT will require careful attention to ART adherence and retention in care.

Myer and colleagues presented 12-month outcome data on loss to follow-up and mortality among pregnant and nonpregnant women initiating ART from IeDEA Southern Africa (Abstract 22). The analysis included 29,653 treatment-naive, HIV-infected women aged 16 years to 56 years with CD4+ counts below 200 cells/μL who initiated ART from 2002 to 2009. Of these, 1956 were pregnant at the time of ART initiation. Pregnant women were younger at the time of ART initiation (29 years vs 33 years old in nonpregnant women) and had higher CD4+ counts (median, CD4+ 145 cells/μL, compared with 96 cells/μL in non-pregnant women). After 12 months on ART, 3% of women who had been pregnant at the time of ART initiation had died, compared with 9% of women who were not pregnant at the time of ART initiation. Loss to follow-up was higher in those who had started on ART when pregnant, with 19% of pregnant women lost to follow-up, compared with 11% of nonpregnant

women lost to follow-up. The HR for loss to follow-up remained elevated even with adjustment for pregnancy, age, baseline CD4+ cell count, year of ART initiation, and participating site (adjusted HR, 1.7; 95% CI, 1.49-1.94). The authors also cited an urgent need for interventions to promote retention of women initiating ART in pregnancy to achieve optimal maternal and child health outcomes, especially in light of aggressive plans to scale up PMTCT programs.

Rawizza and colleagues evaluated rates of loss to follow-up within the PMTCT Care Cascade in a large ART program in Nigeria (Abstract 1017). A retrospective analysis of 33 clinical PMTCT sites was performed between 2004 and 2011. Among 19,303 women who entered care during the antenatal period, 10,078 (52%) completed the entire cascade of services (antenatal care, delivery, and infant follow-up). Among 22,180 women entering care at any point along the PMTCT cascade, only 2933 (13%) of their infants were retained in follow-up care through 18 months. The greatest loss to follow-up occurred after delivery and before infant follow-up with unknown outcomes for infants of 45% of mothers who had received any antenatal care. The authors urged strategies to improve retention in care, especially during the transition from pregnancy to pediatric care.

Outcomes in Children Exposed to HIV but Uninfected

Although outcomes of HIV infection in children have improved dramatically with combination ART, exposure to HIV or ART is also associated with toxic effects, including premature birth, anemia, and impaired growth. Session 34 was dedicated to recognition of the risks of exposure to HIV and ART in infants and children (Abstracts 110-113). Blanche focused on the consequences of zidovudine exposure for PMTCT, acknowledging the extraordinary efficacy of ART for PMTCT; he also described morbidity related to in utero exposure to ART, including premature birth and a spectrum of findings around the effects of zidovudine (Abstract 110). He presented unpublished data on the possible genotoxic effect of zidovudine on hematopoietic stem cells from a comparison of the genotypic profiles of stem cells derived from cord blood of HIV-infected versus -uninfected mothers. There were statistically significant differences between HIV-infected and -uninfected subjects' cord blood stem cells in upregulation and downregulation of various genes involved in cell cycle and DNA repair. There were higher levels of aneuploid cells in HIV-infected mothers as well. The author urged ongoing efforts to identify the safest PMTCT approaches through observational cohorts, randomized trials, and new biologic tools.

Filteau presented an update on the current understanding of the vulnerabilities of HIV-exposed, -uninfected children (Abstract 111), acknowledging several health conditions seen in HIV-uninfected children exposed to HIV or ART. Data have revealed high rates of mortality and hospitalization and poor growth in this group, and raised questions about possible cognitive problems and risks of chronic diseases. The author suggested that HIV exposure, maternal HIV infection and disease severity, ART exposure, increased infections, and decreased breast feeding are responsible for these differences in risks and urged more research to mitigate these differences and maximize community interventions in support of vulnerable HIV-exposed but -uninfected children.

Warsawski and colleagues presented data on infant mortality among children not infected perinatally with HIV during the potent ART era (Abstract 1032). Investigators analyzed infant mortality rates for uninfected infants born between 1997 and 2009 to HIV-infected women in the ANRS French Perinatal Cohort and found higher rates of infant mortality in premature infants compared with term infants (27.0/1000 live births vs 3.5/1000 live births; $P < .001$). Compared with the general population, premature births were more common among HIV-infected women (14.8% in the HIV-infected women vs 6.3% in general population). The authors concluded that the high premature birth rate was responsible for the higher infant mortality rate in children born to HIV-infected women and questioned whether ART could be playing a role.

Cade and colleagues suggested a possible relationship between in utero exposure to ART and lower diastolic function and left ventricular mass index in HIV-uninfected children (Abstract 1034). Investigators studied echocardiographic and other cardiac parameters in 30 HIV-uninfected children born to HIV-infected women with a history of in utero ART exposure and compared the findings with 30 HIV-uninfected children without exposure to ART or HIV. Left ventricular mass index was statistically significantly lower in the ART-exposed children (61 ± 9 g/m^2 vs 66 ± 12 g/m^2 in the control children; $P < .04$) and early diastolic annular velocity was also lower (14.9 ± 2.2 cm/s vs 16.4 ± 2.5 cm/s, respectively; $P < .02$). The authors suggested that these findings could be residual effects of ART exposure, but maternal HIV infection and in utero HIV exposure may also play a role.

ART Resistance

Resistance in RLS

Lack of HIV RNA level monitoring in RLS has been associated with prolonged initial treatment failure and accumulation of drug resistance mutations. The WHO guidelines recommend NNRTI-based ART for initial therapy and a PI/r-based regimen as second-line therapy. Hamers presented patterns of HIV-1 drug resistance in 2 cohorts followed up at 13 sites in sub-Saharan Africa. The first cohort enrolled ART-naive patients and observed them for evidence of failure of initial ART at 12 months and the second cohort included individuals on second-line ART (Abstract 104). More than 2000 ART-naive patients who started NNRTI-based ART were in care at 12 months, at which point 90% of patients had an HIV RNA level of less than 400 copies/mL. Of 166 patients with HIV RNA levels above 1000

copies/mL whose drug resistance test results were available, 100 carried 1 or more drug resistance mutations and 96% of detected drug resistance mutations were not evident at baseline. The most common mutations identified included M184V or an NNRTI resistance-conferring mutation (such as K103N and Y181C). In the second cohort analysis, 243 patients switched empirically to second-line ART, of whom 104 were predicted to receive a fully active second-line regimen and 128 were predicted to receive only a partially active second-line regimen based on the resistance profile at the switch. Those who received a partially active regimen were more likely to have AIDS at switch and to have had a longer median duration of initial ART. Most second-line regimens included lopinavir/r as the PI/r. However, the nRTI selection varied. At 12 months, 173 of 201 (86%) patients in care on a second-line regimen had an HIV RNA level of less than 400 copies/mL. Interestingly, an adjusted multivariate logistic regression analysis model predicting virologic failure of second-line regimens at 12 months did not find an association between expected activity of the second-line regimen and virologic failure (OR, 0.80; 95% CI, 0.33-1.91; $P = .610$).

Patterns of drug resistance among patients on PEPFAR nRTI/NNRTI regimens in Nigeria were covered in Abstract 738. Ndembi and colleagues presented data on patients who experienced virologic treatment failures on an initial NNRTI-based regimen and received HIV-1 RNA testing in 2010. G and CRF02_AG were the most common subtypes. Of 219 patients with virologic failure, 21% had no evidence of drug resistance; 73.1% harbored nRTI resistance; 68.9% had an M184I/V mutation; 13.2% had at least 3 thymidine analogue nRTI mutations; and 17% had K65R, 6 of whom were on tenofovir. NNRTI resistance was found in 74% of samples. Of these, 36.1% were Y181C mutations and 31.0% were K103N mutations. Two or more etravirine-associated mutations were seen in 53% of patients and 2.7% of patients had major PI mutations.[6] The authors recommended genotypic monitoring as part of routine care.

Estimated prevalence of genotypic drug resistance in ART-naive persons in sub-Saharan Africa and Southeast Asia was presented in Abstract 739. Rhee and colleagues analyzed epidemiologic and sequence data from studies of targeted ART-naive populations of at least 25 people in sub-Saharan Africa and Southeast Asia. Drug resistance mutation rates were calculated and compared. In 72 sub-Saharan Africa studies, the median drug resistance mutation prevalence was 3.3% (IQR, 1.6-5.7). In 31 Southeast Asia studies, the median drug resistance mutation prevalence was 2.4% (IQR, 1.3-6.1). Of the combined Sub-Saharan Africa and Southeast Asia populations (representing 8793 persons from 103 studies), 15 drug resistance mutations were identified in at least 0.1% of the population. These 15 mutations accounted for 67% of all drug resistance mutations, which included 8 nRTI resistance mutations (M41L, M184V, K219Q, D67N, T215S, K219N, L210W, V75M); 4 NNRTI resistance mutations (K103N, Y181C, G190A, K101E); and 3 PI resistance mutations (M46L, M46I, L90M). The nRTI resistance mutation V75M and the PI resistance mutation M46I were more common in Southeast Asia, due to increased frequency in HIV subtype CRF01_AE. In both sub-Saharan Africa and Southeast Asia, the prevalence of NNRTI resistance mutations increased over time (OR, 1.003; $P < .001$). In sub-Saharan Africa, but not in Southeast Asia, the prevalence of nRTI resistance mutations increased over time.

Kiertiburanakul and colleagues presented comparisons of major HIV drug resistance mutations in recent and chronic HIV infection among Asian patients (Abstract 740). The investigators included ART-naive patients enrolled in the TREAT Asia studies from 2007 to 2010. There were 458 patients with recent infection and 1340 patients with chronic infection included in the analysis. Patients with recent infection were younger (median age 23 years vs 36 years), more likely to be men (91.9% vs 65.9%), and less likely to report heterosexual HIV exposure (13.1% vs 72.2%) than patients with chronic infection, and also had lower HIV RNA levels (median 4.7 $\log_{10}$ copies/mL vs 5.0 $\log_{10}$ copies/mL) and higher CD4+ count (median 349 cells/μL vs 104 cells/μL). The crude prevalence of patients with at least 1 resistance-associated mutation to any drug class in both cohorts was 4.6%. There was a greater frequency of resistance-associated mutations PIs among those with recent infection than among those with chronic infection (3.9% vs 1.0%, respectively; $P < .001$). In multivariate logistic regression analyses of the chronic infection group, those with heterosexual contact as a risk factor for HIV were less likely to have resistance-associated mutations (OR, 0.34; 95% CI, 0.20-0.59; $P < .001$).

Boltz showed that the risk of virologic failure associated with low-frequency nevirapine-resistant variants of HIV in women initiating nevirapine-containing ART varies depending on the history of exposure to sdNVP in OCTANE/ACTG 5208 (Abstract 105). Previously, investigators reported that nevirapine-resistant variants at frequencies greater than 1% in pretherapy samples were statistically significantly associated with failure of initial ART with nevirapine-based, but not lopinavir/r-based, regimens among women with prior exposure to sdNVP in OCTANE/ACTG 5208 Trial 1. In contrast, OCTANE Trial 2 studied women without prior exposure to sdNVP and found no difference in primary study endpoints (virologic failure or death) with nevirapine-based ART. The authors hypothesized that this was due to the absence of low-frequency nevirapine-resistant variants in women without prior sdNVP exposure. To test this hypothesis, pretherapy samples from both trials were tested for nevirapine-resistant variants by allele-specific PCR (ASP) and the results were related to study endpoints of virologic failure and death. Surprisingly, nevirapine-resistant variants were commonly detected in baseline samples from the non-sdNVP-exposed women in Trial 2 (38 of 211 samples, 18%). Although the frequency of mutation detection was less than in Trial 1 (51 of 114 samples, or 45%; $P < .001$), it was more

frequent than expected. Study endpoints in women without ASP-detected nevirapine resistance had similar study endpoint rates in both trials: 31 of 173 (18%) in Trial 2, versus 9 of 63 (14%) in Trial 1 ($P = .56$). Also surprising was that the nevirapine-resistant variants detected by ASP were not associated with risk of a primary study endpoint in Trial 2 ($P = .88$), whereas in Trial 1 they were associated with increased risk ($P = .001$). The authors hypothesized that this apparent paradox may be explained by the greater size of resistant virus populations after sdNVP exposure, which may increase the likelihood of additional drug resistance associated mutations accumulating on the same viral genome. It could also secondary to the specificity of this assay and the threshold with which it designated nevirapine resistance.

Among HIV-infected infants with a history of nevirapine exposure followed by subsequent treatment with nevirapine-containing ART, low-frequency resistance mutations present at baseline were commonly selected during virologic failure according to Lehman and colleagues (Abstract 721). The authors compared rates of low-frequency mutations by ultra-deep sequencing (UDS) with outcomes in 20 nevirapine-exposed infants. UDS revealed 1 or more resistance-associated mutations in 12 of 20 infants (60%). The risk of virologic failure was increased in infants with baseline mutations (HR, 2.21; 95% CI, 1.41-3.48; $P = .001$). All 7 infants who experienced virologic failure had resistance identified by population sequencing, and of these 7, 6 had multi-class resistance. Mutations present at frequencies of less than 1% did not grow out during virologic failure; however, 3 of 4 mutations present at levels between 3.8% and 50% before ART were detectable at virologic failure with population sequencing. Authors suggested that minority variants present prior to ART in infants with nevirapine exposure may predict virologic failure.

ART Resistance in Children

Session 168 was dedicated to HIV drug resistance and tropism after treatment failure in children (Abstracts 988-991). Westley and colleagues explored the accurate detection of virologic failure and drug resistance in children based on immunologic follow-up without routine HIV RNA monitoring, per the 2010 WHO guidelines (Abstract 988). The investigators studied drug resistance patterns in children under 15 years of age who had been on at least 6 months of initial ART (nevirapine-based in most cases) and compared rates of immunologic failure with virologic and genotypic results. Of 51 children with evidence of virologic failure on initial ART, genotypic analysis revealed drug resistance in 98% of samples. Only 1 case would have been accurately categorized as treatment failure by immunologic criteria. The authors advocated for availability of affordable and routine HIV RNA monitoring for HIV-infected children.

Chohan and colleagues reported rates of the emergence of nevirapine resistance in 22 HIV-1-infected infants initiating nevirapine-based ART in Nairobi, Kenya. All 22 were less than 5 months of age, had not been exposed to nevirapine, and were confirmed to have no preexisting nevirapine resistance mutations (Abstract 989). Resistance emerged in 7 infants after 12 months of nevirapine-based ART (32%) and none of the infants achieved viral suppression. All 7 infants had a nevirapine-associated mutation and an additional M184V nRTI mutation. Based on these high rates of nevirapine resistance, the authors urged consideration of PI/r-based regimens as an alternative to nevirapine.

The InSTI class represents a promising new class of antiretroviral drugs under study for use in children. Nelson and colleagues presented an analysis on the presence of InSTI resistance mutations in InSTI-naive children (Abstract 990). Primers were designed for reverse transcription, nested PCR, and population sequencing using the group M consensus sequence. Primers were validated using adult samples with known mutations. A total of 86 unique samples were sequenced from individual children enrolled in the PACTG (Pediatric AIDS Clinical Trials Group) 390 and IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials) P1066. In all, 76 children had HIV subtype B, 6 had subtype C, and 4 had a circulating recombinant form of HIV-1 (CRF02_AG). Though 3 children had minor resistance mutations, none of the children had any major InSTI resistance mutations. The investigators concluded that baseline InSTI resistance is no more likely in children than adults.

New Drug Resistance Testing Assays

Jabara and colleagues presented a novel technique to accurately resolve low-abundance drug-resistant variants in therapy-naive individuals. Traditional deep sequencing requires a large amount of input material and clinical samples typically possess a limited number of viral templates. PCR is a necessary first step to generate the necessary input material before deep sequencing, and it can introduce a substantial degree of bias. Examples of bias found in standard deep sequencing include increased artifactual diversity, disruption of true linkage, skewed allelic frequencies, failure to control for resampled sequences, and high rates of sequencing errors. In the presented technique, each individual complimentary DNA (cDNA) molecule is tagged with 2 codes: a sequence unique to the sample that serves as a barcode for the sample, and a Primer ID, a string of degenerate nucleotides unique to each cDNA molecule. The Primer ID then serves as a unique tag to track the cDNA origin of all amplified templates. Sequences originating from the same cDNA molecule can be pooled to generate a consensus sequence, which should remove errors present in the individual amplified sequences.[7] The researchers applied this technique to HIV-1 protease and HCV nonstructural protein 3 (NS3) (Abstract 99). In the presented technique, the viral RNA was tagged with the Primer ID during cDNA synthesis, which was followed by the generation of consensus sequences. Examples of use of the Primer ID for deep sequencing of

the HIV-1 protease and the HCV NS3 were presented. The technique demonstrated accurate sampling and deep sequencing of viral populations, detection of resistance mutations with a frequency of less than < 0.5%, and ability to correct for PCR biases, sequencing error, and PCR resampling.

Phylogenetic Modeling and Population Analysis

Several presentations in session 100 were dedicated to phylogenetic and population analysis techniques. Using phylodynamic methods, Volz and colleagues performed an epidemiologic analysis of *pol* sequences that had previously been collected for surveillance of drug resistance in southeastern Michigan (Abstract 534). The authors analyzed 1252 HIV-1 subtype B *pol* sequences collected for drug resistance testing among MSM. The sequences represented 70% of infections diagnosed in southeastern Michigan between 2004 and 2010. Traditional data sources used in tandem with the genetic data included time series of all diagnoses from 1985 to 2010 and demographic covariates for each patient. Phylogenetic analyses showed a high degree of transmission clustering within age (*r*, 16.1%) and race (*r*, 38.2%) categories; early/acute infections were highly clustered within the phylogeny (*r*, 14.2%). The analysis demonstrated an increased incidence of infection among black teenaged MSM since 2007. This increase appears to be driven by transmission within this demographic group rather than spillover from older individuals.

Predictors of Resistance

Zheng and colleagues explored possible associations between pretreatment CD4+ cell count and pretreatment HIV-1 RNA levels and the emergence of drug resistance at virologic failure on efavirenz plus nRTIs (Abstract 705). The analysis included participants in 3 ACTG trials who initiated efavirenz and nRTIs and had genotypic data from baseline and at virologic failure. Drug resistance was defined by new mutations not present at baseline. Rates of drug resistance across CD4+ cell count strata were assessed and multivariable logistic regression models were used to adjust for baseline demographics. There were 196 patients included in the analysis and the median time to study-defined virologic failure was 33 weeks. At virologic failure, 113 patients (58%) had new NNRTI resistance mutations. No statistically significant trend across CD4+ cell count strata in the proportions with new NNRTI mutations was observed (P = .43). Similar results were obtained adjusting for pre-ART HIV-1 RNA (P = .21), prior nonadherence (P = .45), and baseline demographics (P > .10). No statistically significant trend was observed across pre-ART HIV-1 RNA levels strata (P = .29). Analyses of nRTI resistance gave similar results. A multivariable model adjusting for baseline covariates and prior nonadherence showed younger age was associated with new NNRTI resistance (< 30 years vs ≥ 45 years; OR, 4.1; 95% CI, 1.4-12.3, P = .037).

Transmission of Low-Frequency Drug Resistance

Lipscomb and colleagues reported transmission of numerous low-frequency drug–resistant HIV variants detected during acute HIV infection (Abstract 571). The study employed sensitive real-time PCR testing targeted to detect resistance mutations during acute HIV infection in an effort to understand the range of virus expression immediately following transmission. Longitudinal plasma samples were collected from 13 seroconverters every 5 to 7 days and screened for evidence of thymidine analogue nRTI-resistant mutations M41L, K70R, and K65R. This screening was followed by further clonal analysis in samples that screened positive for mutations. Transmitted resistance mutations were found in 3 (23%) of the people with acute infections: 1 with both K65R and K70R mutations, 1 with K65R, and 1 with K70R. In the individual with K65R and K70R mutations, sequencing verified K65R in 16.7% of the clones 5 days prior to seroconversion. The K65R variant coexisted unlinked with 5 distinct thymidine analogue nRTI-resistant variants, clones with M184V/I, and 5 NNRTI-resistant variants. Wild-type virus comprised 38% of the swarm. By 8 days postseroconversion, only 1 mutation was detected, at 2%. Analysis of *env* at 5 days preseroconversion in the dual-mutation infection revealed few clones with 2 or fewer polymorphisms relative to the consensus sequence. No polymorphic clone was represented more than once in the dual infection. In the individual with K65R alone, that mutation was detected at 10 days postseroconversion at 0.4% frequency. A separate clone from that individual 10 days postseroconversion showed a low-frequency variant (1.6%) with 4 didanosine-resistant mutations. In the third individual, virus carrying the K70R mutation at frequencies of 5% to 40% was present only prior to seroconversion. In this sample as in the others, *env* diversity was not proportional to that of RT. The authors pointed out that during transmission the diversity of the RT, including variants with drug resistance mutations, may be more complex than predicted from the *env* sequencing studies to date.

Baseline Resistance

The impact of minor PI mutations on the risk for failure during initial ART was examined by Scherrer and colleagues in an analysis of the SHCS (Swiss HIV Cohort Study) between 1999 and 2010 (Abstract 717). Of 926 patients who started ART with a PI/r-based regimen and 254 who started with an unboosted PI-based regimen, researchers compared outcomes among patients with 0 and 1 or more minor PI mutations. Times to virologic suppression and to virologic failure were similar in both groups. There was no single minor PI mutation that was statistically significantly associated with treatment outcome. This analysis was offered as evidence that the presence of minor PI mutations should not influence PI use.

Baseline ART resistance among treatment-naive patients in Vietnam was analyzed by Nhung and colleagues

(Abstract 718). Among 140 treatment-naive adults beginning ART with an NNRTI-based regimen enrolled between 2008 and 2010 and followed longitudinally, the baseline prevalence of resistance to nRTI, NNRTI, and PI drugs was 3.6%, 5.7%, and 0%, respectively. At 12 months, 27% of patients experienced treatment failure. In the multivariable analysis, resistance mutations were independently associated with immunologic failure (OR, 6.8; 95% CI, 1.2-39), but no correlation with clinical or virologic failure outcomes was seen.

Among HIV-1 subtype C patients in South Africa in whom an initial tenofovir-containing regimen failed, high rates of the K65R mutations at the time of failure were reported by Sunpath and colleagues (Abstract 719). Among 585 patients initiated on an initial tenofovir-containing regimen between 2010 and 2011, virologic failure occurred in 33 patients (5.6%), of whom 18 (54.5%) were found to have the K65R mutation. The authors pointed out that this proportion exceeds reported rates of K65R mutation emergence in similar analyses of subtype B infection, and suggested that genotypic resistance testing be expanded to better understand this phenomenon and shape ART selection in developing countries where non-B subtype HIV is common.

Low-Level Viremia and Virologic Failure

Given the increasing availability of extremely sensitive viral load monitoring assays, clinicians and investigators have sought an understanding of the significance of variations in low-level viremia persisting in patients on ART. Cologni and colleagues explored this issue (Abstract 348). There were 1214 patients with HIV RNA levels less than 50 copies/mL who were prospectively enrolled and serially monitored every 4 months by high-resolution PCR with a lower level of quantification of less than 3 copies/mL. At baseline, HIV RNA level was less than 3 copies/mL in 71.5% of patients and between 3 copies/mL and 50 copies/mL in 28.5% of cases. Over the following 12-month period, 43 patients (3.6%) reached confirmed HIV-1 plasma RNA over 50 copies/mL (virologic failure). The risk of ART failure during the 4-month monitoring period was statistically significantly greater for patients with an HIV RNA level less than 3 copies/mL at 0.4% compared with 3.2% for patients with any value of low-level viremia ($P < .0001$; OR, 7.52; 95% CI, 3.8-15.0). Genotypic analyses revealed that in 13 patients (representing 30.2% of virologic failures), mutations emerged that were able to alter the efficacy of the current ART. NNRTI-based ART was associated with HIV RNA levels less than 3 copies/mL throughout the study period compared with such levels in those receiving a PI/r or a non-boosted PI, with 45.2%, 33.1%, and 29.8% of the groups having HIV RNA levels below 3 copies/mL, respectively ($P < .0001$).

In contrast, Charpentier and colleagues reported an absence of increased risk for virologic failure associated with low-level viremia (Abstract 349). The authors compared rates of virologic failure in 618 patients who maintained HIV RNA levels less than 20 copies/mL and 38 patients with at least 2 HIV RNA levels between 20 copies/mL and 50 copies/mL. The proportion of patients experiencing virologic failure was not statistically significantly different between the 2 groups (4% vs 8%, respectively; $P = .32$). There was also no difference in blips (isolated HIV RNA levels > 50 copies/mL) between the 2 groups (0.09 vs 0.17, respectively; $P = .07$).

Persistent low-level viremia between 50 copies/mL and 500 copies/mL has been associated with virologic failure. However, conventional genotypic analysis may not be routinely performed until HIV RNA levels are as high as 1000 copies/mL. Delaugerre and colleagues reported on the selection of drug resistance mutations in patients with HIV-1 RNA levels less than 500 copies/mL on at least 3 occasions during a period of 6 months or longer on the same ART (Abstract 347). Rates of occurrence and emergence of drug resistance mutations during periods of HIV RNA levels between 40 copies/mL and 500 copies/mL were calculated in 37 HIV-1-infected patients on ART. Overall, 11 of 37 patients (30%) acquired at least 1 (and up to 9) drug resistance mutation during the period of low-level viremia. New drug resistance mutations were detected for an nRTI in 6 patients, for an NNRTI in 1 patient, for a PI in 6 patients, and for raltegravir in 2 patients. During the period of low-level viremia, the median number of drugs associated with confirmed resistance increased from 4.5 to 6. The authors concluded that periods of HIV RNA levels less than 500 copies/mL are associated with increased risk for accumulation of new drug resistance mutations and advised consideration of genotypic analysis at lower HIV RNA levels.

Quantifying Combination ART Effects

Sampah and colleagues reported methods to quantify the antiviral effects of ART on wild-type and drug-resistant HIV-1 infection (Abstract 624). Using a single-round infectivity assay, inhibition of wild-type and drug-resistant HIV-1 infection in primary CD4+ T cells was assessed and compared based on single drugs and drug combinations. The intrinsic antiviral activity of ART drugs and drug combinations at clinical concentrations was calculated relative to an identified target level of viral inhibition associated with treatment success. Previously unappreciated complex nonlinear pharmacodynamics were observed for most antiretroviral drugs. For example, combinations of InSTIs with drugs from all other classes showed a multiplicative effect on viral inhibition, and ART agents binding to the same site showed an additive effect, with the notable exception of PIs. The analysis provided a framework for understanding synergistic and antagonistic interactions between ART combinations, revealed novel regimens with high activity, and allowed for predictions of which regimens retain

residual antiretroviral activity against resistant virus strains.

Nucleic Acid and Drug Resistance Testing (NAT+DR)

In an effort to develop lower cost HIV RNA and drug resistance testing in RLS, Tilghman and colleagues tested a combined screening method based on qualitative nucleic acid testing (NAT) followed by sequencing of RT to detect drug resistance (NAT + DR) (Abstract 683). Plasma was collected from participants receiving at least 6 months of ART in the San Diego primary infection cohort. HIV RNA extraction and reverse transcription were performed on pools of 5 samples each, followed by PCR amplification of a conserved region of HIV-1 RT and sequencing of this region to detect drug resistance-associated mutations. Of the 325 patient samples analyzed, 50 (15%) had HIV RNA levels of at least 50 copies/mL (median 181 copies/mL, range 50 copies/mL to 10,500 copies/mL), and 4 (1%) had virologic failure (defined as HIV RNA level ≥ 1,000 copies/mL). Of the 65 mini-pools tested, 3 yielded product after 1 PCR round, and 19 yielded product after both rounds. The NAT + DR assay was 100% sensitive in the detection of individual samples with HIV RNA levels of at least 1000 copies/mL, using 1 or 2 PCR rounds. Sequences were successfully generated from PCR product of all pools testing positive for the presence of HIV, 36% of which harbored at least 1 important drug resistance mutation. Based on assay costs, the NAT+DR method would have saved $34,310 over standard HIV RNA level testing and genotyping of samples with virologic failure.

CCR5 Coreceptor Antagonists and Resistance

Optimizing detection of entry inhibitor resistance is an important area of study that was covered in CROI session 123. McLaughlin and colleagues shared data on a novel codon-specific PCR-based (CS-PCR) assay to detect HIV-1 subtype B variants using CXC chemokine receptor 4 (CXCR4) (Abstract 712). Relatively inexpensive, the CS-PCR detects codons in HIV *env* V3 that contribute to the CXCR4 phenotype. Optimization was achieved using 77 first-round *env* samples with accompanying population sequences and previously generated pyrosequencing data. In 22 of 77 samples, CXCR4 populations were present at 2% or more of the viral population, and at less than 2% in 23 of 77 samples. No CXCR4 was detected in the remaining 32 samples. CS-PCR detected a primary CXCR4 codon in 20 of 22 samples with 2% or more CXCR4 for a sensitivity of 91.7%, and 4 of 23 low-level (2% or less) CXCR4 populations. The authors offered CS-PCR as a sensitive and economical future alternative to more costly and technically demanding pyrosequencing.

The use of UDS applied to entry inhibitors continues to be an important area of investigation. Hedskog and colleagues evaluated the longitudinal determination of coreceptor usage by using ultra-deep pyrosequencing to examine the V3 loop of the viral envelope to determine the presence of CXCR4 virus as minority variants during primary HIV infection (Abstract 572). Three patients who experienced a coreceptor switch from CCR5 to CXCR4 were analyzed longitudinally from primary infection until after the switch. Each sample produced 480 to 20,893 reads. In 1 individual, low-abundant CXCR4-using viruses were found during primary infection. However, phylogenetic analysis suggested that these viruses were genetically similar to the CXCR4 population detected after coreceptor switch. The investigators offered this as evidence that CXCR4 populations develop from the CCR5 population of each patient during the course of infection.

NNRTI Resistance

Several abstracts explored issues of resistance to NNRTIs. Rimsky and colleagues reported on a week-96 resistance analysis of pooled rilpivirine and efavirenz phase III trials in treatment-naive HIV-infected adults (Abstract 708). Rilpivirine-based and efavirenz-based regimens each resulted in 78% response rate at 96 weeks. The week-96 analysis revealed virologic failures in 14% (96 of 686) of rilpivirine and 8% (52 of 682) of efavirenz regimens. Beyond week 48, increases in virologic failures were similar in both rilpivirine and efavirenz groups. Mutations associated with nRTI resistance emerged more frequently in rilpivirine than in efavirenz virologic failures in the week-96 analysis (56% vs 26%). The most frequently emerging NNRTI and nRTI resistance-associated mutations were E138K and M184I, respectively, in rilpivirine virologic failures, and K103N and M184V, respectively, in efavirenz virologic failures. E138K and M184I was the most frequent combination of resistance-associated mutations among rilpivirine virologic failures (22%). Among patients with baseline HIV RNA level of 100,000 copies/mL or below (low baseline viral load), there were 8% (28 of 368) rilpivirine virologic failures versus 6% efavirenz virologic failures, although a higher proportion of virologic failure in the rilpivirine (21%) than in the efavirenz group (9%) was observed in patients with baseline viral load greater than 100,000 copies/mL (high baseline viral load). In both treatment groups, the proportion of virologic failures with emergent resistance-associated mutations was lower among patients with low rather than high baseline viral load. Of 81 rilpivirine virologic failures, 35 showed resistance to rilpivirine by phenotyping at virologic failure. Of these 35 virologic failures, 16 (46%) were cross-resistant to nevirapine, 30 (86%) to efavirenz, and 32 (91%) to etravirine. Phenotypic resistance and NNRTI cross-resistance were less frequent in patients with low baseline HIV RNA levels than those with high baseline HIV RNA levels.

Hu and colleagues presented data on the effect of RT mutations E138K and M184I/V on rilpivirine susceptibility and viral fitness of HIV-1 (Abstract 706). Mutations at RT codons 138 and 184 were introduced by site-directed mutagenesis of cloned wild-type NL4-3 RT. Infectious recombinant viruses were generated. Viral infectivity and fitness profile, as well as susceptibility

to rilpivirine and replication capacity, were determined. The E138K and E138K/M184V mutations conferred a 2.2-fold increase in 50% inhibitory concentration (IC_{50}) for rilpivirine compared with wild-type mutations, and the E138K/M184I mutation conferred a 4.9-fold increase. The relative infectivity and fitness profiles of the mutants compared with wild-type virus over a range of drug concentrations showed that the E138K/M184I mutant had a replicative advantage over the E138K/M184V mutant at higher rilpivirine concentrations tested (0.0625 nM to 1 nM). The E138K/M184I mutant had similar advantage over the E138K/M184V mutant over the range of drug concentrations tested (0.0039 nM to 0.25 nM for rilpivirine; 0.39 µM to 25 µM for lamivudine). The authors concluded that the higher level of resistance and greater relative replication of the E138K/M184I mutant than of the E138K/M184V mutant likely explained the frequent association of E138K with M184I in HIV-1 strains derived from patients with virologic failure in clinical trials of rilpivirine.

Anta and colleagues assessed the presence of the rilpivirine resistance mutations E138K and M184I in HIV-1-infected patients in whom NNRTI regimens failed in the ResRIS (Spanish AIDS Research Network national drug-resistance database) (Abstract 710). Investigators analyzed 8200 RT genotypes from 5873 different HIV-infected patients, of which 1064 belonged to patients in whom NNRTI therapy had failed. Codon 138 mutants were found to be very rare. However, almost 20% of patients on failing NNRTI regimens would be considered rilpivirine resistant, as a result of other mutations (V90I, V108I, E138K, V179I, and Y181C) that are more often selected when failing nevirapine or etravirine rather than efavirenz, therefore limiting the sequential use of these drugs.

Similarly, Sungkanuparph and colleagues reported on a study to assess primary HIV-1 drug resistance-associated mutations to efaviranez, etravirine, nevirapine, and rilpivirine among ART-naive HIV-1-infected patients in Thailand from 2007 to 2010 (Abstract 709). HIV-1 subtypes and mutations were assayed by sequencing a region of HIV-1 pol gene. The 466 patients included in the analysis had HIV-1 subtypes CRF01_AE (86.9%), B (8.6%), and other recombinants (4.5%). The prevalence of patients with efavirenz, etravirine, nevirapine, and rilpivirine resistance were 3.2%, 1.3%, 3.2%, and 1.5%, respectively. All patients who had etravirine resistance and all patients with rilpivirine resistance (except for 1 patient with E138G) also had efavirenz and nevirapine resistance. The most common NNRTI resistance-associated mutations observed, in descending order of frequency, were V179D, V106I, Y181C, K103N, and V108I. The authors commented that after a decade of ART scale-up in Thailand, there is substantial primary resistance to NNRTIs, which extends to second- as well as first-generation NNRTIs. The authors urged interventions to prevent the transmission of HIV drug resistance and continue surveillance for primary HIV drug resistance.

Integrase Resistance

Several presentations were dedicated to resistance in the InSTI class. Lin and colleagues explored differences in kinetics and magnesium dependency of binding of first-, second- and third-generation HIV InSTIs to wild-type versus raltegravir-resistant G140S/Q148H HIV (Abstract 690). Equilibrium binding and kinetic studies were consistent with a previously proposed 2-step binding model, with equilibrium largely controlled by magnesium-dependent steps and final equilibrium controlled by conformational changes around the terminal deoxyribose/adenine. The relative participation of each binding step to total binding was found to be altered with binding of third-generation InSTIs to the raltegravir-resistant mutant, offering insight into inhibitors that remain potent against raltegravir resistant HIV.

Understanding barriers to resistance among second-generation InSTIs was the focus of several studies. Winters and colleagues reported on the development of InSTI resistance mutations in patients on elvitegravir-containing failing regimens (Abstract 701). RNA was isolated at 52 timepoints from 10 HIV-infected patients with suboptimal virologic response enrolled in the phase II study exploring the use of elvitegravir/r in the absence of PIs in heavily treatment-experienced patients. Plasma samples were taken at baseline and sequentially during treatment (from week 2 until week 48). Genotypic analysis was performed. Primary InSTI drug resistance mutations in clones were determined using the Stanford HIV Drug Resistance Database. Although all patients had PI, nRTI and NNRTI resistance–associated mutations at baseline, no baseline InSTI mutations were detected. During elvitegravir treatment, patients developed primary InSTI resistance–associated mutations as early as 2 weeks after initiation of treatment. Two to 6 strains of different primary InSTI resistance–associated mutations appeared during early treatment failure, predominantly as single mutations. The prevalence of these strains fluctuated over time. New strains, or strains with new combinations of InSTI resistance–associated mutations, developed over time. Final virologic failure timepoints (weeks 14 to 48) typically showed a dominant strain that did not possess InSTI resistance–associated mutations found in the early time points and had multiple mutations or a single N155H mutation. The authors suggested that in patients with multiclass drug resistance, elvitegravir treatment can select for a number of distinct InSTI-resistant strains and this can be a highly dynamic process. Early identification of treatment failure may restrict the emergence of strains highly resistant to elvitegravir.

Oliveira and colleagues explored novel mutational changes involved in delayed emergence of resistance to the investigational drug dolutegravir in HIV-1 B and non-B subtypes during in vitro selection (Abstract 692). Findings included supportive evidence that dolutegravir possesses a high genetic barrier to resistance and that HIV subtype may play a role in the mutant selection process.

Raltegravir was the first InSTI

approved by the FDA to treat HIV-1. Although recent research suggests efficacy against HIV-2 as well, HIV-2 susceptibility data are limited. Smith and colleagues reported on the phenotypic susceptibility to raltegravir and genetic pathways to InSTI resistance in HIV-2 (Abstract 700). Using site-directed mutagenesis of an HIV-2 molecular clone, 11 HIV-2 integrase mutants were constructed. Replication capacity and raltegravir susceptibility of the resultant variants were assessed. Raltegravir had comparable activity against wild-type HIV-1 and HIV-2. Varying degrees of resistance were appreciated with various known mutations. Amino acid changes Q148K, Q148R, N155H, and T97A + N155H individually conferred moderate resistance to raltegravir, whereas the combination of replacements G140S + Q148R and Q148R + N155H imparted high-level raltregravir resistance (> 100-fold). In contrast, mutations T97A, G140S, Y143C, Q148H, and T97A + Y143C had no substantial effect on raltegravir sensitivity in HIV-2 (≤ 3-fold increase in median effective concentration [EC_{50}]).

With regard to replication capacity, mutations Y143C, T97A + Y143C, Q148H/K/R, and Q148R + N155H showed statistically significant declines in infectious titers, and G140S partially restored the replication defect imposed by the Q148R substitution. Authors concluded that clinical studies of raltegravir for treating HIV-2 infection are indicated. Kobayashi and colleagues studied the in vitro antiviral activity of dolutegravir against raltegravir-resistant HIV-2 mutants (Abstract 691). Dolutegravir showed limited cross-resistance to raltegravir-resistant HIV-2 and substantial loss of activity was not appreciated in the presence of single or even combinations of mutations. The authors suggested that dolutegravir might be useful for the treatment of raltegravir- and elvitegravir-resistant HIV-2 infection.

PIs and Resistance

In an effort to further understand HIV-2 susceptibility to PIs, Raugi and colleagues examined the effects of single amino acid changes in protease on the susceptibility of HIV-2 to 3 PIs: darunavir, saquinavir, and lopinavir (Abstract 697). Using site-directed mutagenesis, 8 protease mutants (V10I, I32V, V47A, I54M, I82F, I84V, L90M, and L99F) were constructed and single-cycle assays were used to quantify the sensitivity of wild-type and mutant HIV-2 strains to each PI in culture. Relative to the wild-type strain, the I54M variant of HIV-2 protease showed moderate resistance to darunavir, whereas the L90M mutant was resistant to saquinavir, and the V47A mutant was resistant to lopinavir. Interestingly, 3 amino acid substitutions tested increased the sensitivity of HIV-2, including the V47A (saquinavir), I32V (darunavir), and I82F (both saquinavir and darunavir).

This year's CROI offered many insights into recent advances in antiretroviral therapy. Promising phase I studies of a tenofovir prodrug which may have increased virologic efficacy with decreased systemic toxicity and infusions of zinc-finger nuclease-modified, CCR5-disrupted autologous T cells, were paired with phase III trials of a new once-daily combination of elvitegravir/cobicistat/tenofovir/emtricitabine and dolutegravir, an investigational InSTI. Data regarding mortality on long-term ART emphasized the near-normal lifespan available to individuals initiating ART at CD4+ counts over 500 cells/μL, while highlighting the persistent challenge of early diagnosis and treatment so that people can realize these benefits. Evidence continued to mount regarding the appropriate use and clinical relevance of low-frequency resistance mutations. Finally, data from RLS revealed advances in treatment scale-up and improvements in median CD4+ cell count at ART initiation, although gaps in linkage to care and adherence fatigue remain to be addressed.

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22. Loss to Follow-up and Mortality among Pregnant and Non-pregnant Women Initiating ART: South Africa. Landon Myer, M Cornell, M Fox, D Garone, R Wood, H Prozesky, J Ndirangu, O Keiser, A Boulle, and IeDEA-Southern Africa Collaboration.

23LB. Field Effectiveness of Universal ART for PMTCT: Rural Zambia. M Gartland, N Chintu, M Li, P Musonda, S Mulenga, A Mtaja, E Stringer, J Stringer, and Benjamin Chi.

24. Neurodevelopmental Outcome among HIV+ Children >1 Year of Age Randomized to Immediate vs Deferred ART: The PREDICT Study (NCT00234091). T Puthanakit, Jintanat Ananworanich, S Vonthanak, P Kosalaraksa, R Hansudewechakul, S Kerr, S Kanjanavanit, U Vibol, R Paul, K Ruxrungtham, and PREDICT Study Group.

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26. Significant Reduction in Risk of Malaria among HIV+ Children Receiving Lopinavir/ritonavir-based ART Compared to NNRTI-based ART, a Randomized Open-label Trial. Jane Achan, A Kahuru, G Ikilezi, T Ruel, T Clark, E Charlebois, P Rosenthal, G Dorsey, D Havlir, and M Kamya.

27. Treatment Interruption in Infants following 24 Months of Empiric ART: Kenya. Dalton Wamalwa, S Benki-Nugent, A Langat, K Tapia, E Ngugi, H Moraa, V Otieno, B Richardson, J Overbaugh, and G John-Stewart.

28LB. Early ART followed by Interruption Is Safe and Is Associated with Better Outcomes than Deferred ART in HIV+ Infants: Final Results from the 6-Year Randomized CHER Trial, South Africa. Mark Cotton, A Violari, D Gibb, K Otwombe, D Josipovic, R Panchia, P Jean-Philippe, E Handelsman, J McIntyre, A Babiker, and the CHER Team.

29. ARV PrEP for HIV-1 Prevention among Heterosexual Men and Women. Jared Baeten, D Donnell, P Ndase, N Mugo, A Mujugira, C Celum, and Partners PrEP Study Team.

30. Tenofovir Disoproxil Fumarate Drug Levels Indicate PrEP Use Is Strongly Correlated with HIV-1 Protective Effects: Kenya and Uganda. Deborah Donnell, J Baeten, C Hendrix, N Bumpus, D Bangsberg, J Haberer, A Mujugira, C Celum, and Partners PrEP Study Team.

31LB. Intracellular Tenofovir-DP Concentrations Associated with PrEP Efficacy in MSM from iPrEx. Peter Anderson, A Liu, S Buchbinder, J Lama, J Guanira, V McMahan, L Bushman, D Glidden, R Grant, and the iPrEx Study Team.

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33. Sensitive Tenofovir Resistance Screening of HIV-1 from the Genital Tract of Women with Breakthrough Infections: CAPRISA 004 Tenofovir Gel Trial. X Wei, L Morris, V Naranbhai, S Sibeko, Q Abdool Karim, A Kashuba, J-A Passmore, G Hunt, W Heneine, and Jeffrey Johnson.

34LB. MTN-007: A Phase 1 Randomized, Double-blind, Placebo-controlled Rectal Safety and Acceptability Study of Tenofovir 1% Gel. Ian McGowan, C Hoesley, P Andrew, L Janocko, J Dai, A Carballo-Dieguez, R Kunjara Na Ayudhya, J Piper, R Cranston, K Mayer, and MTN-007 Protocol Team.

35. Rilpavirine-LA Formulation: Pharmacokinetics in Plasma, Genital Tract in HIV- Females and Rectum in Males. Akil Jackson, L Else, J Tjia, N Seymour, M Stafford, D Back, B Gazzard, and M Boffito.

36. Population-level Impact of Male Circumcision on HIV Incidence: Rakai, Uganda. Ronald Gray, G Kigozi, D Serwadda, X Kong, F Nalugoda, F Makumbi, J Kagaayi, T Lutalo, S Watya, and M Wawer.

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46. Telaprevir in Combination with Pegylated Interferon-alfa-2a + RBV in HCV/HIV-co-infected Patients: A 24-Week Treatment Interim Analysis.Douglas Dieterich, V Soriano, K Sherman, P-M Girard, J Rockstroh, B Adiwijaya, S McCallister, N Adda, L Mahnke, M Sulkowski, on behalf of the Study 110 Team.

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54LB. 100% Rapid Virologic Response for PSI-7977 + Ribavirin in Genotype 1 Null Responders (ELECTRON): Early Viral Decline Similar to that Observed in Genotype 1 and Genotype 2/3 Treatment-naïve Patients. Edward Gane, C Stedman, J Anderson, R Hyland, R Hindes, W Symonds, and M Berrey.

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78LB. Microglial Cell Activation Is Visualized with [11C]-PK11195 Positron Emission Tomography in Neurologically Asymptomatic HIV-infected Subjects on Effective ART. Lucy Garvey, N Pavese, M Politis, A Ramlackhansingh, S Taylor-Robinson, D Brooks, and A Winston.

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89. Sex Association with ARV Efficacy Outcomes in a Prospective Randomized Clinical Trial of ART in Diverse Multinational Settings: The ACTG PEARLS Study. Cynthia Firnhaber, L Smeaton, B Grinsztejn, Y Chen, U Lalloo, S Faesen, W Samaneka, J Lama, A Rana, and T Campbell.

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99. Deep Sequencing HIV-1 Protease and HCV NS3 Using a Primer ID: Accurately Resolving Low Abundance Drug-resistant Variants in Therapy Naïve Individuals. Cassandra Jabara, Y Yang, J Anderson, C Jones, J Roach, S Lemon, and R Swanstrom.

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102LB. Dolutegravir in Combination Therapy Exhibits Rapid and Sustained Antiviral Response in ARV-naïve Adults: 96-week Results from SPRING-1 (ING112276). Hans-Juergen Stellbrink, J Reynes, A Lazzarin, E Voronin, F Pulido, F Felizarta, S Almond, M St Clair, N Flack, and S Min.

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105. The Risk of Virologic Failure Associated with Low Frequency Nevirapine-resistant Variants in Women Initiating Nevirapine-containing ART Varies Depending on the History of Exposure to sd-Nevirapine: OCTANE/ACTG 5208. Valerie Boltz, Y Bao, S Lockman, E Halvas, J McIntyre, R Schooley, M Hughes, J Coffin, and J Mellors. 110. Consequences of ARV Exposure for PMTCT: What Have We Learned? Stephane Blanche.

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136LB. Effect of ART Coverage on Rate of New HIV Infections in a Hyper-endemic, Rural Population: South Africa. Frank Tanser, T Bärnighausen, E Grapsa, and M-L Newell.

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149bLB. A Household-based HIV and TB Intervention Increases HIV Testing in Households and Reduces Prevalence of TB at the Community Level: The ZAMSTAR Community Randomized Trial. Helen Ayles and the ZAMSTAR Study Team.

150aLB. Community-wide Isoniazid Preventive Therapy Does Not Improve TB Control among Gold Miners: The Thibela TB Study, South Africa. Gavin Churchyard, K Fielding, J Lewis, L Coetzee, E Corbett, P Godfrey-Faussett, R Hayes, A Grant, on behalf of the Thibela TB Team.

150bLB. Individual-level Effect of Isoniazid Preventive Therapy on Risk of TB: The Thibela TB Study. Katherine Fielding, A Grant, J Lewis, R Hayes, and G Churchyard.

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