Highlights of the 18th Conference on Retroviruses and Opportunistic Infections

Factors Influencing Virus–Host Cell Interplay
Mario Stevenson, PhD
Viral Replication and Cell Cycle • Virologic Synapse: Sensitivity to Neutralization • HIV/Flavivirus GB Virus C Coinfection • Studies on Viral Uncoating • Viral Integration • Mechanisms of Latency • Cellular Restriction • Pathogenesis • Strategies for Viral Eradication

HIV Vaccine Development
David I. Watkins, PhD
Neutralizing Antibodies Against HIV • HIV-Specific Cellular Responses • Results From Vaccinated Monkeys After Heterologous Challenge

HIV Epidemiology and Breakthroughs in Prevention
Susan P. Buchbinder, MD
30 Years Into the AIDS Epidemic
The US HIV Epidemic • Populations at High Risk of HIV-1 Acquisition • Herpes Simplex Virus Type 2 • HIV Testing Strategies • HIV Prevention Strategies

Central Nervous System Complications of HIV Infection
Serena S. Spudich, MD, and Beau M. Ances, MD, PhD
Introduction—What’s in a Name? • New Biomarkers of HIV-Associated Neurocognitive Disorder • Neuropathogenesis of HIV and Simian Immunodeficiency Virus Infection • Treatment With Antiretroviral or Adjunctive Therapies and Biomarkers of HIV-Associated Neurocognitive Disorder • Early Injury

Complications of HIV Disease and Antiretroviral Therapy
Anne F. Luetkemeyer, MD, Diane V. Havlir, MD, and Judith S. Currier, MD
Viral Hepatitis • Cardiovascular Disease • Bone Loss: Host Factors, Antiretroviral Drugs, or HIV Disease? • Lipodystrophy • Renal Disease • Malignancy • Tuberculosis • Cryptococcal Meningitis • Influenza A (H1N1)

Advances in Antiretroviral Therapy
Barbara Taylor, MD, MS, Susan Olender, MD, Timothy J. Wilkin, MD, MPH, and Scott M. Hammer, MD
Investigational Drugs • Clinical Trials of Antiretroviral Therapy in Treatment-Naïve Patients • Clinical Trials of Antiretroviral Therapy in Treatment-Experienced Patients • Antiretroviral Treatment Strategies • Predictors of Antiretroviral Therapy Response From Large Cohort Studies • Antiretroviral Treatment in Resource-Limited Settings • Mother-to-Child Transmission of HIV Infection • Resistance • Pharmacokinetic Considerations
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Abstracts Cited

Announcements

Continuing Medical Education Information  
30  
Continuing Medical Education Activity Posttest and Evaluation Form  
107  
Educational Programs of the IAS–USA  
98  
*Cases on the Web* — Online CME Activities  
47  
Subscription Request/Address Change Form  
111  
Guidelines for Authors and Contributors  
112
The articles in this issue, which highlight presentations from the 18th Conference on Retroviruses and Opportunistic Infections, are available for CME credit.

Instructions

This journal-based continuing medical education (CME) activity provides a review of new data presented at the 18th Conference on Retroviruses and Opportunistic Infections (CROI). It offers a maximum of 8 CME credits. To complete the activity, the learner is instructed to:

- Read the articles in this issue
- Review a selection of the references
- Reflect on how the information might be applied to the clinical practice
- Take the posttest (pages 107–108)
- Complete the evaluation and CME claim forms on pages 108–109, and send them with the completed posttest to the IAS–USA office along with payment of $35.

Learning Objectives

Upon completion of this activity, learners will be able to describe results of recent research presented at the 18th CROI and the potential clinical implications for their patients in the following subject areas:

- Factors influencing virus–host cell interplay
- HIV vaccine development
- HIV epidemiology, testing strategies, and prevention interventions
- Neurologic disorders in HIV disease and their treatment
- Infectious and metabolic complications of HIV disease and antiretroviral treatment, including tuberculosis and hepatitis coinfections
- Advances in antiretroviral therapy, including prevention of mother-to-child transmission and HIV resistance to antiretroviral drugs

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Intended Audience

This activity is intended for physicians involved in the care of patients infected with HIV 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.

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This CME activity is offered from June 8, 2011, to June 8, 2012. Participants who receive a passing score on the posttest and submit the registration and evaluation forms are eligible to receive credit. Physicians (MDs, DOs, and international equivalents) may receive CME credit for completing this activity. Nonphysician health care practitioners will receive a certificate of attendance.
Factors Influencing Virus–Host Cell Interplay

Mario Stevenson, PhD

The Conference on Retroviruses and Opportunistic Infections (CROI) provides an annual international forum for basic scientists and clinical and global health researchers to present and become current on the most recent advances in the field of HIV and AIDS research. The 18th conference contained a number of strong basic science sessions. HIV-1 infection of the cell is opposed by cellular factors that attack the viral replication cycle at various points. However, the virus has evolved defenses against these innate cellular antiviral proteins. CROI continues to be a strong forum for presentation of the most recent developments in this area of research. In addition, there were numerous presentations on cellular factors that regulate virus–host cell interplay as well as on research that is providing detailed insight into the mechanism of action of integrase inhibitors. Some presentations focused on approaches to studying and intervening with viral latency, particularly in primary cell models. Research on the use of zinc-finger nucleases to knock out CC chemokine receptor 5 expression in CD34+ stem cells also received a lot of interest. The hope is that these strategies will provide new therapeutic approaches to generate resistance to HIV-1 infection.

In the Bernard Fields Lecture, Cullen discussed the role of a novel class of small regulatory RNA molecules, called microRNAs (miRNAs), in the replication of viruses, in particular, herpes viruses (Abstract 17). MiRNAs bind to messenger RNA (mRNA) molecules that have partially or fully complementary sequences and as a result are able to impair mRNA translation and reduce mRNA stability. Cullen described miRNAs that play a central role in the regulation of herpes virus latency as well as virus-encoded miRNAs that regulate cellular functions important for virus survival in the host. The search for miRNAs that regulate HIV-1 replication is ongoing, and whether there are microRNAs encoded by HIV-1 is still a matter of debate. Cullen discussed the role of virus-encoded miRNAs in the maintenance of Epstein-Barr virus latency. He described how miRNAs participate not only in the maintenance of latency, but also in maintenance of B-cell transformation that is important to sustain the viral reservoir.

Viral Replication and Cell Cycle

Infection of a cell is initiated by interactions of the viral envelope glycoprotein with receptor and coreceptor molecules on the cell surface. Exposure of fusogenic domains on the viral envelope leads to fusion between viral and cellular membranes; this fusion allows the viral core, which contains the viral nucleic acid, to be inserted into the cytoplasm of the target cell. Research has indicated that the establishment of a latency model using primary cell models. Research on the use of zinc-finger nucleases to knock out CC chemokine receptor 5 expression in CD34+ stem cells also received a lot of interest. The hope is that these strategies will provide new therapeutic approaches to generate resistance to HIV-1 infection.

Abstract 88 demonstrated that chimeric constructs between human CD8α and the cytoplasmic tail of gp41 (gp41CT) induced nuclear factor κB (NF-κB)-dependent luciferase activity in both HIV-1 and simian immunodeficiency virus (SIV). The second tyrosine of the cytoplasmic tail was important for the induction of NF-κB activity. Activation of NF-κB was independent of the activation of either nuclear factor of activated T cells (NF-AT) or activating protein 1 (AP-1). Several important questions arise from the study. For example, it will be necessary to determine whether envelope glycoprotein, within the context of an intact virion, is able to induce sufficient NF-κB to increase target-cell permissivity during infection given the consensus that truly quiescent CD4+ T cells are not permissive to HIV-1 infection. It is unlikely that such a mechanism is sufficient to render quiescent T cells permissive to infection. However, there may be different activation states between phases G0 and G1 in which envelope-dependent signaling may be sufficient to render the cell permissive to infection.

Establishment and maintenance of latency in primary, infected CD4+ T cells in vitro is difficult. This has hampered detailed investigation of the molecular mechanisms regulating viral latency in a physiologically relevant system. Research has indicated that quiescent T cells are difficult to infect in vitro, and this hampers the establishment of a latency model using primary lymphocytes. Abstract 174 presented evidence that quiescent T cells can be infected through an endosomal route. The authors produced HIV-1 variants that were pseudotyped with an R5-tropic HIV-1 envelope and with the fusogenic G glycoprotein of vesicular stomatitis virus (VSV-G). They demonstrated that both CD4+-dependent binding and subsequent VSV-G fusion were necessary for infection of naive CD4+ T cells. This study could be important because it would provide an approach for the establishment of latent infection in vitro, thereby allowing detailed investigation of the mechanisms regulating latency in a physiologically relevant model.
Virologic Synapse: Sensitivity to Neutralization

In lymphoid tissue, where there is a high density of substrate CD4+ T cells, viral spread may occur not only as free viral particles but also directly between cells through cell-to-cell contact. HIV-1 has been reported to form virologic synapses (VS) between the HIV-1-infected cell and the target cell’s interface. Formation of VS involves interaction between the viral envelope and CD4+ cell–coreceptor complexes and further requires cytoskeletal rearrangements and stabilization of infected and target-cell membranes by adhesion molecules. The nature of the VS has prompted speculation that this mode of viral transfer may afford the virus some degree of protection from neutralizing antibodies or from inhibitors that prevent interactions with receptor and coreceptor molecules.

Research presented in Abstract 181 provided evidence that the VS may provide an infection route that is less sensitive to some broadly neutralizing antibodies. The investigators observed that although most neutralizing antibodies blocked both cell-free and cell-associated HIV-1 infection, a 17b antibody that is reactive against a CD4-induced binding site of envelope glycoprotein as well as patient serum both inhibited cell-free infection more effectively than they inhibited VS-mediated infection. Deletion of the gp41CT enhanced sensitivity to 17b after VS-mediated infection.

Abstract 182 presented evidence that 2- to 3-fold higher concentrations of entry or fusion inhibitors including maraviroc, enfuvirtide, and the investigational drug AMD 3100 were required to disrupt transfection between mature dendritic cells and CD4+ T cells than were required for cell-free virus infection of CD4+ T cells.

Abstract 89 presented evidence for cellular factors that regulate envelope incorporation into the virion. During assembly of the HIV-1 particle at the plasma membrane, the viral envelope glycoprotein is incorporated into the budding virus particle. The cellular protein Rab11a plays a central role in the recycling of cellular glycoproteins to the plasma membrane. The authors demonstrated that a dominant negative mutant of Rab11a did not affect envelope incorporation, but expression of a constitutively active form of Rab11a appeared to direct the envelope glycoprotein to a cellular location for degradation, thus dramatically decreasing envelope incorporation into released virions. Therefore, the Rab11a family of interacting proteins appears to be a key mediator of viral envelope glycoprotein trafficking.

HIV/Flavivirus GB Virus C Coinfection

The regulation of cellular activation state and CC chemokine receptor 5 (CCR5) down-regulation were reported to provide mechanisms for limiting HIV-1 target-cell availability in individuals coinfected with the flavivirus GB virus C (GBV-C). GBV-C infects approximately 30% of individuals with HIV-1, and coinfected individuals have longer average survival times than HIV-1-infected individuals without GBV-C.

The mechanisms underlying the GBV-C benefits are not well understood.

Abstract 26 examined the frequencies of CCR5+ CD4+ T cells in GBV-C-seropositive and -seronegative HIV-1-infected individuals. The investigators determined that levels of the cytokine RANTES (regulated on activation normal T-cell expressed and secreted), a ligand for CCR5, were higher in GBV-C-seropositive individuals than in GBV-C-seronegative subjects. The plasma level of RANTES was inversely correlated with the frequency of CCR5+ CD4+ memory T cells, which itself was related to the median fluorescence intensity of CCR5. Therefore, one of the mechanisms underlying the survival benefits conferred by GBV-C infection might involve higher plasma levels of CCR5-binding chemokines, subsequent down-regulation of CCR5 expression, and a reduction in target-cell availability.

Abstract 27 presented additional evidence for decreases in CD4+ and CD8+ cell activation and proliferation in GBV-C/HIV-1–coinfected individuals compared with HIV-1-infected individuals without GBV-C. CD4+ cell count and percentage were statistically significantly higher in GBV-C-seropositive individuals than in GBV-C-uninfected subjects.

However, in contrast to results from Abstract 26, there were no differences in CCR5 or CXC chemokine receptor 4 (CXCR4) expression on CD4+ cells between GBV-C-seropositive and -negative subjects. In individuals who had detectable HIV-1 viremia, CD4+ cell proliferation was lower in GBV-C-seropositive subjects than in GBV-C-uninfected subjects, and activation levels of CD4+ cells and CD8+ cells were also lower in this group. Therefore, GBV-C viremia appears to be associated with decreased CD4+ T-cell proliferation and activation, which may contribute to improved survival in HIV-1 subjects coinfected with GBV-C.

Studies on Viral Uncoating During Infection

After fusion of HIV-1 with the host cell surface, the viral capsid core enters the cytoplasm. The viral capsid deassembles to release viral nucleic acids into the cytoplasm to be reverse-transcribed. How the reverse transcription and uncoating processes are coordinated during infection remains poorly understood. Abstract 90 presented evidence that drugs that inhibit reverse transcription delayed the uncoating process. The study used a fluorescence-based uncoating assay as well as an owl monkey kidney cell line assay that manifests TRIM-CypA-mediated restriction.

Data from both assays indicated that uncoating is initiated within an hour of viral fusion. Inhibition of reverse transcription using nevirapine delayed uncoating from approximately 40 minutes to 2 hours. Furthermore, analysis of reverse transcription products in owl monkey kidney cells indicated that appearance of early reverse transcription products coincided with the initiation of uncoating. This suggests that reverse transcription facilitates, but is not required for, HIV-1 uncoating in infected cells.
Viral Integration

In a plenary presentation, Cherepanov presented structural insights into the process of retroviral integration and the mechanism of action of strand-transfer inhibitors (Abstract 75). After reverse transcription, the viral integrase enzyme binds to the viral DNA ends to form a stable nucleoprotein complex, the intasome. In the nucleus, the intasome interacts with target-cell DNA and catalyzes the joining of viral DNA to cellular DNA. Using the prototype foamy virus (PFV) intasome as a model system, Cherepanov presented the crystal structure of the PFV intasome, which comprises an integrase tetramer tightly associated with a pair of viral DNA ends. Integration inhibitors, including raltegravir, elvitegravir, and related strand-transfer inhibitors, were found to bind within the active site of the PFV intasome to dislocate the reactor viral DNA. Furthermore, because of strong sequence conservation within the active sites of PFV and HIV-1 integrase, the mechanism by which raltegravir resistance mutations impact antiviral activity could be visualized within the PFV intasome model. The availability of crystal structures for the retroviral intasome is an important step in the development of next-generation integrase inhibitors. Integration of viral DNA into host chromatin is not a random process but appears to occur preferentially in transcription units. Lens epithelium-derived growth factor (LEDGF) is a cellular cofactor of HIV-1 integrase that promotes viral integration into gene-rich regions of host chromatin.5,6

Abstract 191 examined the ability of HIV-1 to replicate in the absence of LEDGF in a human LEDGF knock-out cell line. In the absence of LEDGF, integration did not occur in transcription units but instead, showed a preference for the genomic regions termed CpG islands. Although spreading HIV-1 replication was delayed in the knock-out cell line, residual replication was observed. Nevertheless, the authors demonstrated that this residual replication was still sensitive to the investigative compound termed LEDGING, which interrupts the interaction between HIV-1 integrase and LEDGF. These data reinforce the critical role of LEDGF as a cofactor in HIV-1 integration. The mechanism by which HIV-1 is able to integrate in the absence of LEDGF is under investigation.

Mechanisms of Latency

The site of integration has also been proposed as an important component of the mechanism by which HIV-1 latency is regulated. Both HIV-1 integration and latent proviruses appear to occur in actively expressed host genes. As a consequence, transcriptional interference between the HIV-1 long-terminal repeat (LTR) and the juxtaposed cellular transcription unit has been proposed in epigenetic regulation of HIV-1 latency.7 To further understand the mechanisms regulating HIV-1 latency, Abstract 197 described the development of a dual promoter system that examined the interaction between the HIV-1 LTR and upstream promoters. The authors demonstrated that the maintenance of latency requires that viral integrase does not impinge upon the level of expression of the gene proximal to the provirus. This provides a model for how latent infection can be established in actively expressed cellular genes.

Equally important to an understanding of the mechanisms by which latency is established is an understanding of the processes that can trigger reactivation from latency. Because the latent reservoir is considered the most important obstacle to viral eradication, many investigators have turned their attention to strategies that reactivate latency to reduce the size of the latent reservoir. In Abstract 198, Wightman and colleagues described the development of a primary resting-T-cell model of HIV latency. In this model, resting CD4+ T cells are incubated with the CC chemokine receptor 7 (CCR7) ligand CCL19. The authors have previously demonstrated that treatment of resting CD4+ T cells with certain chemokines such as CCL19 is sufficient to render them permissive to HIV-1 infection.8

They used this model to examine the potency and toxicity of histone deacetylase (HDAC) inhibitors and other immune activators in reactivating HIV-1 latency. The authors observed statistically significant variation in the potency and toxicity of a variety of HDAC inhibitors, including the lymphoma drug vorinostat and the investigational cancer drugs pamabinostat and etinostat as well as cytokines including interferon 7 (IL-7), tumor necrosis factor alpha (TNF-α), and prostratin. HDAC inhibitors showed varying degrees of activity in the primary model of HIV-1 latency. However, toxicity in peripheral blood mononuclear cells was also observed with concentrations close to those required to reactivate HIV-1 latency. Vorinostat exhibited the lowest toxicity and highest potency in the primary T-cell model of HIV-1 latency, underscoring a potential role for this drug in clinical trials to eliminate the resting cell reservoir.

Cellular Restrictions

The area of cellular restrictions continued to draw strong interest at the conference. As a virus with a limited genetic repertoire, HIV-1 commandeers cellular factors at various stages in its replication cycle. The seminal discovery, by Malim’s research group, of the cellular restriction APOBEC 3G revealed the existence of cellular factors that oppose viral infection.9 Since that discovery, additional cellular factors that antagonize viral replication have been identified. For example, TRIM5α exerts a species-specific effect on viral uncoating, and tetherin/BST2 interferes with disassociation of viral particles from the cell surface. The existence of these potent antiviral restrictions has forced primate lentiviruses to adopt evasion strategies, and almost all of the viral counterdefenses are directed by the viral accessory proteins. The Vif protein antagonizes APOPEC 3G by promoting its premature proteasomal destruction, and the protein Vpu antagonizes tetherin/BST2 by directing it away from sites of virus assembly. Because Vpu is not encoded by the majority of SIV variants or by HIV-2, an important question is how these viruses evade the antiviral action...
of tetherin/BST2. Studies by Evans previously established that SIV Nef proteins antagonize tetherin/BST2.10

Abstract 85 presented further insight into the mechanism by which SIV Nef antagonizes tetherin/BST2. Nef proteins have previously been demonstrated to bind adaptor protein 2 (AP-2).11,13 SIV Nef mutants incapable of binding AP-2 were unable to antagonize tetherin, and down-regulation of tetherin/BST2 from the cell surface was observed with wild-type Nef but not with AP-2-binding-site mutants. Therefore, SIV Nef proteins antagonize tetherin/BST2 in an AP-2-dependent mechanism that allows displacement of tetherin/BST2 from the site of virus assembly or down-regulation of tetherin/BST2 from the cell surface.

Recent studies from our research group have presented evidence that primate lentiviral Vpx proteins enhance infection of myeloid cells by antagonizing a cellular restriction.13,14 Although the identity of the restriction as well as its viral target are yet to be revealed, the restriction appears to be a major barrier to infection of myeloid cells. Our published studies have demonstrated that although HIV-1 Vpr is unable to neutralize the myeloid cell restriction, HIV-1 is sensitive to restriction, and packaging of Vpx within HIV-1 substantially increases its infectivity for macrophages.

In Abstract 87, Sunseri and colleagues presented evidence that increasing HIV-1 infectivity for macrophages and dendritic cells after Vpx packaging within HIV-1 virions led to an enhanced innate immune response. Vpr and Vpx proteins are packaged into virions through association with the p6 domain of Gag. The authors constructed a chimeric HIV-1 Gag containing the SIV p6 domain, and this allowed packaging of Vpx into HIV-1 virions. HIV-1 that was engineered to package Vpx was more infectious in both macrophages and dendritic cells and induced a strong type 1 interferon response. It is intriguing to speculate that HIV-1 has evolved to lack a strategy to neutralize a myeloid cell restriction in order to avoid activating an innate immune response. Therefore, it would be important to determine whether the ability of HIV-1 to remain sensitive to the myeloid cell restriction impacts its biology within the host.

Abstract 28LB presented evidence that some form of antiviral restriction may be playing a role in viral control within elite controllers. Research from Crumpacker and colleagues demonstrated that the cyclin-dependent kinase inhibitor p21 restricted HIV-1 infection of primary hematopoietic cells.15 In Abstract 28LB, Huang and colleagues examined p21 expression in CD4+ T cells from elite controllers and HIV-1 progressors. Expression of p21 was statistically significantly higher in CD4+ T cells from elite controllers, and silencing of p21 by RNA interference increased HIV-1 replication. This group demonstrated that p21 interacted with the cyclin-dependent kinase 9 (CDK9), which is essential for HIV transcriptional elongation. The authors proposed that p21 acts as an inhibitor of CDK9-mediated transcriptional elongation of HIV-1 in elite controllers.

Pathogenesis

Several clear mechanisms have emerged to explain the processes of lentiviral pathogenesis. In pathogenic primate lentiviral infection, viral replication depletes Th17 cells that are necessary to maintain the integrity of the gut mucosa. A subsequent loss in gut-mucosal integrity leads to translocation of bacterial products that drive cell activation, including lipopolysaccharide (LPS). This increases the pool of cells permissive to viral infection and erodes the architecture of the lymphoid tissue. As originally hypothesized by Giorgi and colleagues, immune activation (as measured by frequency of activated CD8+ T cells) correlates with plasma viral load and is a strong predictor of disease progression.16 Immune activation persists in HIV-1-infected individuals, is not normalized by antiretroviral suppression, and undermines CD4+ cell count gains during treatment.

In one study, no correlation between bacterial translocation and immune activation and low-level viremia was observed in HIV-1-infected individuals who exhibited poor CD4+ T-cell recovery during suppressive antiretroviral therapy (Abstract 304). The researchers examined the association between CD4+ T-cell gains and T-cell activation (CD58+HLADR+CD8 cells), markers of microbial translocation (LPS and 16S ribosomal DNA), as well as monocyte activation (soluble CD14). In 71 participants, no markers of bacterial translocation were associated with CD4+ T-cell counts. Nor was there a correlation of CD4+ T-cell count or immune activation with low-level plasma HIV RNA. There was an association of CD8+ lymphocyte activation with lower CD4+ cell count. Therefore, additional studies are required to identify biological correlates of a nontreatment response in patients receiving suppressive therapy.

Strategies for Viral Eradication

There has been a single documented case of HIV-1 eradication: the “Berlin patient,” an HIV-1-infected individual with leukemia.17 He received chemotherapy followed by transplanted hematopoietic stem cells from a CCR5-negative donor. This case has provided proof-of-concept for strategies that engineer stem cells to become CCR5-negative. Abstracts 164 and 165 discussed the potential use of zinc-finger nucleases to edit the CCR5 gene in stem cells. In Abstract 164, Cannon and colleagues discussed the use of zinc-finger nucleases to knock out the CCR5 gene in human CD34+ stem cells. Those stem cells were then transplanted into immune-deficient mice. Infection of these mice with R5-tropic strains of HIV-1 led to the preferential survival of CCR5-negative T cells, substantial declines in HIV-1 viremia, and eventual restoration of normal levels of CD4+ T cells in lymphoid tissues of the mouse.

Abstract 165 discussed the application of this strategy to humans in ongoing phase I clinical trials involving a group of patients for whom 2 or more antiretroviral regimens have failed and who remain viremic and a second
group of patients who are doing well on antiretroviral therapy. In this study, the CCR5 locus is disrupted with zinc-finger nucleases, and then the CCR5-deficient T cells are transplanted into the patients.

Although these are exciting studies, an important question arises as to whether the preexisting viral reservoirs will persist in individuals who receive transplanted CCR5-negative cells. The success of the Berlin patient likely hinged on the fact that the existing reservoir was depleted through chemotherapy. However, in allogeneic stem cell transplantation, for which chemotherapy is not necessary, the preexisting latent reservoir is likely to persist. Therefore, at best, CCR5 removal through allogeneic stem cell transplantation may offer a means for viral control but may not achieve the goal of viral eradication.

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A list of all cited abstracts appears on pages 99–106.

References


HIV Vaccine Development

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Presentations at the 2011 Conference on Retroviruses and Opportunistic Infections reflected the resurging interest in antibody responses against HIV given the encouraging results of the Thai vaccine trial. A plenary talk and an entire symposium were devoted to HIV-specific antibody responses describing newly isolated, potent neutralizing monoclonal antibodies. These antibodies undergo extensive somatic mutation to achieve their remarkable neutralizing properties. Inducing these types of antibodies by vaccination, however, still represents a challenge. New data were presented suggesting that neutralizing antibodies, but not binding antibodies, can provide protection against infection in the nonhuman primate (NHP) model. Several interesting discoveries were also reported showing that cellular immune responses recognizing HLA-C and HLA class II molecules might also be important in control of viral replication. Finally, new vaccine studies in the NHP model showed that electroporated DNA, along with the adjuvant interleukin 12 may be an efficacious vaccine regimen.

Over the past few years, several new, potent neutralizing antibodies have been described in the HIV vaccine field. These studies have come from many different groups, including those at Rockefeller University, International AIDS Vaccine Initiative (IAVI), and the Vaccine Research Center (VRC). These new studies have shed considerable light on how these critically important antibodies develop. The interesting properties of many of these novel antibodies were discussed at the 2011 Conference on Retroviruses and Opportunistic Infections. Additionally, novel vaccination methods gave the field hope that a vaccine for HIV might eventually be possible.

Neutralizing Antibodies Against HIV

Nussenzweig gave a plenary talk outlining developments in the discovery of neutralizing antibodies against HIV (Abstract 20). The IAVI Neutralizing Antibody Center at the Scripps Research Institute, the VRC, and now Nussenzweig’s group have recently discovered new, highly potent, broadly neutralizing antibodies against HIV. Nussenzweig’s group sorted gp140-staining, single B cells from HIV-infected individuals and then cloned the antibody genes from these cells. They showed that, after expression, most of these antibodies neutralized tier-1 strains of HIV (ie, strains highly susceptible to neutralization), whereas only a few of them neutralized the more difficult-to-neutralize tier-2 strains (ie, strains moderately susceptible to neutralization). These antibodies had undergone extensive somatic hypermutation, facilitating high-affinity binding to Envelope. Nussenzweig showed that T cells played a crucial role in the maturation of these highly specific antibody responses.

One symposium was devoted entirely to anti-HIV antibodies (Session 18). Mascola initiated the session and reminded attendees that HIV was unusual in that broadly reactive, HIV-specific neutralizing antibodies take more than 2 years to develop in infected individuals (Abstract 62). He then discussed the new neutralizing antibodies from the VRC, highlighting the discovery of a broadly reactive neutralizing antibody, VRC01. He suggested that these broad neutralizing antibodies could be used for passive transfer for prevention of mother-to-child transmission, gene delivery, and microbiocides. The new VRC01 antibody had undergone extensive somatic mutation and binds to the conserved CD4 binding site of gp120. Indeed, VRC01 differs from the germ line sequences by 30%, and if changes are made so that sequences are reverted to the germ line, the antibody loses its affinity and neutralizing capabilities. This indicates that somatic mutation is crucial to the development of the affinity and neutralizing properties of these broadly neutralizing antibodies. These findings suggest immunization strategies to induce such effective antibodies.

Verkoczy and colleagues discussed the possibility that membrane-proximal external region (MPER)-specific neutralizing antibodies may be under stringent tolerance control (Abstract 63). Sundling and colleagues showed that even if macaques made antibody responses against a vaccine of soluble Env trimers, these antibodies provided moderate protection against a simian HIV (SHIV) challenge (Abstract 64). On behalf of his colleagues, Kim discussed the latest analyses of the results of the RV144 Thai phase III trial (Abstract 65). He also presented ongoing studies showing that there were antibody recognition profiles that were associated with RV144 vaccination.

Moore and colleagues showed that neutralizing antibodies provide protection in a nonhuman primate (NHP) model, whereas nonneutralizing antibodies provided no or partial protection (Abstract 142). The nonneutralizing b6 antibody directed against the CD4 binding site on gp120 did not provide protection in 4 of 4 macaques in 1 study or in 5 of 5 macaques in a second study. Interestingly, topically applied F240 antibody directed against anti-gp41 (nonneutralizing) protected 2 of 5 animals and resulted in relatively low viral loads in 2 of 3 of the infected animals. By contrast, as has been found before,1 the neutralizing antibody b12 protected all animals in these SHIV-challenge studies.
Troka presented data implicating the V1 and V2 loops in protection against antibodies directed against V3 (Rusert et al, Abstract 141LB). With several elegant experimental approaches, the researchers showed that antibodies directed against the V3 loop in 1 peplomer were inhibited from binding by the V1 and V2 loops from the adjacent peplomer on the trimeric Envelope. Thus, the V1 and V2 loops in the quaternary structure of the gp120 trimer may play a crucial role in conferring resistance to neutralizing antibodies directed against the V3 loop.

**HIV-Specific Cellular Responses**

Several genome-wide association studies have confirmed that a portion of individuals with HLA-B57 or -B27 control viral replication. However, another polymorphism in the major histocompatibility complex (MHC) region, close to HLA-C, was also shown to be associated with control of viral replication. Carrington elegantly demonstrated that this polymorphism may be involved in regulation of HLA-C expression (Abstract 105). Whether this polymorphism is exerting its effect through interactions with cytotoxic T lymphocytes or natural killer cells is still unknown.

In the same symposium, Hirsch and colleagues delineated the effects of TRIM5 polymorphism on simian immunodeficiency virus (SIV) replication (Abstract 107). They showed that TRIM5 alleles can have a profound effect on replication, both in vivo and in vitro, on the SIV<sub>envE545</sub> clone. Interestingly, it was more difficult to see these TRIM5 effects on the closely related SIV<sub>envE660</sub> isolate. This may be related to the use of several different stocks of this quasispecies; some stocks may be more sensitive to TRIM5 variation than others. However, the message for the NHP vaccine field is that vaccine and control groups should be typed for these TRIM5 alleles.

Soghoian and colleagues presented intriguing data suggesting that HIV-specific cytolytic CD4<sup>+</sup> cells may be involved in control of HIV replication (Abstract 158). They studied 12 acutely infected individuals and divided them into 2 groups: those that exerted a measure of control and those that did not. Even though peak viremia was similar in the 2 groups, those that controlled viral replication exhibited higher levels of HIV-specific CD4<sup>+</sup> T cells expressing granzyme, perforin, and CD107a (markers of cytotoxic activity). These data suggest that cytolytic CD4<sup>+</sup> T cells may play an important role in the initial control of HIV replication.

**Results From Vaccinated Monkeys After Heterologous Challenge**

Vaccination using electroporated DNA along with the adjuvancing cytokine interleukin 12 is among the most exciting breakthroughs in vaccine development recently. Pavlakis and colleagues presented data showing that DNA vaccination alone or in combination with aldrithiol 2–inactivated SIV resulted in protection after a heterologous low-dose mucosal challenge (Abstract 360). Indeed, of the 24 vaccinated macaques, 2 animals showed no evidence of viral replication, and 9 macaques showed a peak plasma SIV RNA level of 100,000 copies/mL to 1,000,000 copies/mL, followed by complete control of viral replication. By contrast, none of the 8 naive control animals showed this kind of control of viral replication. The authors speculated that a mixture of vaccine-induced antibodies and cellular immune responses were responsible for this control of viral replication.

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A list of all cited abstracts appears on pages 99–106.

**Reference**


HIV Epidemiology and Breakthroughs in Prevention
30 Years Into the AIDS Epidemic

Susan P. Buchbinder, MD

Thirty years after the first AIDS cases were reported in the United States, the HIV epidemic continues to be heavily concentrated among men who have sex with men (MSM) in the United States. MSM are heavily impacted throughout most of the world and are the predominant risk group throughout the Americas and Western Europe; heterosexuals are the predominant risk group in sub-Saharan Africa; and injection drug users predominate throughout Eastern Europe and Southeast Asia. In the United States, blacks and Latinos continue to be disproportionately affected, despite overall advances in HIV testing and care. The 2011 Conference on Retroviruses and Opportunistic Infections focused on populations heavily impacted throughout the world: adolescents, women, MSM, and serodiscordant couples. Several presentations focused on the unique relationship between herpes simplex virus type 2 (HSV-2) and HIV-1; although many opportunistic infections increase HIV acquisition risk, HSV-2 is likely the only one whose effective prevention or treatment could substantially influence HIV infection rates, because of the high prevalence and persistence of HSV-2. The 2011 conference also celebrated the substantial advances made in the use of antiretroviral drugs for prevention of HIV acquisition (eg, oral preexposure prophylaxis, topical microbicides) and transmission (eg, antiretroviral therapy). Further progress is also being made in evaluating other prevention strategies and their rollout, including male condoms, male circumcision, and HIV testing and linkage to care.

The US HIV Epidemic

Mermin provided an overview of the US epidemic and strategies for implementing high-impact prevention (Abstract 19). He reminded the audience of the substantial disparities in HIV infection, with new infections more than 40 times more likely to be in men who have sex with men (MSM) than in other men and women and more than 8 times more likely in blacks and 3 times more likely in Latinos than in whites. Tremendous strides have been made in prevention, with community-initiated behavior change leading to an 89% reduction in the transmission rate per 100 HIV-infected persons, thereby averting an estimated 350,000 new HIV infections since the beginning of the epidemic. Through expanded HIV testing, the proportion of people in the United States who have ever been tested for HIV has risen to 45%, and the proportion of persons with AIDS diagnosed within 12 months of their first HIV-seropositive test has dropped to 32%. However, given limited resources, Mermin called for targeted prevention strategies based on knowledge of effectiveness, cost, scalability, and coverage of affected populations.

Millett further explored the US epidemic in MSM, the only risk group in the United States in whom new infections continue to rise (Abstract 69). Modeling suggests that even if MSM and heterosexuals had similar numbers of sexual partners and rates of unprotected intercourse, incidence rates in MSM would be higher because of higher background prevalence rates, increased risk of anal versus vaginal sex, and role versatility in which many MSM serve both insertive and receptive roles, thereby accelerating transmission through partner networks.

MSM are disproportionately affected within all racial and ethnic groups, and young black and Latino MSM are at particularly high risk. In examining drivers of the epidemic in MSM, numerous studies have shown lower levels of reported sexual risk and drug use among black and Latino MSM than among white MSM. These racial and ethnic disparities may arise as a result of differences in background prevalence, patterns of intraracial mixing, prevalence of sexually transmitted infections, access to antiretroviral therapy, and rates of undiagnosed HIV infection, all of which may drive increased rates in black and Latino MSM.

Millett and colleagues also presented data from 1214 black and Latino MSM enrolled in the Brothers y Hermanos study in New York City, Philadelphia, and Los Angeles (Abstract 131LB). Overall, 12% were HIV-seropositive and unaware of their infection, with a higher rate among black than Latino men (18% vs 5%, respectively; \( P < .001 \)). Among both groups, having a low perceived risk of testing HIV-seropositive and endorsing the belief that having sex with men of the same race or ethnicity reduces the risk of HIV acquisition were independently associated with being HIV-seropositive and unaware. Among black MSM, having disclosed sexual identity to a health care practitioner, having health insurance, and having fewer than 3 lifetime HIV tests were also independently associated with HIV-seropositive–unaware status.

Millett pointed to the need to address the misperceived risk of HIV acquisition, including the risk associated with intraracial partnerships. He also highlighted the responsibility of practitioners to offer frequent HIV tests to MSM, as even black MSM who disclose their risk to health care practitioners and who have health insurance appear to be at elevated risk of HIV seropositivity. Millett also called for multilevel approaches to prevention and treatment for MSM, including those using...
individual-, interpersonal-, and structural-level interventions.

Heffelfinger and colleagues reported on recent HIV infections among MSM in 21 high-prevalence US cities enrolled in the 2008 National HIV Behavioral Surveillance System (NHBS) (Abstract 130). Of 6864 evaluable MSM, 4% had new infections, defined as having an HIV-seropositive test result with a reported last HIV-seronegative test result within the past 12 months. Independent risk factors for recent infection (compared with uninfected men) were younger than age 30 years; black, non-Hispanic race; Hispanic ethnicity; other nonwhite race or ethnicity; completing less than a high school education; having no insurance or public insurance; and having had 2 or more HIV tests in the prior 24 months. Risk practices were not statistically significantly associated with recent infection.

This report extends the data reported by Millett and colleagues about the independent association of sociodemographic variables with HIV acquisition risk, in the absence of reported differences in sexual practices or drug use. Heffelfinger suggested 3 possible explanations: (1) increased prevalence and sexual mixing patterns within subgroups; (2) differences in access to care among subgroups; and (3) differential underreporting of risk practices. Regardless of reason, successful, culturally appropriate interventions need to be developed and tested in high-incidence populations.

Oster and colleagues reported on a network analysis of 23 black men aged 17 years to 25 years newly diagnosed with HIV infection from 2006 to 2008 in Jackson, Mississippi (Abstract 1044). They found that all men were linked by few venues, suggesting that these venues should be targeted for testing and prevention intervention.

Seroadaptation

Several presentations focused on seroadaptation, the practice of altering sexual behavior based on self- and partner HIV serostatus. Truong and colleagues presented data from a study of seroadaptive behavior among 1207 men recruited from December 2007 to October 2008 in San Francisco (Abstract 133). Behavioral practices were evaluated at the individual, dyad, and episode levels, and were categorized into mutually exclusive practices based on highest to lowest HIV transmission risk. Seroadaptation was reported consistently by 39% of men, whereas only 25% reported 100% condom use, 14% no oral or anal sex, and 12% oral sex only. When the unit of evaluation was partnerships, 100% condom use was the most common practice (33%) compared with seroadaptation (26%). When the unit of evaluation was sexual episode, oral sex was the most common practice (65% of acts), and anal sex with a condom was next most common (16%). Overall, more than 90% of all individuals, dyads, and episodes used some form of safer sex or seroadaptation, suggesting that MSM use several strategies to manage their HIV risk.

Golden and colleagues presented data on the differential impact of serosorting by race among MSM in Seattle, Washington (Abstract 1037). In their study of 7620 white and black MSM who received HIV testing at a sexually transmitted diseases clinic in Seattle from 2006 to 2010, 266 participants received a new diagnosis of HIV infection. White and black MSM reported serosorting (unprotected anal sex only with partners of the same serostatus) at 30% and 28% of their clinic visits, respectively. Although serosorting was associated with lower HIV infection risk among white MSM (odds ratio [OR], 0.48; 95% confidence interval [CI], 0.35–0.66), there was no such protection among black MSM (OR, 1.04; 95% CI, 0.47–2.30; P value for interaction, .02). The reasons for these differences are not clear, as the mean time since the last HIV test was not different between newly diagnosed white and black men. A possible explanation is a higher rate of undiagnosed or undisclosed HIV infection among partners of black men.

Additional data on the possible contribution of sexual mixing patterns in transmission among MSM were presented from a study conducted in Canada. Brenner and colleagues reported on the spread of HIV among MSM in Montreal, Canada, from December 2005 to September 2009 (Abstract 1046). HIV sequence data were collected from surveillance of primary HIV-1 infections (PHIs) and divided into unique transmissions, small clusters (2–4 PHIs), and large clusters (5–31 PHIs). Large clusters of infection accounted for the fastest growing subepidemic, accounting for 25% of all transmissions in 2005 to 39% in 2009 (P < .001). The 34% of infections occurring from MSM born outside of Canada were predominantly unique transmission events. Given the unique sociodemographic and behavioral characteristics of these 3 different types of transmission groups, prevention strategies may need to be targeted differently to reach all 3 subpopulations of MSM contributing to this epidemic.

Population at High Risk of HIV-1 Acquisition

Youth

Pettifor reminded the audience that approximately half of all new HIV infections globally occur in persons younger than 25 years, with 35% occurring in 15- to 24-year-olds (Abstract 66). There are also marked sex disparities: young women have HIV infection rates 2 to 3 times those of men in sub-Saharan Africa, but HIV-infected men substantially outnumber HIV-infected women in the Americas and Europe, where the epidemic occurs predominantly in MSM. Many potential factors drive this epidemic in younger persons, including biological susceptibility, increased individual behavioral risk, as well as societal forces such as age and power inequities within relationships and poverty driving the need for transactional sex.

Pettifor focused on recent promising results from cash-transfer programs whereby families receive cash incentives either unconditionally or conditional upon some requirements (eg, girls must attend school). The
Schooling Income and HIV Risk (SIHR) Trial conducted in Malawi and reported at the 2010 International AIDS Society meeting in Vienna found that HIV prevalence was 60% lower in communities randomly assigned to the conditional and unconditional cash-transfer groups than in control communities. It appears that changes in individual risk behavior accounted for less than half of the beneficial effect; a possible mechanism was that girls in the intervention groups were less likely to have older male partners and less likely to receive cash from their male partners.

Ott and colleagues also presented data on age mixing in sexual relationships from a population-based surveillance study in rural KwaZulu-Natal, South Africa (Abstract 1030). In this community, casual relationships with “sugar daddies” (ie, men at least 10 years younger than their casual partners) are much less common than marriages in which the woman is substantially younger than the man, leading to an increased risk of HIV acquisition in young women.

Santelli and colleagues found demographic factors, risk practices, and sexually transmitted infections increased the rate of HIV acquisition among youth 15 years to 24 years of age enrolled in the Rakai Community Cohort Study (Abstract 690). Incidence in this group remained at 1% to 2% per year from 1999 to 2008. In multivariate analysis, independent risk factors for women and men were lower levels of education, increased numbers of sexual partners, being separated or divorced, and having sexually transmitted disease symptoms. Alcohol use was an independent risk factor for men, whereas for women, alcohol use by the last partner was an important risk factor.

**Women**

John-Stewart and colleagues reported on the peripartum risk of HIV acquisition and factors that drive increased HIV acquisition risk among pregnant women (Abstract 67). In combining a number of studies, they observed that HIV incidence in pregnant women in sub-Saharan Africa is high (4.3/100 women-years; 95% CI, 3.9–4.6). Data comparing the peripartum risk with risk in nonpregnant women suggest a modest increase in HIV acquisition risk (OR, 1.3; 95% CI, 0.96–1.6). Several factors may lead to this increase in HIV acquisition, including behavior change in male partners, or the biological features (hormonal, immunologic, and local genital tract changes) that occur in pregnancy. This is of concern for the women and their infants, as the risk of HIV transmission through breast milk is substantially elevated during the acute infection period. Moreover, if women are not aware of their HIV-seropositive status, they may also be less likely to receive antiretroviral therapy for prevention of mother-to-child transmission (PMTCT).

The authors stated that in the period before initiation of PMTCT programs in Zimbabwe, acute HIV infection accounted for only an estimated 6% of infant infections, whereas after PMTCT programs began, acute infection could account for 44% of new infections in infants. John-Stewart outlined potential behavioral and biomedical prevention strategies to prevent peripartum infections that include recognizing the desire for pregnancy among many women and studying the safety and efficacy of prevention strategies in the peripartum period.

Meditz and colleagues explored immunologic reasons for an increasing rate of infections in women aged 40 years of age or older (Abstract 33). They reported that 24 postmenopausal women had higher CC chemo-kine receptor 5 (CCR5) expression on CD4+ cells and a higher proportion of activated CD4+ cells in the peripheral blood and the cervix than did 21 premenopausal women. This disparity may provide some explanation for increased susceptibility in these women.

**Men Who Have Sex With Men**

Beyrer described the current state of knowledge of the global epidemic in MSM and provided modeling for how increased prevention and treatment could substantially alter the overall HIV epidemic (Abstract 68). In a comprehensive review of global prevalence data in MSM, Beyrer split countries into 4 scenarios: (1) countries where the epidemic predominantly affects MSM (much of the Americas, Ghana); (2) epidemics driven by injection drug users (Eastern Europe and Central Asia); (3) countries with a generalized heterosexual epidemic (much of sub-Saharan Africa); and (4) countries with a mixed epidemic in MSM, IDU, and heterosexuals (South and Southeast Asia, Senegal, Egypt). Unfortunately, there are 94 countries for which there are no data for MSM available, including three-fourths of African countries. Of note, HIV prevalence is high in MSM in all 4 scenarios.

In sub-Saharan Africa, prevalence in MSM exceeds that in heterosexual men in all countries and exceeds prevalence in women in all countries except South Africa, Botswana, and Namibia. In modeling the impact of increasing prevention and treatment for MSM (condom and lubricant availability, community-based prevention programs, and antiretroviral therapy availability for HIV-infected MSM), Beyrer showed that such programs would have a substantial impact in countries in all 4 types of scenarios, enhanced by drug treatment for IDUs in scenarios 2 and 4. He ended with a tribute to David Kato, the Ugandan activist recently murdered for his work on human rights for MSM. Beyrer reminded the audience that improving access to prevention and treatment and addressing human rights issues are central to the HIV practitioner community’s ability to impact the global HIV epidemic.

New data were presented on MSM in Kenya and Thailand as well. Sanders and colleagues reported that HIV-1 incidence was 6.5 per 100 person-years among 666 men with various sex partners or recent sex (within 3 months of screening) at a clinic in coastal Kenya (Abstract 1042). Incidence was highest among men reporting sex with men only (21.7/100 person-years; 95% CI, 15.9–29.5), intermediate in men who reported sex with men and women (4.9/100 person-years;
Serodiscordant Couples

Transmission between partners in stable serodiscordant relationships may account for a substantial proportion of new HIV infections globally. Ndase and colleagues point out that interventions for serodiscordant couples also need to take into account the possibility of outside partnerships (Abstract 1040). In their study of 3380 HIV-1 serodiscordant couples observed over a minimum of 24 months, there was a statistically significant decline in the proportion of couples who engaged in sexual activity (from 94% at enrollment to 73% at 24 months; \( P < .001 \)) and an increase in the proportion of HIV-infected persons having an outside partner (from 3% to 14%, respectively; \( P < .001 \)). The rate of outside partnerships is likely higher than reported, as 22% of seroconverting participants who reported no outside partners were infected with genetically distinct viruses from their seropositive main partner. This proportion was substantially higher among seroconverting participants who did report outside partnerships (86%; \( P < .001 \)).

Ngolobe reported on 444 serodiscordant couples in Uganda (Abstract 1041). On multivariate analysis, condom use was not associated with antiretroviral drug use (adjusted odds ratio [AOR], 1.26; 95% CI, 0.81–1.96), suggesting no risk compensation associated with treatment. However, condom use at last sex was inversely associated with male-controlled sexual decision making (AOR, 0.49; 95% CI, 0.32–0.77), reminding practitioners of the challenges of condom acceptability among men.

Hughes and colleagues studied a cohort of 3297 serodiscordant couples to probe factors affecting the per-act infectivity of HIV-1 (Abstract 135). They observed a 2.9-fold increase in infectivity per 1 log_{10} increase in plasma viral load in the infected partner. Differences in male-to-female and female-to-male transmission rate were driven by the plasma viral load in the HIV-infected partner, herpes simplex virus type 2 (HSV-2) serostatus, and the age of the HIV-uninfected partner.

Baeten and colleagues evaluated the association of genital tract HIV-1 RNA levels with the risk of HIV transmission in the same cohort of serodiscordant couples (Abstract 154). They reported that genital tract HIV-1 RNA level was independently associated with HIV-1 transmission risk after adjusting for plasma HIV-1 RNA levels. A total of 11 transmissions occurred in couples with very low or undetectable genital HIV-1 RNA, but all had detectable plasma HIV-1 RNA.

Herpes Simplex Virus Type 2

HSV-2 causes genital ulcers and has previously been associated with an increased rate of HIV acquisition among heterosexual men and women as well as MSM. McClellan and colleagues reported that HSV-2 prevalence and incidence were substantially higher among women than men enrolled in a cohort study of 5543 Zimbabwians (Abstract 1028). Prevalent HSV-2 infection more than doubled the odds of acquiring HIV-1 infection in men and women in the study. Hughes and colleagues also found a doubling of HIV-1 acquisition risk among HSV-2-seropositive men and women in 3297 heterosexual HIV-1–serodiscordant couples in Africa (Abstract 135).

Okuku and colleagues evaluated risk factors for HSV-2 acquisition in a cohort study in Kenya (Abstract 29). Among 443 men, HSV-2 incidence was 9.0 per 100 person-years and was associated with incident HIV-1 infection (adjusted incidence rate ratio [aIRR], 3.9; 95% CI, 1.3–12.4). Among 164 women, HSV-2 incidence was 22.1 per 100 person-years (\( P < .001 \)) and was associated with incident HIV-1 infection (aIRR, 8.9; 95% CI, 3.6–21.8). Interestingly, genital washing with soap was protective against HSV-2 acquisition in men (aIRR, 0.3; 95% CI, 0.1–0.8), but vaginal washing with soap increased the risk of HSV-2 acquisition in women (aIRR, 1.9; 95% CI, 1.0–3.4).

Tenofovir gel halved the risk of HSV-2 acquisition in the CAPRISA (Center for the AIDS Programme of Research in South Africa) 004 study.2 Lama and colleagues presented data from the iPrEx (Chemoprophylaxis for HIV Prevention in Men) trial of 2499 MSM, half of whom were assigned to receive oral tenofovir/emtricitabine and half placebo (Abstract 1002). In this study, HSV-2 incidence was similar among those assigned to the active study drug and those assigned to placebo (6.2 vs 5.8 per 100 person-years, respectively). There was no difference in the proportion of genital ulcers in the 2 groups, although there was a reduction in participants with anal ulcers (relative risk [RR], 0.4 vs placebo; 95% CI, 0.22–0.85) and a trend toward a reduction in herpes genital ulcer–defined adverse events of grade 2 or higher (13 in the treatment group vs 24 in the placebo group; \( P = .06 \)).

Tan and colleagues reported no decrease in HSV-1 or HSV-2 shedding from oral, genital, or anal mucosa among 40 HIV-infected patients taking oral tenofovir compared with those not receiving tenofovir (Abstract 979). These data suggest that higher levels of tenofovir at mucosal surfaces may be required to reduce the risk of HSV acquisition and viral shedding among those already HSV-infected.

HIV Testing Strategies

HIV testing among at-risk persons remains suboptimal globally, as does knowledge of HIV serostatus. Oster and colleagues reported on adherence to HIV testing guidelines among 7271 MSM participating in the 2008 NHBS (Abstract 1048). Older men were less...
likely than younger men to have been tested in the previous year, and there were no differences in testing rates by race or ethnicity. However, among men reporting an HIV test within the prior year, the proportion testing newly positive was 14% for blacks, 7% for Hispanics, and 3% for whites. Of the 5864 (81%) of the sample reporting 1 or more high-risk characteristics for whom testing is recommended at least every 6 months, only 44% reported receiving an HIV test in the past 6 months. This suggests the need for both better adherence to testing guidelines and guidelines targeted for highest incidence populations. Calderon and colleagues reported on a novel community pharmacy–based HIV testing and counseling program in New York City (Abstract 1052). Nearly three-fourths of eligible patients offered HIV testing accepted.

Delaney and colleagues presented data from a randomized trial of a rapid HIV testing algorithm (RTA), in which the second rapid test was used to confirm an initial positive rapid test result (Abstract 132LB). This approach was compared with standard HIV testing: one rapid test followed by off-site confirmatory laboratory testing. An RTA was implemented at 9 testing sites in Los Angeles and San Francisco to evaluate the impact on referral to health care practitioners and on CD4+ cell counts or viral load within 90 days of the initial positive rapid test, as compared with standard testing at 23 control sites.

The positive predictive value of the RTA was 100% and of the initial rapid test using a standard algorithm was 86%. All persons receiving the RTA received referrals to medical care, whereas only 47% of those with a positive rapid test result who received standard testing (requiring that they return for their confirmatory test results) actually returned for care. Overall, two-thirds of participants referred to care received a CD4+ cell count or viral load test within 90 days of their initial test (regardless of whether they were referred from the intervention or control groups), whereas only half of those not receiving a referral received this clinical testing within 90 days (P < .001). Both Los Angeles and San Francisco Public Health Departments plan to use an RTA at all of their test sites by July 2011.

Choko and colleagues reported on the first evaluation of self-testing in Africa using an oral HIV test kit (Abstract 42). Four geographic areas in Blantyre, Malawi, were selected for participation, and 92% of participants opted for self-testing over clinic-based or no HIV testing. Sensitivity and specificity were excellent (97.9% and 100%, respectively), and overall, 99.2% of self-test users read an accurate result on their first try. However, 10% of participants needed help beyond the initial instructions. 10% made some type of error in preparing the test, and more than half stated that they thought that some type of additional counseling was needed with HIV testing. Overall, 99% stated that they would be likely to self-test again, and self-testing was the most common choice for the next test that participants would like to take.

The same test was evaluated for 987 participants in Singapore (Abstract 1075). Among HIV–seronegative, at-risk participants, sensitivity and specificity of self-testing was 100%. As reported in the previous abstract, participants responded favorably to the testing (eg, 89% liked the privacy of testing, and 96% found the instructions easy to follow), but nearly three-fourths felt the need for confidential pre- and posttest counseling. This suggests that self-testing may increase the uptake of testing in various populations but that accommodations should be made to provide additional counseling, as needed.

HIV Prevention Strategies

Conference presentations on HIV vaccine development are reviewed by Watkins elsewhere in this issue (see pages 36–37).

Condoms

Hughes and colleagues reported data on determinants of per-contact HIV-1 infectivity among serodiscordant couples (Abstract 135). Self-reported condom use reduced risk by 78% (95% CI, 58%–89%). Bachanas and colleagues reported on condom use by 3538 HIV-seropositive patients attending clinics in Kenya, Namibia, and Tanzania (Abstract 136). Overall, 54% of participants had an HIV-seronegative partner or a partner of unknown serostatus. Inconsistent condom use was statistically significantly associated with being female, desiring pregnancy, being a spouse (compared with casual and steady, nonmarital partners), and not taking antiretroviral therapy.

Male Circumcision

Kong and colleagues reported on long-term effects of male circumcision in Rakai, Uganda (Abstract 36). Overall, 80% of control subjects returning for a visit chose male circumcision. Overall, 80% of control subjects returning for a visit chose male circumcision. Over- all efficacy remains high through 4.8 years of follow-up (adjusted effectiveness, 73%; 95% CI, 55%–84%). Risk behavior increased comparably in both circumcised and uncircumcised men, suggesting that risk compensation has not been observed in this setting. Tobian and colleagues reported that male circumcision does not decrease human papillomavirus (HPV) transmission from HIV-seropositive men to their female partners (Abstract 1008). Several other abstracts focused on strategies for scale-up of male circumcision services (Abstracts 1005–1007).

Preexposure Prophylaxis

Efficacy, adherence, safety, and resistance. This year, 1 plenary (Session 35) and 2 oral abstract sessions (Sessions 8 and 25) focused on the strategy of using topical or oral antiretroviral drugs to prevent HIV acquisition, that is, preexposure prophylaxis (PrEP). Cellmi provided a framework for thinking about how and when antiretroviral drugs are used for prevention: drugs initiated before exposure (PrEP), drugs used for postexposure prophylaxis (PEP), and those used as therapy after infection (Abstract 120).

Grant and colleagues presented updated data from the iPrEx trial, a random-
daily tenofovir/emtricitabine in 2499 MSM and transgender women in North and South America, Africa, and Asia (Abstract 92). Extending data from the published interim analysis censored on May 1, 2010, Grant and colleagues presented safety and efficacy data through August 2010, including HIV seroconversions occurring by 8 weeks after the study drug was discontinued. There were 37 additional HIV infections since the interim analysis, but overall efficacy remained largely unchanged (modified intention-to-treat analysis; efficacy, 42%; 95% CI, 18%–60%). These efficacy analyses did not vary by age, race, education, or geographic location.

In exploratory analyses, efficacy was somewhat lower in uncircumcised men (efficacy, 36% vs 83%, respectively; \( P = .10 \)) and lower among men not reporting unprotected receptive anal sex at baseline than among men who did report this risk (efficacy, −25% vs 52%, respectively; \( P = .03 \)). These estimates are not adjusted for other potentially confounding variables but raise the possibility of differential PrEP efficacy by route of exposure. Efficacy data from heterosexual men and women and IDUs should be available in the next few years (see Global Advocacy for HIV Prevention Web site, http://www.avac.org).

Grant and colleagues also presented data demonstrating that efficacy was highest among those reporting taking their study drug more than 90% of the time, intermediate in those reporting 50% to 90% adherence, and lowest in those reporting taking less than half (efficacy estimates, 68%, 34%, and 16%, respectively). Anderson and colleagues reported on drug levels among a subset of 179 iPrEx trial participants in the active study drug group at the 24-week study visit (Abstract 96LB). Overall, 50% had detectable metabolites of tenofovir and emtricitabine in their peripheral blood mononuclear cells (PBMCs), indicating no study drug had been taken for at least 1 week to 2 weeks before the visit. Participants 25 years or older were more likely to have detectable drug than younger participants (73% vs 44%, respectively; \( P < .001 \)). Drug was most commonly detected in men reporting unprotected receptive anal sex, less common in sexually active men without this risk, and least common in men reporting no sexual activity in the prior 12 weeks (in 76%, 59%, and 35%, respectively; \( P = .003 \)), suggesting that men may have used sexual risk to determine whether or not to take the study drug.

Celedon reviewed data from the IAVI (International AIDS Vaccine Initiative) E001 and E002 studies and reminded attendees that adherence by electronic measurement of opening pill bottles was highest with daily dosing; intermediate with fixed-dose, twice-weekly dosing; and lowest for fixed-dose plus postcoital dosing (Abstract 120). There also appears to be substantial heterogeneity between populations, with adherence higher among 34 US iPrEx study participants than among 145 non-US iPrEx study participants (\( P < .0001 \) (Abstract 96LB). In an adherence substudy from the Partners PrEP efficacy trial in Uganda, median adherence as measured by pill count and unannounced home visits was greater than 99% (Abstract 488).

Amico and colleagues reported on the correlation of self-report, pill count, drug dispensation records, and blood detection of study drug among the same 179 iPrEx study participants included in Anderson’s presentation (Abstract 95LB). Men had a median self-reported adherence level of 100% by each of 4 measures, despite no detectable study drug in half of the samples tested. Even among men self-reporting never missing a pill in the prior month, study drug was detectable in only 68%. On the other hand, reports of low levels of adherence (less than half of pills taken) were uncommon (2%), but in this group, study drug was substantially less likely to be detected (22%).

Clearly, better measures of adherence than self-reporting and pill counts are needed. Liu and colleagues reported on drug levels present in hair samples among 15 HIV-uninfected persons taking tenofovir for 2, 4, or 7 days per week under modified directly observed dosing, in a cross-over study design (Abstract 995). Tenofovir levels in scalp hair were strongly correlated with dose, suggesting that this may be a useful strategy for monitoring adherence in clinical trials.

Concerns have been raised about whether tenofovir-based regimens would be associated with an unacceptable rate of adverse events (AEs) in an otherwise healthy population. Grant and colleagues reported that participants randomly assigned to take tenofovir/emtricitabine in the iPrEx trial had no higher rate of serious, grade 3, or grade 4 AEs than did placebo participants (Abstract 92). The only symptoms reported more commonly in participants in the active study group than in the placebo recipients were nausea (2% vs <1%, respectively; \( P = .04 \)) and weight loss (2% vs 1%, respectively; \( P = .04 \)). Participants given tenofovir/emtricitabine were somewhat more likely to have elevated creatinine levels (2% vs 1%, respectively; \( P = .08 \)), although only 5 participants in the tenofovir/emtricitabine group had elevated creatinine levels lasting for 2 or more visits. All creatinine elevations resolved after drug discontinuation; 4 of the participants restarted the study drug and exhibited no recurrence of creatinine elevation.

Mulligan and colleagues reported on bone mineral density (BMD) among a subset of 503 iPrEx trial participants on 4 continents (Abstract 94LB). At baseline, before initiation of the study drug, BMD was low (ie, z score, < −1.0) in 36% of participants in the spine and in 18% in the hip. There were small but statistically significant decreases in BMD in participants receiving tenofovir/emtricitabine compared with those receiving placebo for the total hip (−0.65 at 24 weeks; −0.95 at 48 weeks) and spine (−0.95 at 24 weeks), although no difference was observed between the groups in bone fractures or international standards for low BMD (z score, < −2.0).

Liu and colleagues also reported on BMD changes in a group of 200 HIV-seronegative men in San Francisco enrolled in a phase II tenofovir PrEP study (Abstract 93). They reported that 10% of men had low BMD at baseline.
Drug resistance is another concern that has been raised about the use of PrEP. Grant and colleagues reported no additional cases of drug resistance in the iPrEx study; the only cases previously reported consisted of 3 participants who were already HIV-infected at enrollment (Abstract 92). Liegler and colleagues searched for minor variant drug resistance among iPrEx trial participants and found 1 K65R minor variant and 1 M184V minor variant in 2 placebo recipients (Abstract 97LB). No minor variants were found among participants given active drug, including the 3 participants with breakthrough infections, in whom low levels of study drug were detected at the first-infection time point. Levels of drug-resistant virus in the 2 participants HIV-infected at baseline who received study drug declined to below the lower limit of detection (< 0.5%) through week 40 of follow-up, suggesting that drug-resistant virus, when it emerges, may revert quickly to wild type.

García-Lerma presented data on the efficacy of oral tenofovir/emtricitabine against an emtricitabine-resistant simian-HIV (SHIV) variant (Cong et al, Abstract 31). In this study, all 5 animals treated with twice-weekly oral tenofovir/emtricitabine (3 days before and 2 hours after challenge) were protected against 14 weekly, low-dose, rectal challenges with SHIV162p3M184V. All 5 control animals became infected (P = .0008). This suggests that oral PrEP may protect against some resistant viral strains.

Drug penetration into genital tissue.

Celum reminded attendees that the effectiveness of PrEP will depend on “getting the right drug to the right place at the right time” (Abstract 120). Several presentations focused on the timing and levels of drug penetration into genital tissues. Dobard and colleagues presented in vitro data suggesting that tenofovir/emtricitabine provides protection only 2 hours after challenge, whereas raltegravir provides protection up to 8 hours to 10 hours after challenge (Abstract 30). In a low-dose, twice-weekly, vaginal-challenge model, 1% raltegravir gel administered 3 hours after challenge protected 5 of 6 macaques through 20 challenges. All 4 control animals became infected. This suggests that integrase inhibitors may be particularly useful as PEP drugs.

Brown and colleagues reported on concentrations of darunavir, ritonavir, and etravirine in seminal plasma and rectal tissue of 12 HIV-seropositive men, to consider these drugs’ utility for PrEP in HIV-uninfected persons (Abstract 992). Seminal plasma levels were 80% to 93% lower than blood plasma levels for the 3 drugs, and rectal tissue levels were 3 to 13 times higher, perhaps reflecting fecal elimination of these drugs.

Nel and colleagues presented pharmacokinetic and safety data on the investigational dapivirine vaginal ring in 48 women (Abstract 1001). The ring was well tolerated and was not associated with serious AEs. Drug concentrations remained high through 35 days of use. Celum reported on plans to conduct an efficacy trial of the dapivirine ring (Abstract 120).

Singer and colleagues reported on the ethylene-vinyl acetate (EVA) ring containing 100 mg of the investigational nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) MIV-150 in a macaque high-dose, vaginal-challenge model (Abstract 1003). Only 2 of 14 animals with the MIV-150 ring became infected compared with 3 of 4 control animals (14% vs 75%, respectively; P = .04). Silicone vaginal rings tested without study drug were reported to be safe and well tolerated among 169 women in South Africa and Tanzania (Abstract 1004).

Hendrix and colleagues reported on the relative safety, adherence, and acceptability of oral versus vaginal tenofovir (Abstract 35LB). In total, 144 women were enrolled at 4 US and 3 African sites and assigned to receive sequential 6-week periods of vaginal, oral, or both formulations. Although relatively infrequent, women reported substantially more nausea, diarrhea, and headache during periods when they were taking tenofovir orally. Self-reported adherence was high, but drug was detected in only 35% to 65% of samples, with no difference between study groups. Tissue levels observed with vaginal dosing were more than 100 times higher than with oral dosing; addition of oral dosing did not further raise tissue levels. US women preferred the oral formulation, whereas African women were evenly divided between preference for oral and vaginal use.

Rectal delivery of pre- and postexposure prophylaxis. Anton and colleagues reported on the safety and acceptability of this 1% tenofovir gel used rectally among 18 men and women. This hyperosmolar gel was neither well tolerated (ie, many reported lower-gastrointestinal AEs) nor highly acceptable (ie, only 25% of participants liked the gel) (Abstract 34LB). However, a single rectal dose resulted in 100 times the rectal tissue concentration of tenofovir compared with a single oral dose.

Dezzutti and colleagues presented data on a reformulated tenofovir gel prepared for rectal use (Abstract 983). The reformulated gel had lower osmolality, increased spreadability, enhanced transepithelial resistance, and elimination of the epithelial stripping of the colorectal implants that was observed with tenofovir gel. The anti-HIV activity was similar between gels, suggesting that the reformulated gel may be a useful rectal microbicide.
Levy and colleagues evaluated 3 enemas of varying osmolality in 9 men (Abstract 993). Hyperosmolar enemas (sodium phosphate) caused the most epithelial disruption in the colorectum. Hypoosmolar enemas (distilled water) had the greatest colonic permeability. Isoosmolar enemas had the best colonic distribution and retention and were the most preferred by participants, suggesting that if larger quantities of rectal microbicides are required, isoosmolar enemas may be explored as a vehicle for microbicide delivery.

Models and surveys on preexposure prophylaxis. Abbas and colleagues (Abstract 98LB) and Hallett and colleagues (Abstract 99LB) modeled the relative benefits and risks of using only antiretroviral therapy for HIV-infected persons versus combining antiretroviral therapy with PrEP for HIV-uninfected persons; the models examined effects on the HIV epidemic in South Africa and among serodiscordant couples, respectively. In Abbas and colleagues’ model, the use of both antiretroviral therapy and PrEP in a community led to a larger prevention impact on the epidemic than either alone. Antiretroviral therapy is predicted to contribute substantially more HIV resistance at a community level than PrEP, although inadvertent PrEP use among HIV-infected persons would also contribute to cases of resistance.

Hallett and colleagues posed the question of whether it would be more cost-effective in preventing HIV transmission to provide PrEP to the HIV-uninfected partner or antiretroviral therapy earlier to the HIV-seropositive partner. Assuming all HIV-seropositive partners are treated when CD4+ cell count falls below 200/µL, PrEP again becomes more cost-effective at lower thresholds of effectiveness because of the lower possibility of transmission from partners with CD4+ cell counts above 350/µL.

Park presented an evaluation of the cost-effectiveness of PrEP in South African women (Walen skewy et al, Abstract 37LB). At the efficacy ranges observed in the CAPRISA 004 and iPrEx trials, they report that PrEP would be cost-effective ($4600/year of life saved). If PrEP could be targeted to women at very high risk (ie, incidence >9%/year), be very effective (ie, >70%), and cost less than $40 per year, PrEP could be cost-saving for South African women.

Mayer and colleagues examined practitioner preferences for oral versus topical PrEP (Abstract 1000). More than two-thirds of the 121 physicians in Massachusetts completing the survey preferred topical PrEP, because of perceptions of fewer AEs (93%), increased ease of use (66%), and common use of lubricants for sex (54%). Nearly all (97%) stated that the major factor influencing their prescribing PrEP would be formal guidelines from the US Centers for Disease Control and Prevention (CDC).

Treatment as Prevention

One themed discussion session (Session 42) and several additional posters addressed how summary measures of viral load within communities (community viral load, CVL) are related to HIV infection rates and provision of care in different US cities. Das and colleagues reported that progress has been made in San Francisco in mean CD4+ cell count at diagnosis, rates of antiretroviral therapy initiation, and time to virologic suppression (Abstract 1022). In particular, time from diagnosis of HIV infection to virologic suppression decreased substantially from 32 months in 2004 to 8 months in 2008 (P<.001). Decreases in CVL also correlated with decreases in newly diagnosed and reported HIV cases (P<.001).

Similarly, HIV incidence decline correlated temporally with a reduction in CVL among a cohort of IDUs in Baltimore (Abstract 484). Castel and colleagues reported on CVL as a population-based biomarker of HIV transmission in Washington, DC, from 2004 to 2008 (Abstract 1023). Although only half of the more than 15,000 HIV cases diagnosed during that time had a viral load measurement available, mean CVL decreased substantially over that time. CVL was highest in geographic areas with the highest levels of poverty and unemployment and the lowest proportion of high school graduates. The mean of the most recent viral load was highest among women, blacks, and those infected heterosexually, through IDU or “other” modes of transmission.

Laraque and colleagues also showed disparities in CVL in New York City, with higher viral loads observed in men, young and middle-aged adults, MSM, persons with AIDS or low CD4+ cell counts, persons with more recently diagnosed cases, and persons in specific neighborhoods (Abstract 1024). Terzian and colleagues also reported on CVL in New York City to monitor the effectiveness of care (Abstract 1025). Most HIV-seropositive persons had repeated viral load testing, suggesting they were receiving ongoing clinical care. Although nearly half had fully suppressed viral load over the prior year, a small proportion had sustained high viral load, and these persons were more likely to be younger, black, or female.

Several models suggest that although treatment is likely to have a beneficial effect on HIV transmission rates, prevention interventions must also be used to change the course of the current HIV epidemic. Prabhu and colleagues used data from South Africa, Kenya, Malawi, and Mozambique to project the proportion of new infections attributable to different stages of HIV infections (Abstract 482). Less than 10% of new infections are attributable to untreated HIV infection, whereas two-thirds to three-fourths of new infections are associated with chronic, undiagnosed infection, and one-fifth to one-fourth are attributable to acute infection. This would suggest that substantial effort should be focused on increasing HIV
testing uptake, particularly for those with established infection.

Van Sighem and colleagues used a mathematical model to evaluate the impact of various interventions on the annual number of new infections in MSM in the Netherlands (Abstract 483). Although immediate treatment for all HIV-infected persons would lead to a rapid decrease in HIV infection rates, this decline would not be sustained. Decreasing risk practices and reducing the time from infection to diagnosis (leading to a decrease in risk behaviors) are needed to fundamentally alter the trajectory of new HIV infections.

Bongaarts presented models from a 2010 Institute of Medicine report (Bongaarts and Pelletier, Abstract 173). In projecting the future of the African epidemic, increasing rates of treatment would slow the rates of new infections and AIDS deaths but increase costs over time. Only by adding prevention to treatment would new infections and AIDS deaths decline and costs decline over time. This led to the conclusions from this report that “treatment costs...are unsustainable” and “greater emphasis must be placed on prevention of new infections.”

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A list of all cited abstracts appears on pages 99–106.

References


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** Diagnosis and Treatment Options for Acute HIV Infection
Elizabeth Reddy, MD, and Charles B. Hicks, MD
CME Credit Available: 1.75 AMA PRA Category 1 Credits™
Level: Advanced

“Acute” HIV infection generally refers to the phase of rapidly evolving HIV antibody test results when viral replication is at its peak. “Primary” HIV infection often refers to the entire period from transmission through the first year of infection. Despite its perceived importance, diagnosing primary or acute HIV infection remains challenging for many reasons. Health care practitioners who are likely to come in contact with newly infected persons should be versed in recommendations and options for diagnosis and treatment. This COW presentation discusses important concepts in the diagnosis of and treatment options for acute HIV infection.

**NEW** Dermatologic Complications of HIV Infection
Jennifer Cafardi, MD, and John Cafardi, MD
CME Credit Available: 2.5 AMA PRA Category 1 Credits™
Level: Advanced

A variety of common skin conditions often develop in HIV-infected patients that may be difficult to treat and may provide clues to the patients’ underlying immune status. Three major categories of skin conditions are observed: dermatoses specific to HIV infection, common dermatoses that occur with greater frequency in HIV infection and AIDS, and less common conditions that have been reported in association with HIV. This COW presentation discusses a selection of some common and some serious cutaneous diseases and the options for treating them.

**HIV and Hepatitis B Virus Coinfection**
Elizabeth Reddy, MD, and Susanna Naggie, MD
CME Credit Available: 1.75 AMA PRA Category 1 Credits™
Level: Advanced

Hepatitis B virus (HBV) infection rates are higher among HIV-infected persons than in the general population, owing to common modes of transmission and a decreased likelihood that the HBV infection will clear. In addition, HIV/HBV-coinfected persons are more susceptible to liver disease and related mortality than monoinfected persons. This COW presentation discusses risks of acquiring HBV infection, means of prevention, and treatment options for coinfected persons.

**Treatment of Opioid Dependence in Patients with HIV/AIDS**
Hillary Kunins, MD, MPH, MS, and Chinazo Cunningham, MD, MS
CME Credit Available: 1.75 AMA PRA Category 1 Credits™
Level: Advanced

HIV-infected patients with opioid dependence can now receive buprenorphine treatment in HIV care, primary care, or substance abuse treatment settings. Offering colocated treatment provides the opportunity to improve HIV outcomes and to reduce substance use among patients. This COW presentation discusses the use of opioid agonist medications and explains specific pharmacotherapeutic properties of buprenorphine that can pose challenges in clinical practice.

**Human Papillomavirus Infection in the HIV-Infected Woman**
Erna Milunka Kojic, MD, and Susan Cu-Uvin, MD
CME Credit Available: 1.75 AMA PRA Category 1 Credits™
Level: Advanced

The widespread use of potent antiretroviral therapy has resulted in dramatic improvements in life expectancy among HIV-infected women, but the incidence of human papillomavirus (HPV)-related diseases remains high and continues to rise. This COW presentation discusses the epidemiology of HPV among HIV-infected women, explains the effect of antiretroviral therapy on HPV-related anogenital diseases, and reviews the use of the prophylactic HPV vaccine.

**Management of Depression and Alcohol Dependence in an HIV/HCV Coinfected Patient**
Gareen Hamalian, MD, MPH, and Joseph Z. Lux, MD
CME Credit Available: 1.5 AMA PRA Category 1 Credits™
Level: Advanced

Treatment of psychiatric illness in HIV-infected patients, especially when this illness is accompanied by substance abuse, is a common and complex concern for HIV health care providers. On completion of this COW activity, the learner will be able to compare psychopharmacologic treatment options for depressed HIV-infected patients, discuss neuropsychiatric concerns related to the use of efavirenz, and discuss prophylaxis and treatment options for HIV/hepatitis C virus coinfected patients on interferon alfa therapy.

**CREDITS**

These enduring-material activities have been approved for AMA PRA Category 1 Credit™.
Central Nervous System Complications of HIV Infection

Serena S. Spudich, MD, and Beau M. Ances, MD, PhD

Issues relevant to the nervous system garnered substantial attention at the 18th Conference on Retroviruses and Opportunistic Infections. Several topics emerged as areas of importance both for informing current understanding of HIV-related neurologic disorders and their treatment, and for spurring future investigations. Measurable biomarkers of HIV-associated neurocognitive disorder (HAND) were a major theme, with studies ranging from new investigations of known laboratory and imaging markers to identification of novel molecules that might be investigated as potential means to follow disease activity as well as to better understand etiology of disease. Studies of pathogenesis of HAND and simian immunodeficiency virus–mediated neurologic injury added to prior understanding of lentivirus neuropathogenesis. Another broad area of investigation was the interplay between treatment with antiretroviral or adjunctive therapies and biomarkers of HAND. New data were presented on the potential importance of acute and early infection on the integrity of the central nervous system, complemented by studies of the effects of early treatment interventions.

Introduction—What’s in a Name?

Several recent studies indicate that HIV-associated neurocognitive disorder (HAND) persists in patients taking potent antiretroviral therapy, with a prevalence that ranges from 39% to 52% in varied settings.1,2 HAND is a potentially multifactorial condition defined by a combination of the patient’s reported symptoms and measured abnormalities on neuropsychologic (NP) test performance. Unlike other dementias, the diagnosis of HAND does not formally include additional biomarkers (either from the cerebrospinal fluid [CSF] or through neuroimaging).

In the current treatment era, HAND represents a broader spectrum of disease than that underlying the classic AIDS dementia complex (ADC) described in the era before potent antiretroviral treatment was widely available, perhaps with a greater heterogeneity in presentation, and importantly, etiology. Predominantly characterized by mild forms of disease that may either be perceived by patients (mild neurocognitive disorder, or MND) or recognized only through NP testing (asymptomatic neurocognitive impairment, or ANI), HAND is frequently detected in patients receiving antiretroviral treatment. Even HIV-associated dementia (HAD), which overlaps in clinical presentation considerably with severe forms of ADC as described in the past, includes a spectrum of disease from inactive to active and may reflect neuropathologic events within the central nervous system (CNS) distinct from those associated with dementia that occurs solely in the absence of antiretroviral therapy.

Patients now assessed as having HAND likely have a complex interplay of factors affecting their neurologic status. Current HIV-1 infection and attendant immune activation within the CNS may be important. Past events (eg, CD4+ cell count nadir, prior exposure to neurotoxic antiretroviral drugs or drugs subject to abuse) may have increasing impact on a patient’s current status as individuals with HIV survive longer and have more time for such effects to accumulate. With longer-term survival of HIV-1-infected individuals, HAND is also perhaps influenced by distinct factors in the current era such as cerebrovascular disease, abnormal glucose metabolism, prolonged exposure to therapeutic drugs including psychiatric medications and antiretroviral drugs, and natural neurodegeneration occurring with aging. Thus, in review of the data presented at the 2011 Conference on Retroviruses and Opportunistic Infections (CROI), it continues to be important to keep in mind the complex features that likely underlie HAND, the subject population examined in each study, and how HAND was assessed in each analysis.

Studies of animal models continue to provide a more controlled setting in which to investigate the direct effects of lentiviruses in the nervous system, and many important studies reported at CROI 2011 employed such models to inform an understanding of human disease. Future studies need to address rigorous characterization of subject populations, comorbid factors that may affect results, and detailed understanding and integration of systemic parameters into study analyses. Such definitions will allow the effects of HIV-1 in the CNS to be understood for patients in a variety of circumstances, including those with optimal viral suppression with treatment, virologic failure during treatment, treatment complicated by comorbidities such as mental illness and substance dependence, and delayed therapy resulting from limited access to treatment.

New Biomarkers of HIV-Associated Neurocognitive Disorder

Numerous studies presented at the conference sought to identify and validate new biomarkers of HAND. Some aimed to judge the relevance to the nervous system of biomarkers from blood or other clinical sources that are known to be important in systemic HIV progression. Others investigated biomarkers considered specifically relevant to the CNS, assessing their role...
in or association with the presence of HAND. A few studies employed means to generate new candidates for biomarkers relevant to the presence or prediction of CNS disease in lentiviral infection in primates. Although the following reports focused on identification of biomarkers, many studies investigating pathogenesis of HIV in the nervous system and effects of treatment in the CNS employed neurologic biomarkers as endpoints or further examined the mechanisms of such markers in producing HAND, indicating the central importance of such markers in the investigation and management of the neurologic complications of HIV.

**New Insights Into Recognized Biomarkers**

**Detection and measurement of HIV-1 RNA.** In the early epidemic, measurable levels of HIV-1 RNA within the CNS were ubiquitous in patients with classic HAD. Although presence of CSF HIV-1 RNA was not specific to dementia, and levels of HIV-1 RNA did not consistently associate with severity of disease, declines in HIV-1 RNA level could be observed with the initiation of therapy, and these changes correlated with improvements in neurologic performance. In the current era,HAND can be detected in patients whose treatment successfully suppresses plasma and CSF HIV-1 RNA levels to those below the level of detection by standard assays (<50 copies/mL), rendering assessment of the “activity” of HIV infection in the context of neurologic disease difficult. A major question is the extent to which persistent, low-level HIV-1 RNA replication in the CNS may underlie ongoing neurocognitive impairment in treated patients.

Dahl and colleagues presented a novel application of the single-copy assay for HIV-1 RNA detection to paired blood and CSF samples in 17 treated, suppressed subjects before and after addition of raltegravir in an intensification study, as well as in 11 “elite controllers” (subjects with endogenous control of HIV) (Abstract 423). Very low levels of CSF HIV-1 RNA were detected in treated subjects, and there was no change in HIV-1 RNA level after intensification with raltegravir. Elite controllers also had extremely low levels of HIV measured in the CNS despite slightly more detectable virus in the periphery. The single-copy assay thus can be applied to CSF and can measure low-level HIV-1 RNA in some cases in CSF in suppressed subjects. The subject population for the study was highly selected for treatment adherence and successful viral suppression measured by standard assays (requiring evidence of plasma HIV-1 RNA level <50 copies/mL for at least 1 year and CSF HIV-1 RNA level <50 copies/mL at baseline); it attracted highly treated subjects including those receiving 4- or 5-drug antiretroviral regimens. Future studies of subjects treated with more standard current regimens and under more routine circumstances may reveal the importance of low-level replication of HIV-1 RNA as detected by the single-copy assay in CSF.

**Neuronal injury markers.** Three studies focused on CSF markers utilized as markers of neurodegeneration. Krut and colleagues reported on a new, more sensitive assay for the light subunit of the neurofilament protein (NFL) with which they observed a broad spectrum of values within the lower range (Abstract 392). Whereas the prior CSF NFL assay had value as a predictor of dementia in some subjects not receiving treatment and indicated very high NFL values in patients with progressive HAND or HAD, the older NFL assay also showed NFL levels to be normal in most subjects in the neuroasymptomatic stages of HIV infection. This group demonstrated, however, that the new NFL assay has different “upper-limit of normal” values for HIV-uninfected subjects that vary according to age, discriminating between younger and older infected subjects.

Using this new assay, the investigators found NFL levels high for median age in neuroasymptomatic HIV-1-infected patients across the spectrum of CD4+ cell counts from below 50/µL to above 350/µL, suggesting that the new test is sensitive to subtle neural injury that may accompany asymptomatic HIV infection. The percentage of abnormal values correlated inversely with current CD4+ cell count across the span of disease. At the ends of the spectrum, 79% of patients with CD4+ cell counts below 50/µL and only 7% of those with counts higher than 350/µL had abnormal NFL levels. NFL level correlated with level of CSF neopterin, a macrophage-activation marker, but not with CSF viral load. This new assay provides promise as a tool for assessment of “subclinical” progressive neurologic injury in people with HIV infection. These findings suggest that active injury in currently asymptomatic patients is especially relevant in advanced immunosuppression and occurs in association with CNS immune activation.

Nath presented a complementary report investigating the potential utility of measures of the heavy chain of neurofilament (neurofilament H) in detecting neuronal injury in asymptomatic HIV infection (Anderson et al, Abstract 407). Density measurements of Western blot bands confirmed by antibodies to neurofilament H were obtained in CSF samples from 44 HIV-infected subjects mostly receiving antiretroviral treatment and from HIV-uninfected subjects with other neurologic disorders or clinically stable multiple sclerosis. Neurofilament H level was higher overall in the HIV-infected group than in either HIV-uninfected group. Furthermore, when HIV-infected subjects were separated into diagnostic groups according to the clinical definitions of neurocognitively normal, ANI, MND, and HAD, neurofilament H level was elevated without variation across the spectrum of disease. Subjects who clinically deteriorated over 6 months had larger increases in neurofilament H levels during this period than did those with no change or with improvement in neurologic status.

These results corroborate the findings in the NFL report, in that CSF neurofilament H may indicate smoldering neuronal injury during neuroasymptomatic HIV infection. However, the finding that neurofilament H levels in subjects with overt HAD were similar to those in neurocognitively normal subjects is surprising. This may be ex-
plained by variable levels of treatment and viral suppression in the different diagnostic groups. That is, a larger number of subjects in the “normal” group may have had ongoing high levels of HIV replication and inflammation, driving active CNS injury, whereas subjects in the progressively more “abnormal” groups might have had more suppression of current pathologic processes, with performance based on prior irreversible injury. Alternately, HAD in the current era may represent processes not associated with enhanced detection of neurofilament H. Future studies should clarify the relationship between neurofilament H levels and active neuropathologic processes in people with HIV infection and in various treatment scenarios.

Tau proteins are microtubule-associated proteins that stabilize microtubules in axons. Total Tau (tTau) protein in CSF is elevated in neurologic disease associated with HIV infection, presumably reflecting disruption of neurons. However, a hyperphosphorylated Tau protein (pTau) is thought to promote neurofibrillary “tangles” in the brain, and recent studies have found CSF pTau levels to be normal in HIV disease but elevated in Alzheimer disease and other “Tauopathies.”

Letendre and colleagues investigated the relationships between HIV infection, age, and pTau levels in 23 HIV-uninfected subjects, 53 HIV-infected subjects on antiretroviral therapy, and 17 HIV-infected subjects off antiretroviral therapy (Abstract 406). HIV-infected patients had elevated CSF pTau levels. Analyses of only the HIV-infected subjects indicated that CSF pTau levels correlated with older age, larger change in CD4+ cell count from nadir to current measure, antiretroviral therapy use, and worse prospective memory performance but not with worse global neurocognitive impairment. HIV-infected subjects in this study were substantially older than HIV-uninfected controls (median ages, 45 years and 36 years, respectively), suggesting that the differences observed in this study and in another by Brew, both of which contrast with others finding normal pTau levels in HIV infection, may be influenced by age. Future studies might investigate whether alterations in CSF pTau levels reflect distinct HIV- or non-HIV-related neuropathologic processes occurring at different ages and further clarify the relationships between CSF pTau levels and comorbid factors.

Inflammatory markers. The variable utility of currently recognized plasma and CSF biomarkers of HIV-associated immune activation has fostered investigation into new biomarkers of inflammation relevant to CNS HIV disease. Plasma lipopolysaccharide (LPS), an indicator of microbial translocation, may contribute importantly to chronic systemic immune activation and immunopathogenesis in HIV infection. Prior work has shown a correlation between plasma LPS levels and presence of HAD, but assessment of a more mildly affected group with chronic HIV infection receiving antiretroviral therapy showed no correlation between degree of impairment and LPS level.

To further investigate the utility of LPS level in predicting milder forms of HAND, Carsenti-Dellamonica and colleagues performed a subanalysis of data from 179 subjects in the NeuroAIDS Tissue Consortium (NNTC) and the CHARTER (CNS HIV Antiretroviral Therapy Effects Research) study with nadir CD4+ cell counts less than 300/µL (Abstract 405). Approximately three-fourths of the subjects were receiving antiretroviral treatment; the median CD4+ cell count (87 cells/µL) was low; and there was a broad distribution of HAND diagnoses. In this group, plasma sCD14 (but not LPS or CCL2) level was associated with worse global neurocognitive performance and impairment in specific domains (attention and learning T scores). Using area under the receiver operating characteristic curve analysis, plasma sCD14 level was also more closely associated with impaired scores than were plasma or CSF HIV-1 RNA levels or CD4+ cell count. It is possible that the interaction between plasma sCD14 level and cognition identified in this study was also influenced by variable antiretroviral treatment status or comorbidities, including use of narcotics or cocaine and HCV infection.

Markers of blood-brain barrier integrity. The blood-brain barrier provides a protective environment for the CNS by naturally restricting diffusion of large molecules and potential neurotoxins into the brain. Markers of blood-brain barrier disruption have been associated with severity of HIV-associated neurologic disease. However, data
presented at this year’s conference by Letendre and colleagues introduced the suggestion that a less permeable blood-brain barrier might have a negative impact on HIV-1 RNA suppression within the CNS (Abstract 408). Using one measure of blood-brain barrier permeability, the CSF to serum albumin ratio (CSAR), this group assessed data from 190 treated CHARTER subjects, most of whom had normal CSAR for age. Using cutpoint analyses, which divided values within the normal range of CSAR values, lower CSAR values in patients treated with low-CNS-penetrating regimens was associated with higher CSF HIV-1 RNA level as well as with global neurocognitive impairment. These preliminary studies require further assessment of the biological importance of the spectrum of CSAR values within the normal range, their relationship to markers of neuroinflammation, and the potential specific relationships between lower CSAR values and levels and effects of antiretroviral drugs within the CNS.

Markers of vascular disease. Several groups have shown that cardiovascular disease (CVD) risk factors such as hyperlipidemia, hypertension, and past history of CVD are associated with hyperlipidemia, hypertension, and past disease (CVD) risk factors such as markers of vascular disease. 

Neuroimaging markers. The role of neuroimaging in understanding the pathogenesis of HAND continues to grow as evidenced by the burgeoning number of posters and talks at the 2011 CROI. Many presentations highlighted roles for morphometry, magnetic resonance spectroscopy (MRS), and diffusion tensor imaging (DTI) as possible noninvasive techniques to assess the effects of HIV infection in the brain. 

Ragin and colleagues performed a cross-sectional study of subjects at a mean of 1 year after HIV transmission (n = 43) and compared results with those of age- and sex-matched HIV-seronegative control subjects (n = 22) (Abstract 55LB). Volumetric analysis using semiautomated tools demonstrated a statistically significant reduction in cortical structures in HIV-seropositive patients at this early stage of infection compared with HIV-seronegative control subjects. These results nicely complement posters by Tate and colleagues (Abstract 443), Kallianpur and colleagues (Abstract 441), and Ortega and colleagues (Abstract 442), who studied brain volumetric measures in chronically HIV-infected patients. Statistically significant decreases in brain volume were observed in HIV-infected patients and may be related to sex (female > male), race (African American > white), nadir CD4+ cell count, presence of detectable plasma or CSF HIV-1 RNA, or duration of antiretroviral therapy. Ragin and colleagues showed an association between plasma levels of macrophage chemoattractant protein-1 (MCP-1) as measured by multiplex assay and evidence of brain injury by analyzing brain volume fractions for a variety of regions in 10 HIV-infected subjects (Abstract 446). Larger longitudinal studies of both HIV-infected and -uninfected patients are needed to tease out the possible impact of each of these components.

Valcour and colleagues performed MRS in a cohort of acutely HIV-infected patients, chronically HIV-infected patients, and HIV-uninfected control subjects from Bangkok (Abstract 54). Acutely infected patients tended to have higher choline (Cho) ratios (a measure of cell turnover, as compared with creatine [Cr], a stable measure of energy metabolism) within the basal ganglia than those of either chronically infected patients or uninfected control subjects. A correlation was observed between MRS-measured metabolites and CSF biomarkers for acutely infected individuals. Cho:Cr ratios from the frontal lobe were positively correlated with MCP-1 values. These results suggest that even in acute infection, changes can be observed within subcortical structures; they also validate previous neuroimaging studies of early HIV-infected individuals. Similar results were also observed in chronically HIV-infected individuals. Navia and colleagues showed that neuronal injury was present in chronically infected participants despite antiretroviral therapy (Abstract 56). Both current CD4+ cell counts and baseline MRS-measured metabolite values (specifically, decreases in N-acetylaspartate [NAA] and Cho levels in the basal ganglia) were good predictors of progression from unimpaired to subclinical impairment. Letendre and colleagues investigated associations between plasma and CSF biomarkers associated with systemic and CNS immune activation with imaging biomarkers in a group of chronically infected subjects. Subjects had a mean CD4+ cell count nadir less than 50/µL, with the majority receiving suppressive antiretroviral therapy (Abstract 444). A total of 212 subjects underwent blood sampling, lumbar puncture, and cerebral metabolite measurement by MRS. In plasma, findings included associations between MCP-1 levels and levels of markers of both neuronal integrity (ratio of NAA to creatine [Cr]) and inflammation (Cho:Cr ratio). In CSF, MCP-1 levels also directly correlated with lower NAA:Cr ratios in some regions, whereas fractalkine level inversely correlated with NAA:Cr ratios, and levels
of sCD14 and interferon-inducible protein-10 were directly correlated with Cho:Cr ratios. MRS-measured metabolite abnormalities were also observed in perinatally HIV-infected patients (Abstract 450). All of these MRS findings support the hypothesis that immune activation within the brain occurs soon after seroconversion and may persist even during effective systemic virologic control with antiretroviral therapy.

The conference also highlighted DTI, an imaging technique that measures the restricted diffusion of water within the brain in order to visualize neural fiber tracts. Results from HIV-monoinfected participants were compared with those from individuals coinfected with HIV and HCV (Abstract 448). Gongvatana and colleagues demonstrated that the coinfected patients had statistically significant decreases in white matter integrity (ie, decreased fractional anisotropy and increased mean diffusivity) in all lobes of the brain.

**Identification of Novel Biomarkers**

Witwer and colleagues used an accelerated simian immunodeficiency virus (SIV) macaque model of HIV, in which AIDS and CNS disease occur within 3 months of infection, to unveil new biomarkers potentially associated with the development of CNS disease in primate lentiviral infection (Abstract 409). This group previously demonstrated that levels of CSF HIV-1 RNA, CSF interleukin 2 (IL-2), and MCP-1 are predictive of CNS disease in this accelerated SIV model. MicroRNA (miRNA) was identified in plasma to seek molecules associated with progression to SIV encephalitis (SIVE). Profiles of miRNA were assessed in plasma sampled from animals before acute SIV infection and 10 days after infection. A total of 45 miRNA molecules were differentially expressed in acutely infected and uninfected samples, revealing a plasma miRNA “signature” of acute infection. Of these miRNA molecules, at least 6 were statistically significantly different between animals that did or did not develop encephalitis. Two of these latter miRNA molecules have previously been linked to senescence and CNS disease.

Another study employed high-throughput proteomic methods to identify novel proteins expressed in the CSF in HIV infection and through the course of antiretroviral treatment. Price presented an analysis comparing CSF samples from HIV-uninfected and -infected subjects to identify peptides (> 2000 peptides per sample) with increased abundance in the HIV-infected patients, and to identify recognized proteins (> 300 proteins per sample) present in CSF (Angel et al, Abstract 61). This study also assessed peptides identified in 11 longitudinal sample sets from subjects at different stages of HIV-related CNS disease, before and after initiation of antiretroviral treatment. These investigators used correlation with CSF neopterin, a pteridine marker of macrophage activation, as a “probe.” Thus, proteins identified by the proteomic discovery that either positively (eg, complement) or negatively (eg, autotaxin) correlated with the known marker CSF neopterin were highlighted as potential novel biomarkers with mechanistic importance in the etiology of HAND.

These investigators also used Ingenuity Pathway Analysis (IPA) to map known interconnections between identified proteins, suggesting pathways of disease mechanism. IPA mapped 3 major networks of identified proteins that correlated with neopterin and were potentially associated with neurologic function and disease. Applying state-of-the-art proteomic technologies to CSF samples of well-characterized HIV-infected subjects provides a powerful discovery method for identifying new biomarkers and, potentially, the pathways of HIV-related CNS disease.

**Neuropathogenesis of HIV and Simian Immunodeficiency Virus Infection**

Whereas many biomarker and treatment studies presented at the conference had implications for understanding the pathogenesis of HAND across the spectrum from mild disease to HAD, a number of presentations focused directly on the identification of mechanisms of HIV- and SIV-related CNS injury. Studies examining properties of HIV associated with neurologic injury, including genetic analyses of CSF and blood species, were complemented by studies focusing on the host characteristics associated with the development of HAND, centering on host CNS immunologic characteristics in HIV and SIV infections.

**Virologic Determinants of HIV-Associated Neurocognitive Disorder**

Swanstrom reported on the env gene sequences of HIV-1 derived from paired CSF and plasma samples in a study to determine phylogenetic relationships between blood and CSF in subjects with HAD in the absence of antiretroviral treatment (Schnell et al, Abstract 58). The study also sought to evaluate entry properties of HIV-1 species associated with distinct decay characteristics. All subjects with HAD had highly compartmentalized HIV-1 between the CNS and the plasma, but HIV-1 species from subjects with rapid reduction in CSF HIV-1 RNA levels in response to antiretroviral treatment showed no infectivity in cells expressing low levels of CD4 receptors, suggesting that these species must be infecting and independently replicating within T lymphocytes in the CNS. Viral species from subjects with slower decline in CSF HIV-1 RNA levels after initiation of antiretroviral therapy were more complex, suggesting that they had been growing as separate populations for a long period of time, and were able to enter cells with low levels of CD4 receptors, indicating replication within macrophages or microglia. These macrophage-infecting viruses were almost exclusively found in CSF viruses rather than virus from plasma. In one subject, a macrophagetropic virus was detected within the CNS 2 years before the onset of dementia. This study provides novel evidence for 2 types of compartmentalized CNS infection in patients with HIV infection and dementia: a form supported by T-lymphocyte infection and another fostered by infection within...
macrophages and microglia. These investigators also showed the first evidence of CNS compartmentalization of subtype-C HIV-1 species.

Hightower and colleagues presented data on the degree of genetic diversity within plasma HIV species in chronic infection (Abstract 57). They used a method derived from a population-based sequence that takes into account the number of mixed bases occurring in the sequence, normalized by the total sequence length, which produced a Total Mixed Base Index. They validated this approach as a measure of intra-individual HIV-1 population diversity by comparison of these findings with Shannon entropy and average pair-wise distance. Multivariable logistic regression was used to model the relationship between viral diversity and AIDS, and viral diversity and NP. Blood HIV-1 population diversity was found to be associated with both presence of AIDS and presence of neurocognitive impairment.

Diversity and compartmentalization of SIV variants were investigated in a more controlled setting through studies utilizing the accelerated macaque model of neuroAIDS (accelerated via HIV and neurovirulent SIVmac251) (Abstract 437). This group examined gp120 SIV sequences from plasma and postmortem brain tissue in 2 animals euthanized at 21 days postinfection and 4 animals with disease that progressed to meningitis or encephalitis and died. A V2-C2 amino acid variant associated with macrophage tropism unique to brain and lung tissue (and absent from all plasma samples) was identified in 4 animals, suggesting selective outgrowth of a macrophage-tropic variant in these tissues. These studies support the possibility that specific macrophage-tropic variants present in low quantities in transmitted HIV species in humans might selectively replicate within the CNS and be associated with predisposition to immune dysregulation and development of HAND.

Further investigation of the viral determinants of HAND will be fostered by the development of a novel, publicly available “HIV Brain Sequence Database,” presented by Holman and colleagues (Abstract 436, http://www.hivbrainseqdb.org/). This group assembled a database of clonal HIV env sequences available in the National Institutes of Health genetic sequence database, GenBank, relevant to CNS HIV infection. Importantly, sequences included had to be either derived from the CNS (from the brain, meninges, or CSF; n=1272) or from other tissues from subjects for whom CNS sequences were also available (n=1245). Numerous annotation details were assembled for each subject at each point of sampling, including antiretroviral drug history, current laboratory indices including CD4+ cell count and HIV-1 RNA levels, and cognitive and pathologic diagnoses. The database was designed to be readily searchable by all annotation criteria as well as sequence and tissue criteria.

**Host Features Associated with HIV-Associated Neurocognitive Disorder**

Schrier and colleagues investigated host genetic factors associated with development of HAND in a study of HIV-infected subjects in Anhui, China (Abstract 390). A prior study by this group found an association between the presence of the HLA allele HLA-DR*04 and a diagnosis of HAND in 191 participants recruited within the United States. The current investigation confirmed this finding in 178 HIV-infected Chinese subjects with a distinct genetic background and a different spectrum of comorbidities (including a 94% prevalence of HCV infection).

Furthermore, in subjects with detectable plasma HIV-1 RNA, cognitive decline was greater in the HLA-DR*04 group than in the non–HLA-DR*04 group over a 12-month interval. No individual class 1 HLA allele (A,B), recognized as associated with slower systemic HIV progression, had an apparent protective effect against HAND. However, subjects with at least 1 protective allele had better NP performance scores and less progression of HAND over 12 months. HLA alleles, which confer important characteristics of host immune function, plausibly contribute to the systemic and CNS immune responses involved in HIV neuropathogenesis.

In an effort to understand the relationships among lentiviral primate infection, the CNS host immune response to infection, and the development of neuronal injury, Fell and colleagues examined blood, CSF, brain tissue, and patterns of cerebral metabolites in an accelerated (CD8-depleted) SIV macaque model wherein 85% of animals develop SIVE (Abstract 59). They quantified SIV RNA levels in CSF, plasma, and frontal cortex of the brain, and they obtained MRS results every 2 weeks in 24 animals, including 7 placed on minocycline for weeks 4 through 8 postinfection and 4 animals administered antiretroviral drugs for weeks 6 through 12 postinfection. They also quantified activated monocytes (identified as CD14+CD16+ cells) in the blood over time in these animals.

In the absence of treatment, NAA:Cr ratio steadily decreased through the early weeks postinfection, with a 20% reduction below baseline by 8 weeks postinfection. The percentage of activated monocytes correlated with plasma and brain SIV RNA levels but not with CSF SIV RNA levels. A statistically significant inverse correlation was identified between the percentage of CD14+CD16+ monocytes in blood and concentrations of NAA and Cr in the frontal cortex. Both minocycline and antiretroviral treatments prevented further decline in the NAA:Cr ratio and halted expansion of the monocyte subset, but neuronal recovery was not observed. These data suggest that neuronal dysfunction in the early stages of SIV infection in an accelerated macaque model is associated with the presence of activated monocytes in the periphery.

Cells of the monocyte and macrophage lineage were the focus of another study employing an accelerated macaque model of neuroAIDS (using the neurovirulent strain SIVmac251), in this case in an investigation of the time course of monocyte recruitment into the CNS and of the characteris-
tics of perivascular macrophages accumulating during SIV infection and SIVE (Abstract 430). Nowlin and colleagues used intracranial injection of dextran conjugated to different fluorescent labels at distinct timepoints to demonstrate greater accumulation of perivascular macrophages in meninges and brain in animals with SIVE, occurring mostly between days 20 and 49 postinfection. Perivascular macrophage recruitment was estimated to be increased 6-fold in animals with SIV infection without encephalitis, and increased 8-fold in animals with SIVE. These studies also revealed that although CD163+ macrophages are a main component of perivascular macrophages in SIV-uninfected and -infected animals, in animals with SIV, a distinct population of macrophages lacking SCD163 is also recruited.

**Treatment With Antiretroviral or Adjunctive Therapies and Biomarkers of HIV-Associated Neurocognitive Disorder**

**Effects of Standard Antiretroviral Treatment on Biomarkers**

Important information on the effects of initiation of antiretroviral treatment on CNS function in antiretroviral-naive subjects in diverse resource-limited settings was presented by Robertson and colleagues (Abstract 428, AIDS Clinical Trials Group [ACTG] 5199, The International Neurological Study). A total of 860 subjects recruited in Africa (6 sites), India (2 sites), and South America (3 sites) were randomly assigned to 1 of 3 antiretroviral regimens for initial therapy and monitored for changes in NP test performance every 24 weeks; final analysis was done at 192 weeks. Subjects had CD4+ cell counts less than 300/µL at entry and were a median of 34 years old; a majority (53%) were women. Randomization led to equal distribution among the 3 treatment groups: efavirenz/lamivudine/zidovudine, emtricitabine/atazanavir/didanosine (enteric coated), or efavirenz/emtricitabine/tenofovir. Results from a short battery of language-adjusted NP tests (grooved pegboard, timed gait, finger tapping, and semantic verbal fluency) along with standardized neuropsychologic examinations and dementia assessments were obtained at each visit.

Statistically significant improvements in NP test performance were detected in all treatment groups at each follow-up visit over the 192 weeks. Although practice effects from the repeat testing could have contributed to this improvement, antiretroviral treatment may also have positively affected the CNS through control of HIV replication and related processes. The proportions of patients with neurologic abnormalities, dementia, or milder forms of HAND also decreased over the study period.

This study confirms that in resource-limited settings, the initiation of antiretroviral therapy is associated with improvement in NP test performance. The fact that the regimens in the first and third treatment groups are currently initial treatment recommendations from the World Health Organization underscores the clinical importance of witnessing performance improvement in these 2 groups. Additionally, although the 3 different treatments comprised regimens with distinct levels of presumed effectiveness in penetrating the blood-brain barrier (with “clinical penetration effectiveness [CPE],” scores of 9, 6, and 7, respectively15,16), similar improvement was observed in all groups.

Improved NP performance in patients receiving antiretroviral therapy in a broad variety of geographic settings was also observed in an analysis of data obtained from baseline to month 6 in the SMART (Strategies for Management of Antiretroviral Therapy) study (Abstract 402). A total of 292 participants with CD4+ cell counts greater than 350/µL were enrolled in Australia, the United States, Brazil, and Thailand and randomly assigned to either episodic antiretroviral treatment (if CD4+ cell count fell below 250/µL) or continuous antiretroviral treatment.

Five NP tests (grooved pegboard average, color trails 1 and 2, timed gait, and finger tapping, summarized as the quantitative NP z-score of the 5 tests [QNPZ-5]) were administered to subjects at baseline and at 6 months, at which point the study was terminated because of increased AIDS and non–AIDS-related complications in the episodic treatment group. Subjects were a median of 40 years of age, were composed of 42% women, and had a baseline median CD4+ cell count of 513/µL and abnormal NP test performance (mean QNPZ-5, −0.7). During the 6-month follow-up period, 86% of subjects in the episodic treatment group had started antiretroviral treatment according to study indications; thus, the total average exposure to antiretroviral treatment in this group was 3.6 months versus 5.9 months in the continuous treatment group.

In both treatment-strategy groups, improvement in QNPZ-5 scores and in each individual test was noted between study entry and 6-month follow-up. There were no clear correlations between changes in NP test performance and CD4+ cell count (which declined in the episodic group and rose in the continuous group) or plasma HIV RNA level (which rose in the episodic group and declined in the continuous group). The authors note that because there were changes in both groups independent of the usual laboratory-based predictors of NP test performance, the performance improvement between baseline and follow-up might have been influenced by practice effect. The study did not find a difference in improvement between the 2 groups but was underpowered to detect a difference as a result of the early closure of the study. Further studies of treatment strategies that use repeated NP testing would be enhanced by inclusion of a well-matched control group to assess the effect of learning.

Ongoing low-level CNS immune activation during antiretroviral treatment may contribute to the persistence of HAND in patients receiving suppressive treatment in the current era.17,18 Yilmaz and colleagues sought to investigate the response of CSF neopterin level, as a biomarker of intrathecal macrophage activation, to initiation of antiretroviral treatment in chronic HIV infection (Abstract 429). Subjects (n=114) who were antiretroviral-naive or had...
been off treatment for at least 6 months underwent lumbar puncture before and after initiation of a variety of antiretroviral regimens that successfully suppressed plasma HIV RNA to levels below standard detection. A total of 107 neuroasymptomatic subjects had a median CD4+ cell count of 190/µL and abnormal median levels of CSF neopterin (26.3 nmol/L) and plasma neopterin (24.2 nmol/L) at baseline.

A mixed-effects model, which took into account each subject’s serial neopterin values and the days of follow-up after treatment initiation, was used to examine the decay pattern and final “set point” of CSF neopterin for the group. After a median 89 weeks of suppressive treatment during follow-up, the estimated CSF neopterin set point was 7.7 nmol/L, statistically significantly higher than the upper normal limit of CSF neopterin in HIV-uninfected healthy subjects (5.8 nmol/L). Seven subjects with HAD were evaluated separately. Despite similar plasma levels, they had higher baseline levels of CSF neopterin, slower decay, and statistically similar elevations in final CSF levels compared with the neuroasymptomatic group. This longitudinal study provides a window into the dynamics of the intrathecal inflammatory response after initiation of standard antiretroviral treatment, and it provides further evidence that immune activation persists in the CNS for a prolonged period during treatment that reduces HIV-1 RNA below levels of standard detection.

**Effects of Adjunctive or Intensified Therapy During Antiretroviral Treatment**

Because residual neuroimmune activation during antiretroviral treatment may be a contributing mechanism of HAND, treatment with adjunctive therapies that directly suppress CNS inflammatory processes might provide additional benefit in amelioration of HAND. Sacktor and colleagues presented findings from an ACTG study investigating the effect of the addition of minocycline, an antiviral drug with possible immunomodulatory effects, to the antiretroviral regimens of subjects with progressive HAND (Abstract 421). This study was conducted as a randomized, double-blind, placebo-controlled trial with an endpoint of change in NP test performance (on a battery of 8 tests, summarized as NPZ-8) after 28 weeks of therapy. The 107 subjects had a mean CD4+ cell count of 543/µL; 86% had suppression of plasma HIV RNA level to less than 30 copies/mL; and most had subclinical or mild neurocognitive disease at baseline. The subjects were equally divided between 2 treatment groups of oral minocycline or placebo.

Minocycline treatment showed no evident effect distinct from placebo on the NPZ-8 scores or on any individual scores except the grooved-pegboard test, which did not reach statistical significance after correction for multiple comparisons. After 50% of the target enrollment completed the 24-week treatment phase, an interim review by the study’s data safety monitoring board recommended early termination for futility.

The concept that ongoing brain injury during antiretroviral treatment may be facilitated by low levels of persistent HIV-1 replication driving immune activation within the CNS provides rationale for attempted “intensification” of standard regimens to better suppress these potential residual processes. Price and colleagues presented a pilot study of raltegravir intensification, in which 18 subjects (mean CD4+ cell count, 513/µL) with evidence of sustained suppression of HIV-1 in the plasma and successful antiretroviral treatment of CSF HIV-1 to levels below 50 copies/mL were randomly assigned to receive either treatment intensification with the addition of the integrase inhibitor raltegravir or no treatment intensification (Abstract 424). Subjects maintained the assignment for 12 weeks, and those in the no-intensification group had the option to roll over to receive raltegravir intensification after that time. Sampling of blood and CSF and NP testing (timed gait, grooved pegboard, finger tap, and digit symbol; QNPZ-4) was performed for clinical and laboratory outcomes at baseline and at weeks 4, 8 (blood only), and 12. A total of 14 subjects (including roll-over subjects), preselected for no detectable plasma or CSF viral burden by standard assays, were administered raltegravir intensification; their results were compared with those of 9 subjects without intensification. Overall baseline CSF neopterin levels were within the normal range (mean, 5.6 nmol/L; normal, < 5.8 nmol/L), and no change in CSF neopterin level was observed in either treatment group. Raltegravir intensification also had no effect on most other CSF markers of inflammation examined (white blood cell [WBC] count or CD38+ HLA-DR+ CD8+ T-lymphocyte percentages), blood-brain barrier integrity (CSAR), or QNPZ-4 score.

**Early Injury**

The possibility that the earliest phases of HIV infection set the stage for subsequent neurologic injury by seeding the CNS with persistent HIV infection, causing early injury to the nervous system, or initiating a cascade of neuroinflammation, has received increasing focus in recent years. Several presentations this year focused on the effects of early lentiviral infection in animal models and in human infection with HIV.

**Natural History of Early Central Nervous System Infection**

Dash and colleagues presented multimodal findings of the CNS effects of acute and early HIV-1 infection in a humanized mouse model, which was created by reconstituting immunodeficient mice with human CD34+ cells derived from fetal liver (Abstract 458). Longitudinal blood sampling indicated that HIV-1-infected humanized mice had changes in absolute CD4+ and CD8+ cell counts similar to those accompanying typical acute HIV-1 infection in humans, with peak elevation in plasma HIV-1 RNA levels at 4 weeks postinfection. Serial 7 Tesla brain MRS over the first 15 weeks of infection revealed reduced NAA concentrations in the cerebral cortex of HIV-infected mice at weeks 8 through 15 compared with
baseline measures, corresponding to reduced mean diffusivity and fractional anisotropy in this region as detected by DTI. Postmortem examination of animals euthanized at 15 weeks of infection showed human cells infiltrating meninges and perivascular spaces, activation of microglia and astrocytes, and decreased levels of neuronal and astrocyte markers (including synaptic scaffolding, neurofilament, microtubule-associated protein 2 [MAP2], and glial fibrillary acid protein) compared with those of uninfected humanized mice.

Two studies employing neuroimaging biomarkers as crucial endpoints focused upon the effects of HIV infection in the human brain during the early stages of infection (Abstracts 54 and 55LB). Valcourt and colleagues found not only CNS inflammation during acute infection by detection of elevated cerebral metabolites with MRS, but also documented some of the earliest evidence of HIV neuroinvasion in humans, detecting CSF HIV-1 RNA as early as 8 days after HIV transmission (Abstract 54). This group characterized the relationship between CSF and plasma levels of HIV-1 RNA in 17 subjects with acute HIV infection (a median of 15 days after transmission), finding that mean CSF HIV-1 RNA levels were approximately 2.5 log10 copies/mL lower than levels in the plasma. Three subjects had undetectable CSF HIV-1 RNA despite having detectable virus in plasma that reached baseline measures, corresponding to reduced mean diffusivity and fractional anisotropy in this region as detected by DTI. Postmortem examination of animals euthanized at 15 weeks of infection showed human cells infiltrating meninges and perivascular spaces, activation of microglia and astrocytes, and decreased levels of neuronal and astrocyte markers (including synaptic scaffolding, neurofilament, microtubule-associated protein 2 [MAP2], and glial fibrillary acid protein) compared with those of uninfected humanized mice.

Additional studies sought to investigate the mechanisms underlying neurologic and behavioral characteristics present in the first months after HIV transmission. Lee and colleagues performed a cross-sectional study assessing the relationship between the occurrence of neurologic disorders during primary infection and blood, CSF, and clinical parameters assessed in a group of 85 subjects evaluated at a median of 75 days after HIV transmission (Abstract 411). Of the 85 participants, 17 were determined by a neurologist’s history and physical examination to have specific neurologic manifestations related to recent infection either before or at evaluation; manifestations included meningitis, encephalitis, facial palsy, and peripheral nerve disorders. Age, CD4+ cell count, sex, and number of days since HIV transmission were similar between the subjects with or without neurologic symptoms. Abnormalities in CSF were common in both neuropsychiatric and neuroasymptomatic subjects during primary infection. Of laboratory factors including blood and CSF HIV RNA level, CSAR, and CSF WBC count, only CSF WBC count was independently associated with the presence of neurologic symptoms in a logistic regression multivariable analysis. These results suggest that host CNS immune response (rather than primarily CSF viral burden) is a determining factor in the neurologic manifestations of HIV during primary infection.

Grill and colleagues investigated the association between reported fatigue and CNS changes as indicated by measures of systemic and intrathecal viral burden and inflammation in 43 men with recent HIV infection (at a median estimated 129 days after transmission) (Abstract 413). Degree of fatigue was measured by the “fatigue subscore” portion of the Profile of Mood States inventory and correlated with scores on the Beck Depression Inventory (BDI) as well as laboratory measurements that included blood and CSF HIV RNA levels, CSF WBC count, and CSF levels of neopterin, cytokines regulating cellular trafficking, interferon-gamma-inducible protein 10 [IP-10], and MCP-1. In linear regression analysis of fatigue subscore and individual markers, CSF MCP-1 levels were statistically significantly associated with degree of fatigue. Fatigue subscore also strongly correlated with levels of depression as measured on the BDI. In a multivariable regression model incorporating CSF WBC count (a marker of inflammation), CD4+ cell count, and HIV RNA levels in plasma and CSF as possible predictors of fatigue, only CSF WBC count was independently correlated with fatigue subscore. During the first months of HIV infection, the experience of fatigue, although tied closely to symptoms of depression, may be in part related specifically to inflammatory processes within the CNS.

**Effects of Treatment During Early Infection**

Several studies focused on the effect of early antiretroviral treatment on the CNS. Though numerous studies have evaluated the effect of early initiation of therapy on the course and outcomes of systemic HIV infection, these studies have not been conclusive regarding the value of early treatment for systemic outcomes. Whether early treatment may be effective in suppressing HIV RNA levels, preventing establishment of viral reservoirs, and controlling neuroimmune activation within the CNS has not been systematically investigated.

Graham and colleagues examined the effects of extremely early initiation of antiretroviral therapy in an accelerated SIV macaque model of neuroAIDS (Abstract 410). At 4 days after intravenous inoculation with SIV, 5 animals were treated with saquinavir, atazanavir, and an integrase inhibitor; 3 animals were treated with atazanavir and an integrase inhibitor; and 6 animals were untreated. The animals were euthanized at 21 days, and tissues were examined for presence of SIV RNA, SIV DNA, and cell and cytokine levels. In treated animals, CSF SIV RNA was statistically significantly reduced compared with untreated animals at days 7 and 10 after inoculation, as was CSF MCP-1 (also known as CCL2) at day 10. Levels of CD4+ and CD8+ lymphocytes were increased in treated animals, and SIV RNA levels were reduced in brain tissue at day 21. However, SIV DNA levels in brain did not differ between treated and untreated animals, and some measures of inflammatory responses within the CNS, including major histocompatibility complex class II molecules and glial fibrillary acid protein, were elevated in all infected animals. These findings in an animal model of lentiviral infection that leads to accelerated brain injury suggest beneficial effects of hyper-
acute treatment of SIV. Such effects include reducing the burden of viral replication (SIV RNA level), preserving elements of the immune response within the CNS, and reducing markers of immune activation associated with macrophage recruitment and the inflammatory cascade within the CNS. In a related presentation, Mankowski reported that maraviroc monotherapy given to rhesus macaques 24 days after SIV inoculation reduced brain and CSF levels of SIV RNA and levels of brain markers of macrophage activation (CD68+ cells) and neuronal degeneration (accumulation of amyloid precursor protein) in the brain in a similar accelerated model of lentiviral CNS disease in primates (Kelly et al, Abstract 60LB).

A study examining the effects of early initiation of antiretroviral therapy on the CNS in humans with recent HIV infection was presented by Muthulangam and colleagues (Abstract 412). Results from longitudinal blood, CSF, and NP (grooved pegboard, timed gait, finger tapping, and digit symbol; the NPZ-4) testing were obtained for 14 subjects with laboratory-confirmed primary HIV infection who initiated antiretroviral therapy at a median of 6.4 months after HIV transmission. Changes in laboratory values and NPZ-4 scores over time after initiation of therapy were examined in longitudinal follow-up over a median of 458 days; results were compared with those from a group of nondemented subjects who initiated antiretroviral therapy during chronic HIV infection (at a median of 93 months after diagnosis) with a median 328 days of follow-up. Although treatment regimens were variable, CPE scores were similar between the 2 groups. In response to antiretroviral therapy, primary-infection subjects demonstrated complete suppression of detectable HIV-1 RNA in plasma and CSF, but treatment in a subset of chronic-infection subjects failed to completely suppress plasma and CSF HIV RNA levels in follow-up. Median CSF WBC count, a nonspecific marker of inflammation, did not reach normal levels in either group by the end of the follow-up period, suggesting that mild intrathecal immune activation may persist even in subjects who initiate antiretroviral therapy early during the course of HIV infection. NPZ-4 scores improved in response to antiretroviral treatment in the primary-infection subjects in parallel with expected improvements in the chronic-infection subjects. This phenomenon may have been the result of practice effect but also might indicate that treatment initiation even during primary infection has benefit to neurocognitive performance.

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A list of all cited abstracts appears on pages 99–106.

References


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Complications of HIV Disease and Antiretroviral Therapy

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Studies on new direct-acting antivirals (DAAs) for hepatitis C virus infection were a focus of the 2011 Conference on Retroviruses and Opportunistic Infections. Although the majority of the data were from HIV-uninfected patients, much-needed work has begun to characterize DAA and antiretroviral drug interactions and to evaluate performance of DAAs for HIV/HCV-coinfected patients. There was continued emphasis on pathogenesis, management, and prevention of the long-term complications of HIV disease and its therapies, including cardiovascular disease, lipodystrophy, renal disease, and alterations in bone metabolism. Malignancies, particularly non–AIDS-defining cancers, have emerged as a leading complication and cause of death in HIV infection that may not be fully mitigated by immune reconstitution with antiretroviral therapy. This year’s conference also highlighted important data on the optimal timing of antiretroviral therapy in tuberculosis coinfection, as well as the treatment and prevention of common coinfections including cryptococcal meningitis and influenza.

Viral Hepatitis

Hepatitis C Virus Protease Inhibitors: Boceprevir and Telaprevir

Some of the most exciting data presented at the 2011 Conference on Retroviruses and Opportunistic Infections came from the rapidly evolving field of new oral direct-acting antivirals (DAAs) for the treatment of hepatitis C virus (HCV) infection, with the majority of data coming from HCV-monoinfected patients. Zeuzem gave an exceptional plenary presentation summarizing the current status of the HCV drug pipeline for both HIV-infected and -uninfected patients (Abstract 121). Data were presented on boceprevir and telaprevir, both of which are oral HCV NS3 protease inhibitors (PIs), the class of oral HCV drugs furthest along in development. Both NS3 PIs currently need to be given with pegylated interferon alfa and ribavirin to avoid the emergence of drug resistance; however, development of entirely oral, interferon-sparing HCV treatment is actively being pursued.

Sulkowski and colleagues evaluated the use of boceprevir in HIV-uninfected HCV-genotype-1-infected, treatment-naive patients in the SPRINT-2 (Serine Protease Inhibitor Therapy 2) study (Abstract 115). After an initial 4-week lead-in treatment period with pegylated interferon alfa plus ribavirin, patients were randomly assigned to 1 of 3 groups: a control group receiving 44 weeks of pegylated interferon/ribavirin; a group receiving boceprevir plus pegylated interferon/ribavirin for 44 weeks; and a group receiving boceprevir plus pegylated interferon/ribavirin in a response-guided strategy. In the response-guided group, participants with undetectable HCV RNA between week 4 and week 20 of 3-drug therapy discontinued treatment after a total of 24 weeks, whereas those with detectable HCV RNA between week 4 and week 20 of triple-drug therapy received an additional 24 weeks of pegylated interferon/ribavirin.

In the nonblack cohort, sustained virologic response (SVR) was attained in 40%, 67%, and 68% for the control group, the boceprevir response-guided group, and the 44-week boceprevir group, respectively. As anticipated, cure rates in the black cohort were less than in the nonblack group, with SVR attained in 23%, 42%, and 53%, respectively.

Overall, patients receiving 44 weeks of boceprevir had SVR rates almost double those of the control group, and boceprevir response-guided therapy led to equivalent SVR rates in the nonblack participants. In those with a favorable response to the initial 4-week pegylated interferon/ribavirin treatment (≥1 log10 drop in HCV RNA level), SVR was 2-fold higher than in those without initial favorable results. In patients not attaining SVR, those who responded to the lead-in treatment experienced reduced boceprevir resistance compared with those not responding to the lead-in treatment (4% vs 35%−47%, respectively). The most common adverse effects associated with boceprevir were anemia, which developed in 49% of boceprevir-treated participants, and dysgeusia.

Boceprevir treatment also led to robust SVR rates in HCV-treatment-experienced, HIV-uninfected patients. Boceprevir more than doubled SVR rates in patients with previous HCV treatment relapse (ie, undetectable HCV RNA at the end of therapy without subsequent attainment of SVR), with SVR rates of 29%, 69%, and 75%, respectively, after 48-week treatment with pegylated interferon/ribavirin, 44 weeks of boceprevir, or boceprevir response-guided therapy (32 weeks of boceprevir plus pegylated interferon/ribavirin, with an additional 12 weeks of pegylated interferon/ribavirin for those with detectable HCV RNA at 4 weeks of triple therapy) (Abstract 116). As observed in other HCV treatment series, patients previously nonresponsive to HCV treatment (ie, those showing a ≥ 2 log10 IU/mL decrease in HCV RNA by week 12 from baseline...
but with detectable HCV RNA on the remaining course of treatment) had lower rates of SVR than did patients with relapse, with SVR rates of 7%, 40%, and 52%, in the 3 groups, respectively. As in treatment-naive patients, response to the initial 4-week lead-in therapy predicted SVR, with SVR rates of 53% to 54% (if <1 log_{10} IU/mL HCV RNA drop at week 4 from baseline) increasing to 73% to 79% (if ≥ 1 log_{10} IU/mL decrease) in the boceprevir groups, and from 0% increasing to 26%, respectively, in the control group.

In terms of anticipated drug interactions between boceprevir and antiretroviral drugs, boceprevir appears to be a strong inhibitor and modest substrate of cytochrome P450 3A4 (CYP3A4) (Abstract 118). Ritonavir coadministration had only a minimal effect on boceprevir steady state and reduced the boceprevir area under the curve (AUC) by 19%, whereas efavirenz coadministration reduced the boceprevir minimum plasma concentration (C_{min}) by 44%, the clinical importance of which is unclear. Conversely, boceprevir modestly increased efavirenz AUC by 20% and maximum plasma concentration (C_{max}) by 11%. Studies of boceprevir for HIV-infected, treatment-naive and -experienced, HCV-coinfected patients are planned.

The first interim data on HCV PI use in HCV-coinfected, HCV-genotype-1-infected patients were presented by Sulkowski and colleagues (Abstract 146LB). The NS3 HCV PI telaprevir was administered for 12 weeks with pegylated interferon/ribavirin, followed by 36 weeks of pegylated interferon/ribavirin alone, and results were compared with those of a control group receiving 48 weeks of pegylated interferon/ribavirin alone. Unlike for boceprevir, studies of telaprevir have not used a 4-week lead-in treatment. Telaprevir treatment was associated with rapid virologic response (RVR, defined as undetectable HCV RNA after 4 weeks of triple-drug therapy) in 70% of participants, compared with 4.5% of control patients; it was also associated with complete early virologic response (cEVR, defined as undetectable HCV RNA at 12 weeks of triple-drug therapy) in 68% versus 14%, respectively. These high early response rates with telaprevir treatment in hard-to-treat HIV/HCV-coinfected patients are very promising; SVR data from this trial are forthcoming. There was a trend toward lower cEVR rates with atazanavir-based antiretroviral therapy (57%) versus efavirenz-based antiretroviral therapy (75%) or no antiretroviral therapy (71%). However, the study was small (n = 60) and had insufficient power to distinguish the effect of antiretroviral therapy on treatment response.

Van Heeswijk and colleagues examined the pharmacokinetic interactions of telaprevir and antiretroviral therapy (Abstract 119). Like boceprevir, telaprevir is also a substrate and inhibitor of CYP3A4. Despite increasing telaprevir dosing schedule to 1125 mg every 8 hours for coadministration with efavirenz, treatment with efavirenz plus telaprevir still leads to an 18% reduction in telaprevir AUC and a 25% reduction in telaprevir C_{min}.

Telaprevir had a heterogenous effect on HIV PI levels, raising atazanavir and lopinavir levels and decreasing darunavir and fosamprenavir levels. Telaprevir modestly decreased efavirenz levels and had minimal effect on tenofovir plasma levels. Until more data are available on appropriate dosing of coadministered telaprevir and antiretroviral therapy, caution is advisable with telaprevir use in antiretroviral-treated HIV/HCV-coinfected individuals, once telaprevir becomes available after US Food and Drug Administration (FDA) approval, which is anticipated to occur later in 2011.

**Acute Hepatitis C Virus Infection**

As has been demonstrated in HCV monoinfection, treatment of acute HCV infection (typically defined as the period up to 1 year since infection occurred) in HIV/HCV-coinfected patients leads to superior cure rates over those with chronic HCV infection. Boesecke and colleagues (Abstract 113) reported an overall 65% SVR rate in HIV-infected patients treated for acute HCV infection with pegylated interferon alfa–based regimens, with higher SVR rates occurring in HCV genotypes 2 or 3 than in genotypes 1 or 4 (85% vs 61%, respectively; P = .003). Heterogenous treatment regimens were used, but the median duration was 24 weeks, which is shorter than the 48 weeks typically recommended for treatment of chronic HCV infection in HIV coinfection. Ribavirin may not be needed for the full 24 weeks of pegylated interferon alfa administration for the treatment of acute HCV infection in those with a favorable early response in HCV RNA level. In a pilot study of a kinetically guided treatment strategy, in which ribavirin was discontinued at week 8 and week 12, all patients who discontinued ribavirin attained an SVR after 24 weeks of pegylated interferon alfa, as did all patients who attained undetectable HCV RNA at week 4 (ie, RVR) (Abstract 959).

**Genetic Predictor of HCV Clearance: IL28B**

Interleukin 28B (IL28B) single nucleotide polymorphisms (SNPs) have emerged as an important predictor of treatment response and spontaneous clearance of HCV in HCV mono- and HIV/HCV-coinfected patients. Favorable IL28B haplotypes predicted spontaneous clearance of HCV (Abstract 944) as well as response to pegylated interferon/ribavirin treatment for patients with HCV genotypes 1 and 4 (Abstracts 945 and 946) but interestingly not for those with genotype 3, for unclear reasons (Abstract 945). Consistent with data from HCV-monoinfected patients, IL28B genetic polymorphisms do not appear to predict treatment response for patients with acute HCV infection (Abstract 943).

The favorable C/C IL28B genotype was associated with a higher baseline level of HCV RNA, which is somewhat counterintuitive, as a high HCV RNA level is associated with a worse response to therapy (Abstract 947). The authors postulate that this genotype may be associated with low endogenous levels of interferon alfa,
thus permitting high HCV RNA levels to develop, with enhanced sensitivity to exogenous interferon–based therapy and resultant higher SVR rates. Given the predictive value of IL28B status, this genetic marker is anticipated to become an important part of risk-versus-benefit analyses of optimal timing of HCV treatment.

Complications of HIV/HCV Coinfection

Evidence for the nonhepatic complications of chronic HCV infection continues to accumulate. HIV and HCV infec-
tions are both known to independently reduce bone mineral density (BMD). A cohort study of Medicaid patients indicated that HIV/HCV coinfected patients treated with antiretroviral therapy had a higher adjusted hazard ratio of both spine and hip fractures than did either HIV-monoinfected or HIV/HCV-coinfected patients. Coinfected patients also had a higher relative hazard of hip fracture than did HCV-monoinfected patients; the fracture risk was higher for HIV/HCV-coinfected women than for coinfectcd men (Abstract 914).

Viral hepatitis may also be associated with increased intestinal permeability and an associated proinflammatory state, as indicated by findings from 3 studies: higher levels of gut-microbe-associated lipopolysaccharides (LPS) in HIV/HCV-coinfected patients than in HIV-monoinfected patients (Abstract 936); higher LPS and soluble CD14 (sCD14) levels in HIV/hepatitis B virus (HBV)-coinfected patients than in HIV-monoinfected patients (Abstract 937); and higher LPS, sCD14, and interleukin 6 (IL-6) levels in HCV- and HBV-monoinfected patients (Abstract 939) than in uninfected control subjects. Treatment of HIV and viral hepatitis infections was associated with reduction of these markers in some but not all of these studies.

In terms of predicting progression of liver fibrosis, low CD4+ cell count nadir and coinfection with HCV were independently associated with progression from no or moderate fibrosis (fibrosis stages F0–F2) to advanced fibrosis (stages F3–F4) over a 5-year time period (Abstract 921), support-
ing the need for early initiation of antiretroviral therapy for HIV/HCV-coinfected patients to avoid immunosuppression and progression of liver disease. Low-density lipoprotein (LDL) cholesterol level has also emerged as an important predictor of progression to hepatic fibrosis (Abstract 925). It is postulated that HCV uses the LDL cholesterol receptor to enter hepatocytes and disrupts the LDL cholesterol secretion pathway; low serum levels of LDL cholesterol may therefore reflect high levels of HCV intrahepatic activity.

Two studies were a sobering reminder for clinicians to counsel patients that they remain susceptible to HCV reinfection after HCV infection has cleared spontaneously or with treatment. In a cohort of 58 HIV/HCV-coinfected men who have sex with men (MSM) studied longitudinally, 21% were found to have a different strain of HCV virus from that at baseline, indicating interim reinfection (Abstract 912). Similarly, 6 of 26 HIV-infected MSM successfully treated for acute HCV infection were reinfected with a different strain during a median follow-up period of 1.1 years (Abstract 958).

Hepatitis B Virus Infection

Although HCV coinfection with HIV infection is more common in the United States, coinfection with HBV remains an important contributor to morbidity and mortality. In the MACS (Multicenter AIDS Cohort Study) of HIV-infected and -uninfected MSM, liver-related death was statistically significantly higher for patients with chronic HBV infection than for those with HCV infection (incidence rate ratio [IRR], 2.04; \( P = .03 \)), including patients with HIV coinfection (IRR, 2.26), in whom the majority of liver-related deaths occurred (Abstract 968).

HIV/HBV-coinfected patients are frequently treated with tenofovir-based regimens for the drug’s anti-HBV activity. In a model adjusted for several variables including race, CD4+ cell count, and plasma HIV RNA level, the presence of advanced liver fibrosis (fibrosis stages F3–F4) was associ-
ated with a 3.74 higher hazard ratio (95% confidence interval [CI], 1.57–8.9) of mild renal impairment (defined as glomerular filtration rate < 80 min/mL/1.73 m² by the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) in HIV/HBV-coinfected patients treated with tenofovir (Abstract 977). Monitoring of renal function may be of particular importance for HIV/HBV-coinfected, antiretroviral drug–treated patients with advanced fibrosis.

HBV/HIV-coinfected patients traditionally have a disappointing response to HBV vaccination. Potsh and colleagues report a promising hepatitis B surface antibody (HBsAb) seroconversion rate of 83% with an accelerated schedule of a 40-µg HBV vaccination administered at 0 months, 1 month, and 2 months, which increased to 91% with an additional dose administered at 6 months (Abstract 971). As in other series, a CD4+ cell count greater than 350/µL was associated with a higher response rate to the additional dose at 6 months (85% for the 3-dose schedule and 93% for the additional dose).

Cardiovascular Disease

There continues to be strong interest in the relationship between HIV infection and cardiovascular disease (CVD), with additional studies confirming independent contributions of HIV infection (Abstract 809) and immunodeficiency (Abstract 810) to myocardial infarction (MI) risk in large cohorts. New data on the pathogenesis, clinical outcomes, and risk factors for CVD were presented this year. The relationship between markers of inflammation and disordered coagulation remain an active area of investigation.

Endothelial Function and Altered Coagulation

Measurement of the capacity of endothelium to release tissue type plasminogen activator (t-PA) is one index of endothelial function. Mestek and colleagues previously reported that treatment-naive, HIV-infected patients have impaired release of t-PA as as-
sessed by the response to infusion of bradykinin and nitroprusside into the brachial artery. At this year’s meeting, the group examined t-PA release in treated HIV-infected patients and in age-matched and older HIV-uninfected adults and found that the HIV-infected group, regardless of treatment status, had impaired endothelial t-PA release (Abstract 802). Of note, the HIV-infected patients had a level of impairment comparable with that of uninfected adults 25 years to 30 years older, suggesting that vascular aging might be contributing to the higher rates of CVD observed in HIV-infected patients.

The SMART (Strategies for Management of Antiretroviral Therapy) study demonstrated a strong relationship between levels of D-dimer at baseline and all-cause mortality in patients who either discontinued or continued antiretroviral therapy. The relationship between D-dimer and mortality was further explored using stored samples from the completed, randomized trials of interleukin 2 (IL-2), ESPRIT (European/Australasian Stroke Prevention in Reversible Ischaemia Trial), and SILCAAT (Study of Interleukin 2 in People with Low CD4+ T-Cell Counts on Active Anti-HIV Therapy) (Abstract 375). Overall, higher D-dimer levels were associated with mortality. Of note, those with the D-dimer levels in the highest quartile had an excess risk of death if they were assigned to receive IL-2; the mechanism explaining this association remains elusive.

Hsue and colleagues performed a comprehensive assessment of coagulation biomarkers, comparing 308 HIV-seropositive men with a small group (n=38) of uninfected control men to determine which abnormalities were more prevalent in treated and untreated HIV-infected patients than in control subjects (Abstract 797). Untreated HIV infection was associated with a decrease in thrombin generation (which did not appear to be further altered by antiretroviral therapy) and an increase in a thrombin inhibitor, whereas no difference in D-dimer, tissue factor, or other coagulation markers were noted in this group of asymptomatic patients, suggesting a more complex interaction of factors contributing to vascular events. On the other hand, higher levels of D-dimer, along with P-selectin and hyaluronic acid, independently predicted the risk of venous thromboembolic events in a case-control study of HIV-infected patients (Abstract 799).

Morse and colleagues from the National Institutes of Health compared biomarkers of coagulation and endothelial function in a group of HIV-infected patients with those of uninfected control subjects (Abstract 798). Higher levels of D-dimer correlated with levels of plasma HIV-1 RNA, markers of endothelial function, and tumor necrosis factor alpha (TNF-α) in the HIV-infected group. Higher levels of the endothelial activation markers soluble intracellular adhesion molecule (sICAM), soluble vascular adhesion molecule (sVCAM), TNF-α, IL-6, and tissue factor, but not D-dimer, were noted in the HIV-infected group. These authors hypothesize that HIV infection may increase D-dimer levels through induction of endothelial activation, mediated by TNF-α released from monocyte and macrophage activation.

**Risk of Myocardial Infarction**

Novel markers that might help identify increased CVD risk continue to be evaluated. Müllerian inhibiting substance (MIS), a marker of ovarian reserve, is an objective measure of menopause in women. LaCross and colleagues examined the association between levels of MIS and surrogate markers of atherosclerosis, carotid intima media thickness (IMT), and coronary artery calcium (CAC) in HIV-seropositive women (Abstract 804). Low levels of MIS, but not self-reported menopausal status, was strongly associated with the presence of CAC but not carotid IMT after control for age. The authors conclude that measurement of MIS might help identify HIV-seropositive women who are candidates for more aggressive risk factor management to prevent CVD.

The prognostic values of different lipid indices as predictors of MI risk were evaluated in a case-control study from the SMART study (Abstract 807). Using age- and gender-matched cases (n=100) and controls (n=176), the ratio of apolipoprotein B to apolipoprotein A1 and the ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol level had similar predictive value and provided more information about MI risk than did individual lipoprotein measures in HIV-infected patients. Finally, measurement of soluble CD163, a marker of activated macrophages, was shown to be increased in men with well-controlled HIV disease and was associated with the presence of noncalcified coronary plaque, as measured by multidetector computed tomography (CT) angiography (Abstract 813).

The outcomes of acute coronary syndromes in HIV-seropositive patients were compared with those of HIV-seronegative control subjects using data from the Nationwide Inpatient Sample, a database of almost 300,000 patients at US hospitals (Abstract 801). Excluding patients over the age of 65 years, the authors reported that HIV-infected patients admitted to the hospital with acute coronary syndrome were younger and more likely to have a history of renal disease but less likely to have hypertension, hyperlipidemia, or diabetes than uninfected control patients. Importantly, HIV-seropositive patients had an increased risk of in-hospital death (3.3%) compared with HIV-seronegative patients (2.3%) and were more likely to incur acute renal failure during the hospitalization. These findings suggest that clinicians need to remain vigilant for signs and symptoms of coronary syndromes in younger patients with HIV infection who may not have traditional risk factors.

The relationship between recent abacavir exposure and MI risk remains controversial. An FDA meta-analysis of 26 randomized clinical trials with nearly 10,000 patients attempted to lay the issue to rest (Abstract 808). The analysis found no association between abacavir treatment and MI events, and the authors calculated that the sample size evaluated had sufficient power to exclude an MI-risk difference of 1%. The lack of independent adjudica-
tion of MI events and the comparison of abacavir to PI-based antiretrovi-ral therapy in many of the trials still leaves some degree of lingering uncertainty. Studies evaluating in vitro and in vivo (animal model) effects of abacavir on leukocyte adhesion suggest a potential mechanism that could underlie this uncertain association (Abstract 815).

**Bone Loss: Host Factors, Antiretroviral Drugs, or HIV Disease?**

Several studies this year helped untangle the contributions of host factors, HIV disease status, and antiretroviral drugs to the prevalent condition of bone loss observed in patients with treated HIV infection. Randomized clinical trials of tenofovir/emtricitabine or tenofovir alone used as preexposure prophylaxis (PrEP) in HIV-uninfected MSM provided the opportunity to evaluate the contribution of these drugs to bone loss in the absence of HIV infection.

Mulligan and colleagues reported the results of a bone substudy from the larger iPrEx (Preexposure Prophylaxis Initiative) trial (Abstract 94LB). Dual-energy x-ray absorptiometry (DEXA) scans measuring BMD at the hip and spine were performed at 24-week intervals in 503 men randomly assigned to receive tenofovir/emtricitabine or placebo. The groups were well matched at baseline: notably, 36% had low BMD (z score < -1) in the spine and 18% in the hip. BMD tended to increase in the placebo group (as would be expected in young men); however, the decrease in the tenofovir/emtricitabine group resulted in a modest (-0.7% to -1.0%) but statistically significant difference between the groups by week 24.

In the smaller tenofovir PrEP safety study (Abstract 93), conducted in men with a median age of 40 years, there was a 1.1% decrease in mean BMD in the tenofovir versus pretreatment or placebo groups at the femoral neck and a 0.8% net decline at the total hip; both decreases reached statistical significance. Overall, 13% of the tenofovir recipients compared with 6% of the placebo group experienced a 5% or more loss in BMD at the femoral neck in this study. Together, these studies demonstrate that low bone density appears to be common among young MSM at risk for HIV infection and that exposure to tenofovir, either alone or combined with emtricitabine, and in the absence of HIV infection, is associated with a small but statistically significant decline in BMD. The clinical importance of these changes is currently unknown and requires further study.

Peak bone mass is achieved in early adulthood, hence the effects of HIV infection and exposure to antiretroviral therapy among younger patients has become an active area of research, with several groups reporting new data this year (Abstracts 705–707, 823). Investigators in the Adolescent Trials Network examined associations between antiretroviral therapy exposure and HIV serostatus on BMD in a cross-sectional study of age-matched and race- or ethnicity-matched youth aged 14 years to 25 years (Abstract 705). Importantly, norms for the DEXA z scores included in this study were from a similarly aged population.

Total and regional fat measures were higher in the HIV-seronegative groups and lower in the antiretroviral therapy–naive groups. Lean body mass and total and regional fat measures were lower in all HIV-seropositive groups and higher in the HIV-seropositive group that was antiretroviral therapy–naive than in those receiving treatment. Mean BMD and z scores were consistently lower among HIV-seropositive participants receiving antiretroviral therapy, particularly in those receiving PIs, than in the HIV-seronegative group.

Of note, the low BMD in those receiving antiretroviral therapy was not explained solely by tenofovir use. Brazilian investigators identified low BMD in about a third of perinatally infected youth and a strong correlation between low BMD and lean body mass, highlighting the importance of interventions to improve nutrition to prevent bone loss in this age group (Abstract 706). An Israeli study of young women with HIV infection reinforced the importance of sun exposure, calcium intake, and vitamin D status, in addition to skin color as contributors to BMD status (Abstract 823).

In one of the first randomized intervention studies for bone health among HIV-seropositive youth, perinatally HIV-infected children and ado-lescents aged 6 years to 16 years were randomly assigned to receive vitamin D (100,000 IU bimonthly) and calcium (1 g daily) (n = 30) or placebo for both (n = 29) for 2 years (Abstract 707). At follow-up, 25-hydroxy vitamin D concentrations were higher among the treated patients at 1 year and 2 years. However, although BMD improved in both groups, there was no additional improvement in the group receiving the supplemental vitamin D and calcium. The observation that three-fourths of the children in the intervention group had vitamin D levels below 30 ng/mL at least once during study follow-up suggested that challenges with adherence may have undermined the benefits of the supplements evaluated in this trial.

**Is Bone Loss Mediated by Immune Reconstitution?**

Several studies have demonstrated that bone loss occurs within the first 6 months after the initiation of antiretroviral therapy but then stabilizes. To date, much of the work in this area has focused on the contributions of antiretroviral therapy to bone loss. Ofotokun and colleagues from Emory University examined the time course of changes in bone resorption among a small group of treatment-naive HIV patients initiating antiretroviral therapy (tenofovir/emtricitabine/lopinavir/ritonavir) (Abstract 78). The researchers measured changes in the serum biomarker C-terminal telopeptide of type 1 collagen (CTx), an index of in vivo bone resorption, and in the recep-tor activator of nuclear factor kappa-B ligand (RANKL), an osteoclastogenic cytokine that can be secreted by T cells) at weeks 0, 2, 12, and 24.

During the early timepoints, they observed statistically significant increases in both of these markers, suggesting that early improvements in
immune cell function might mediate bone loss. The same group also examined the effects of T-cell reconstitution by the adoptive transfer of T-cells into T-cell null, T-cell receptor beta chain (TCRβ) knockout mice and found that when the mice received the new T cells, a loss of bone density occurred that mirrored the effects observed in humans, with a rise in levels of CTx and RANKL.

Early changes in markers of bone resorption were also identified in HIV-infected populations. In a randomized clinical trial that demonstrated a greater degree of bone loss with zidovudine/lamivudine/lopinavir/ritonavir than with nevirapine/lopinavir/ritonavir (Abstract 833). Bone biomarkers of resorption (tartrate-resistant acid phosphatase 5b [TRAP5b] and CTx) and biomarkers of bone formation (bone-specific alkaline phosphatase [BAP] and procollagen type 1 N-propeptide [P1NP]) were measured on stored samples at baseline and at months 3, 12, and 24. Peak resorption occurred to appear by month 3; no data from earlier timepoints were available. Together these studies suggest a possible early-intervention window to prevent bone loss after the initiation of antiretroviral therapy. In addition, these findings suggest that a component of early bone loss may be mediated by immune reconstitution.

Connections Between Bone Density and Fat Depots

Associations between regional body fat and bone density were explored in a cross-sectional study from the Women’s Interagency HIV study (WHIS) (Abstract 835). Total fat and lean mass were independently associated with greater BMD in HIV-infected and -uninfected women. Of note, greater amounts of leg fat correlated with lower BMD, suggesting that regional fat depots may contribute to changes in BMD independently.

The impact on bone density of drugs used to manage lipodystrophy in HIV infection was evaluated in 2 studies. In a small, randomized clinical trial, rosiglitazone did not reduce BMD compared with placebo (Abstract 832). The impact of tenofovir, a growth hormone–releasing hormone agonist recently approved for the treatment of fat accumulation in HIV-infected patients, on markers of bone turnover (osteocalcin and N-terminal telopeptide [NTx]), was evaluated over 26 weeks in a randomized, placebo-controlled study among HIV patients with excess abdominal fat (Abstract 834). Treatment with tenofovir 2 mg daily resulted in higher increases, relative to placebo, in markers of bone formation (osteocalcin) than in NTx, a marker of resorption. Whether these changes in bone turnover markers will translate into improvement in BMD remains to be seen.

Fracture Risk and Antiretroviral Therapy

Cohort studies have suggested that HIV-infected adults are at higher risk of fracture than the general population. Whether specific antiretroviral drugs contribute to this risk remains an active area of investigation. Yin and ACTG (AIDS Clinical Trials Group) colleagues examined the association between antiretroviral drug classes and risk of fracture in the ALLRT (ACTG Longitudinal Linked Randomized Trials) study, a long-term follow-up study of patients who have been enrolled in randomized trials of antiretroviral therapy (Abstract 830). In this analysis of 3372 mostly male (85%) HIV-seropositive participants with a median age of 39 years, the incidence of new fractures was 0.3 per 100 person-years (95% CI, 0.2–0.4). In univariate analysis, no single class of antiretroviral drug (PI, nucleoside analogue reverse transcriptase inhibitor [nRTI], or nonnucleoside analogue reverse transcriptase inhibitor [NNRTI]) or individual drug (tenofovir or efavirenz) examined was associated with fracture. In a multivariate analysis, factors associated with increased fracture risk were HCV coinfection and a diagnosis of osteoporosis at study entry, whereas Hispanic ethnicity was protective. These data suggest that over the long term, antiretroviral therapy may not be an important contributor to fracture risk.

Vitamin D

There continues to be great interest in the relationship between vitamin D deficiency and a variety of outcomes in HIV-infected populations. Investigators from the WHIS confirmed the high prevalence of low vitamin D levels in HIV-infected women and observed the absence of the expected variation with season (Abstract 822). Stored serum samples from the echo (Efficiency Comparison in Treatment-Naive HIV-Infected Subjects of TMC278 and Efavirenz) trial were used to compare changes in 25-hydroxy vitamin D (25(OH)D) serum levels and proportions of patients with 25(OH)D deficiency in patients receiving the investigational drug TMC278 (rilpivirine) versus efavirenz over 48 weeks (Abstract 79LB). The study demonstrated a decline in 25(OH)D with efavirenz (−6.2 ng/dL) and no change with TMC278 (−0.6 ng/dL). Patients with an insufficiency or deficiency in 25(OH)D at baseline had a statistically significantly lower risk of experiencing severe 25(OH)D deficiency with TMC278 (4%) than with efavirenz (20%).

Low levels of vitamin D and use of tenofovir both appear to be associated with elevations in parathyroid hormone (PTH) levels in HIV-infected patients (Abstract 825). The impact of vitamin D₃ replacement on levels of vitamin D and PTH was evaluated in an Adolescent Trials Network randomized, placebo-controlled trial of directly observed, monthly dosing of 50,000 IU vitamin D₃ or placebo for 12 weeks. Subjects were 18- to 24-year-olds stratified by use of tenofovir. At week 12, 52% in the vitamin D replacement group had sufficient 25(OH)D serum levels, an increase from 17% at baseline, compared with 16% at baseline and at week 12 in the placebo group (P < .001). A statistically significant decline in PTH levels (−6 pg/mL) was observed only in the tenofovir group receiving vitamin D₃. These results suggest that vitamin D₃ replacement may...
mitigate hyperparathyroidism in patients taking tenofovir; whether this translates into improvements in bone density must await the DEXA data from this trial.

Other studies evaluated the relationship between vitamin D and diabetes and surrogate markers for CVD. A retrospective Italian study suggested that vitamin D₃ supplementation was associated with a lower risk of incident diabetes (Abstract 827); however, data on vitamin D levels were not reported. No improvement in brachial artery flow-mediated dilation (FMD) was observed in a randomized controlled trial of vitamin D₃ supplementation (4000 IU daily for 12 weeks) (Abstract 829). Although the study was adequately powered to detect a 3% improvement in FMD, it was notable that during the relatively short period of follow-up, vitamin D₃ replacement led to only modest increases in vitamin D levels. Recent recommendations for screening and replacement of vitamin D may provide a starting place for patients with HIV infection until more definitive studies are available.⁹

Lipodystrophy

Fat in All the Wrong Places

There is little doubt that increased visceral fat is associated with poor long-term outcomes in HIV-uninfected adults,¹⁰ but the contribution of visceral fat to mortality in HIV-infected persons has not been well studied. Investigators from the Fat Redistribution and Metabolic Change in HIV Infection (FRAM) study (Abstract 76) examined the relationships between muscle mass, visceral fat, and survival in the HIV-infected cohort of this observational study. Participants in the highest tertile for visceral fat had a 2-fold higher mortality than those in the lowest tertile. Causes of death were not known, nor was it possible to compare the magnitude of the effect of visceral fat on mortality with that from an uninfected population. Despite these limitations, the findings serve as a reminder that excess visceral fat may have important long-term consequences in patients with HIV infection.

The relationships among visceral fat, coronary plaque, and coronary artery calcification were examined in HIV-infected and -uninfected men using data from the MACS (Abstract 806). Noninvasive coronary computed tomography angiography (CCTA) was used to measure total plaque area and coronary artery calcium (CAC). Abdominal (total, visceral, and subcutaneous) fat was measured by noncontrast CT scans; liver fat was also assessed. After adjustment for age, there were strong associations observed between visceral abdominal tissue (VAT) and subclinical atherosclerotic plaque (defined as CCTA-diagnosed, combined calcified and noncalcified plaque) in HIV-uninfected men than in HIV-infected men. No associations were found between measures of CAC and specific fat depots in either group.

Epicardial adipose tissue (EAT) can be measured when coronary calcium is measured with noncontrast CT scans. EAT was associated with older age, greater amounts of VAT, male sex, waist girth, and liver fat in an Italian study (Abstract 805). Not surprisingly, increased amounts of EAT were associated with greater amounts of fat in other places (VAT and liver) and with CAC. The only clinical variable associated with greater amounts of EAT was CD4+ cell count increase from nadir, suggesting that immune reconstitution might play a role in the pathogenesis of the excess fat observed.

Antiretroviral Therapy and Body Fat Changes: Coming and Going

Weight and body fat content are known to increase when antiretroviral therapy is initiated, especially among those with more advanced disease and pre-treatment weight loss. Newer regimens have been assumed to have minimal effects on body composition before now. A metabolic substudy of the ACTG study 5202¹¹ was a 4-arm trial of HIV-infected, treatment-naive subjects randomly assigned equally to double-blinded abacavir/lamivudine versus tenofovir/emtricitabine with open-label efavirenz or ritonavir-boosted (r) atazanavir. Endpoints in A5224s included changes from baseline to week 96 in VAT and the ratio of VAT to total adipose tissue by CT scan (Abstract 77).

The study demonstrated that trunk fat and VAT increased 28% and 19%, respectively, for all subjects, with greater gains for those receiving atazanavir/r than for those receiving efavirenz, 36.5% versus 21.1%, respectively. Similar increases in trunk fat and VAT were observed between those receiving abacavir/lamivudine and those taking tenofovir/emtricitabine. The clinical importance of the greater amounts of VAT gained in the atazanavir/r arm are not immediately clear and may depend on the baseline starting point. These findings highlight the concept that different antiretroviral regimens may vary in their contributions to various metabolic and body fat changes.

The question of whether switching from a PI/r-based to a raltegravir-based antiretroviral regimen might reverse changes in abdominal and subcutaneous fat was evaluated in the 48-week SPIRAL (Switching from Protease Inhibitor to Raltegravir in HIV Stable Patients) study (Abstract 845).¹² In this study, patients (n = 73) who were virologically suppressed with any PI/r regimen were randomly assigned to either continue the same treatment or switch to a raltegravir-based regimen.

After 48 weeks, statistically significant increases in total abdominal fat area and visceral fat area as measured by CT were observed in the PI/r group, without changes in the subcutaneous fat area or in the ratio of subcutaneous fat to visceral fat. At the same time, no statistically significant changes were observed within the raltegravir group or between treatment groups. No significant changes were observed within or between groups in body fat distribution measured by DEXA (measures of limbs, trunk, total fat, and fat mass ratio). Although statistically significant increases occurred in total BMD and femoral BMD within the raltegravir group, these differences were not statistically significant when compared with the PI/r group. These findings, while not definitive, suggest that with a larger sample size or longer follow-up period, differences between the study
zidovudine and stavudine are both naive patients examining these issues from comparative studies in treatment groups might emerge. Results from comparative studies in treatment-naive patients might be less definitive.

Earlier studies demonstrated that zidovudine and stavudine are both associated with loss of subcutaneous fat. The degree to which this fat loss improves when zidovudine is switched to tenofovir has been well studied but is important to determine as tenofovir becomes more widely available in resource-limited settings. A comprehensive, randomized study examined changes in limb fat, subcutaneous abdominal fat, and mitochondrial DNA (mtDNA) quantity and quality as well as adipocyte size and measures of gene expression in patients who continued with zidovudine or switched to tenofovir (Abstract 846). The tenofovir group experienced statistically significant increases in both subcutaneous adipose tissue and limb fat at week 48, with a statistically significant between-group difference in percentage of change in subcutaneous adipose tissue at week 48. In the molecular substudy, switch to tenofovir resulted in statistically significantly greater increases in mtDNA content and quality at weeks 24 and 48 and an increase in adipocyte size.

Renal Disease

Chronic kidney disease (CKD) remains an important cause of morbidity in HIV patients. Investigators from the UK Consumer Health Information Consortium examined the effects of baseline renal function to long-term outcomes in more than 20,000 patients observed for a median of nearly 6 years (Abstract 836). Although the results are not surprising—lower baseline measures of renal function predicted which patients were at greater risk of progression of renal disease and risk of death—these findings underscore the importance of careful monitoring of renal function in patients who enter care with impairment.

Investigators from the SMART study evaluated the relationship between lipid levels and measures of renal function using stored samples from 396 patients. They found that unfavorable lipid profiles (unfavorable total cholesterol: HDL cholesterol ratios and apolipoprotein B: apolipoprotein A1 ratios) were associated with higher cystatin C levels but not with estimated glomerular filtration rate (GFR) (Abstract 839). Another analysis from SMART observed that the rate of new or progressive CKD was higher among patients randomly assigned to discontinue antiretroviral therapy and that among those who continued antiretroviral therapy, progression of CKD was predicted by hepatitis coinfection and, as expected, by diabetes, hypertension, and older age (Abstract 837).

As the availability of tenofovir continues to expand in resource-limited settings, it is important to understand the patient characteristics that might preclude the safe use of fixed-dose regimens. In a randomized 3-arm trial, a small but statistically significant and nonprogressive decline in GFR was observed when tenofovir/emtricitabine was combined with atazanavir/ritonavir compared with efavirenz or abacavir/zidovudine (Abstract 841). Investigators from the University of North Carolina Project in Malawi reviewed data on patients (predominantly young women) who were screened for clinical trials that required a creatinine clearance of greater than 50 mL/min; the study aimed to identify factors associated with exclusion to inform strategies for antiretroviral treatment programs. Fortunately, among the 1224 patients eligible for antiretroviral therapy (those with CD4+ cell counts <350/µL), 98% had creatinine clearance above the required 50 mL/min level (Abstract 838). Only lower BMI predicted reduced renal function. These results suggest that few patients would need to be excluded from a tenofovir-based initial regimen in this setting.

Malignancy

AIDS-defining malignancy (ADM) and non–AIDS-defining malignancy (NADM) continue to grow as important causes of mortality. The Swiss HIV Cohort Study (SHCS) reported that NADM (19.1%) surpassed AIDS (16.4%) as the primary cause of death from 2005 through 2009 (Abstract 789). Together, NADM and ADM accounted for 25.8% of all deaths, in this largely antiretroviral therapy–treated cohort. HCV coinfection status substantially impacted the cause of death. Liver disease (excluding hepatocellular carcinoma) was the most frequent cause of death (27.2%) in HCV-coinfected individuals, whereas NADM (24.2%) was most common in HCV-uninfected persons.

The risk of death from NADM, as well as from liver disease and CVD, appears to increase with cumulative exposure to antiretroviral therapy in the EuroSIDA cohort, compared with those receiving antiretroviral therapy for less than 2 years (Abstract 790). These data suggest that viral viral control alone may be insufficient to reverse the higher rates of malignancy associated with HIV infection. The US HIV Outpatient Study (HOPS) also reported an increase in rates of non–infection-related NADM but stable rates of infection-related NADM (Abstract 867). Encouragingly, however, HOPS data also indicated that survival in HIV-infected patients with any cancer diagnosis improved over time.

In a German cohort with limited immunosuppression and high uptake of antiretroviral therapy, mortality caused by lung cancer remained high, with a 2-year overall survival rate of 23.7% for HIV-infected patients with lung cancer (Abstract 868). Fifty of 51 (98%) of these patients were former or current heavy smokers, a reminder that smoking cessation is a key part of cancer prevention in the HIV-infected population, in whom smoking rates remain alarmingly high.

Records from US children diagnosed with HIV infection between 1980 and 2008 indicate that the risks of Kaposi sarcoma and non–Hodgkin lymphoma remain elevated but have declined with widespread antiretroviral therapy use and that rates of NADM have remained stable, with a persistent, elevated risk of leiomyosarcoma in particular (Abstract 82LB). Persons diagnosed with HIV infection in childhood will need ongoing surveillance for cancer in adulthood, despite adequate immune reconstitution with antiretroviral therapy.
Human Papillomavirus

Human papillomavirus (HPV) is an important driver of malignancy in HIV infection, and the risks of HPV acquisition and related complications do not appear to decline with antiretroviral treatment. Hoffmann and colleagues found the development of anal squamous cell carcinoma was not associated with level of immunodeficiency or HIV viremia and that disease-related mortality after a median of 2 years was 13% (Abstract 870). In a group of HIV-infected MSM, 24 months of antiretroviral therapy did not reduce rates of acquisition of HPV, with 25% and 12% acquiring new oncogenic HPV strains 16 and 18, respectively (Abstract 871). It was notable that HPV infection in this group was dynamic, with 29% and 57% clearing HPV strains 16 and 18, respectively.

In several HIV-infected cohorts of men and women from the United States and international settings, HPV strain 16 prevalence ranged from 30% to 50% and HPV strain 18 from 12% to 23% (Abstracts 762, 763, and 871), suggesting that HPV vaccination in HIV-infected individuals may have the potential to prevent acquisition of further oncogenic strains. However, a Thai study reported that 43% of high-grade anal intraepithelial neoplasia was associated with non-HPV 16 or 18, respectively (Abstract 871).

The frequency of TB immune reconstitution inflammatory syndrome (IRIS) was statistically significantly higher in the immediate- (11%) than in the early-treatment group (5%; P = 0.009).

In the SAPIT (Starting Antiretroviral Therapy at Three Points in Tuberculosis Therapy) study, 429 HIV-seropositive subjects in South Africa with CD4+ cell counts less than 500/µL and culture-positive TB were randomly assigned to initiate antiretroviral therapy either within 4 weeks of TB therapy initiation or within 4 weeks of completion of the intensive phase of TB therapy (Abstract 39LB). There was no difference between the 2 groups in the primary endpoint of AIDS or death. Similar to findings in the STRIDE study, in a prespecified analysis of those with CD4+ cell counts less than 50/µL, the rates for AIDS or death were lower in the immediate-treatment (8.5/100 person-years) than in the early-treatment (12.9/100 person-years) group (IRR, 0.32; P = 0.06).

Rates of viral suppression and CD4+ cell count rise did not differ between groups, but rates for TB IRIS were higher in the immediate-treatment than in the early-treatment group (46.8/100 person-years vs 9.9/100 person-years, respectively; in those with CD4+ cell counts <50/µL; IRR, 4.71; P = .01 and 15.8/100 person-years and 7.2/100 person-years in those with CD4+ cell counts ≥50/µL; IRR, 2.2; P = .02). Patients in the immediate-treatment group also had more antiretroviral drug switches than those in the early-treatment group.

In a symposium titled “Colliding Epidemics: Controlling HIV-Related TB,” Burman summarized the results and insights from the STRIDE, SAPIT, and CAMELIA (Cambodian Early Versus Late Introduction of Antiretrovirals) studies (Abstract 166). The important message from these studies is that combined antiretroviral therapy and TB therapy reduces mortality. For patients with CD4+ cell counts less than 50/µL, antiretroviral treatment needs to be initiated within 2 weeks of TB therapy initiation to reduce AIDS or mortality. For those with higher CD4+ cell counts, antiretroviral therapy can be initiated after the intensive phase of TB therapy (8 weeks) to avoid higher rates of TB IRIS that occur when antiretroviral treatment is initiated early.

Burman pointed out that TB meningitis may be the one exception to these recommendations because a prior randomized study in this population revealed no benefit, and possible detrimental effects, of initiating antiretroviral therapy immediately in this situation. Challenges to implementing the new findings from the STRIDE, SAPIT, and CAMELIA investigations include ramping up HIV testing rates in TB patients, improving linkages between HIV and TB treatment programs, improving access to antiretroviral therapy for patients with HIV and TB, and equipping practitioners with information to manage TB IRIS.

In this year’s posters on TB in HIV-infected patients, a large observational study of 4908 HIV-seropositive patients with TB living in western Kenya reported improved survival among those starting early antiretroviral therapy, consistent with the results of the randomized clinical studies (Abstract 881). In a clinic-based study evaluating 1499 patients with HIV and TB from South Africa, it was similarly reassuring that there was no compromise in viral suppression rates or CD4+ cell count restitution among those initiating antiretroviral therapy earlier than later (Abstract 882).
New TB diagnostics is a very active and exciting field, although there was surprisingly little data presented at this meeting. Neither the interferon-gamma-release assay measuring free interferon gamma levels nor the urine lipoarabinomannan test showed good performance for the diagnosis of TB in HIV-seropositive patients (Abstracts 877 and 878).

However, in a very interesting abstract by Van Rie and colleagues, investigators from South Africa evaluated the performance of a new rapid polymerase chain reaction (PCR) assay (manufacturer: Cepheid, Sunnyvale, CA) as a diagnostic test for Mycobacterium tuberculosis and for resistance to rifamycin for the diagnosis of TB from lymph node aspirates (Abstract 879). They reported a sensitivity of 100% and a specificity of 95.8% compared with TB culture using a Mycobacteria growth indicator tube. Importantly, the PCR assay results were used to justify TB treatment initiation in 19 of 51 subjects.

Prior studies indicated that the performance of this rapid assay would be excellent using sputum specimens; however, the performance of this rapid assay would be surprising little data presented at this meeting. Neither the interferon-gamma-release assay measuring free interferon gamma levels nor the urine lipoarabinomannan test showed good performance for the diagnosis of TB in HIV-seropositive patients (Abstracts 877 and 878).

Combining HIV and TB care poses additional challenges, as highlighted by work presented by Bassett and colleagues (Abstract 886). Among 144 subjects identified with TB by sputum culture in an HIV care clinic in Durban, South Africa, only 42% had documented TB treatment completion at the end of 1 year. Twenty-five percent of the treatment-noncompleter subjects died, and 16% were lost to follow-up. The authors suggested that financial constraints and poor TB education represented barriers to accessing care in this population.

On a more optimistic note, Brown and colleagues examined the time to antiretroviral therapy initiation among patients with TB at a Khayelitsha, South Africa, clinic both before and after the clinic integrated HIV and TB care (Abstract 890). The median time to antiretroviral therapy initiation decreased from 110 days to 58 days for pre- and postintegration, respectively. Comparing outcomes with those of a clinic without treatment integration, the authors confirmed that “one-stop” care for HIV and TB was associated with a shorter time to antiretroviral treatment initiation, and that TB outcomes were not adversely affected.

**Cryptococcal Meningitis**

Cryptococcal meningitis remains a major cause of morbidity and mortality, even in areas that have experienced rapid scale-up of antiretroviral therapy in resource-limited settings. Amphotericin-based regimens remain the gold standard in the developed world, but even properly treated patients with severe disease still have suboptimal outcomes; amphotericin toxicity is substantial, and cost and delivery are challenging for many areas in Africa, where the burden of disease is high. For these reasons, investigators have designed a new generation of treatment studies for cryptococcal meningitis in attempts to improve efficacy and identify alternatives to the standard amphotericin regimens.

Several pilot studies were presented at the conference this year. Jarvis and colleagues randomly assigned 90 patients with cryptococcal meningitis to standard treatment of amphotericin B plus 5-fluorocytosine versus standard treatment plus either interferon-gamma 2-dose therapy (on days 1 and 3 of treatment) or 6-dose therapy (on days 1, 3, 5, 8, 10, and 12) (Abstract 40). The primary outcome of the study was the decline in quantitative cryptococcal cultures from the cerebrospinal fluid. Rates of fungal clearance were faster in each of the 2 interferon-gamma groups than in the standard treatment group. There was no increase in cryptococcal IRIS or toxicity in the interferon-gamma groups. Of note, mortality was 31% overall at 10 weeks and did not differ between the groups.

Muzoora and colleagues presented results of a single-arm pilot study evaluating a short-course amphotericin B-containing regimen in western Uganda (Abstract 894). Subjects were treated with amphotericin B (1 mg/kg/day) plus fluconazole for 5 days and then fluconazole for the remainder of the treatment regimen. Serial quantitative cryptococcal cultures showed a consistent decline that continued beyond the administration of amphotericin B. Patients tolerated the treatment well, and there were no interruptions for toxicity. Mortality was also high in this study—28% at 10 weeks.

In a third study, 80 patients with cryptococcal meningitis were randomly assigned to 1 of 4 groups: amphotericin B plus 5-fluorocytosine; amphotericin B plus fluconazole 800 mg daily; amphotericin B plus fluconazole 1200 mg daily; or amphotericin B plus voriconazole 300 mg twice daily (Abstract 895). There was no difference in fungicidal activity as measured by the decline in cerebrospinal fluid cryptococcal burden between the 4 treatment groups. Mortality was 39% at 10 weeks. Together, these studies demonstrate the possibility of deploying all oral, more effective, and more affordable regimens. However, much more work is needed in this area as evidenced by the extraordinarily high mortality rates (30%) observed among these patients in a carefully monitored, clinical trials setting.
Influenza A (H1N1)

The focus on influenza A (H1N1) this year at the conference was not on clinical aspects of influenza A, as the number of cases has waned globally over the past 2 years. Rather, several new and follow-up studies examined the frequency, intensity, and durability of immunologic responses elicited by various H1N1 influenza A vaccination strategies.

Bickel and colleagues evaluated 135 HIV-seropositive patients after the first and second dose of adjuvanted H1N1 influenza A vaccine (Abstract 906). Seroconversion was 68% after the first dose and increased to 92% after the second dose; low CD4+ cell count was associated with lower rates of seroconversion. Cooper and colleagues examined the effects of a booster to an initial H1N1 adjuvant vaccine immunization in a randomized study of HIV-infected adults (Abstract 907). Seroconversion and seroprotection titers with the first vaccine were comparable to historical controls and were increased from the initial range of 73% to 76% to levels in the range of 83% to 94% in persons who received the booster, at days 21 and 42, respectively. Similar changes were not observed in the control group.

In a follow-up study from France that showed the benefit of adjuvant over nonadjuvant H1N1 influenza A vaccine, Durier and colleagues demonstrated that seroprotective titers persisted at 12 months in 60% of adjuvant-vaccine recipients and that predictors of a durable response included use of adjuvant versus nonadjuvant vaccine and the use of antiretroviral therapy (Abstract 909).

In an ongoing study comparing 2 single doses of adjuvanted H1N1 influenza vaccine in HIV-infected and HIV-uninfected adults, seroconversion and seroprotection H1N1 titers were higher among HIV-infected patients than among HIV-uninfected patients. Within the strata of HIV-infected patients with CD4+ cell counts less than 200/µL, seroconversion was higher with the double than with the single dose (Abstract 910).

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A list of all cited abstracts appears on pages 99–106.

References

13. Dubé MP, Komarow L, Mulligan K, et al. Long-term body fat outcomes in antiretroviral-naive participants randomized to nelfinavir or efavirenz or both plus dual nucleosides. Dual X-ray absorptiometry results from A5005s, a substudy of Adult Clinical Trials Group 384. JAIDS. 2007;45:508-514.
Advances in Antiretroviral Therapy

Barbara Taylor, MD, MS, Susan Olender, MD, Timothy J. Wilkin, MD, MPH, and Scott M. Hammer, MD

The 18th Conference on Retroviruses and Opportunistic Infections maintained its tradition of being the preeminent forum for detailing the state-of-the-art in antiretroviral therapy. There were important presentations on investigational antiretroviral drugs, clinical trials in treatment-experienced patients, and new antiretroviral strategies. Relevant data on resistance to antiretroviral drugs and pharmacokinetic interactions were discussed. There were extensive presentations on antiretroviral therapy in resource-limited settings, including large-scale clinical trials, scale-up of antiretroviral therapy, adherence, retention in care, and treatment outcomes for children and adults. Prevention of mother-to-child transmission continued to be an important part of the conference.

Investigational Drugs

GS-7340

Zolopa presented study data on GS-7340, a novel amidate prodrug of tenofovir designed to deliver high concentrations of tenofovir diphosphate to lymphatic tissues in an effort to minimize systemic exposure and toxic effects while maximizing efficacy (Markowitz et al, Abstract 152LB). Eligible participants were HIV-infected adults naive to antiretroviral therapy who had plasma HIV-1 RNA levels greater than 15,000 copies/mL and CD4+ cell counts of at least 200/µL. Participants were randomly assigned to tenofovir disoproxil fumarate 300 mg daily (n = 10), GS-7340 150 mg daily (n = 10), GS-7340 50 mg daily (n = 10), or GS-7340 150 mg daily (n = 10). All subjects received monotherapy for 14 days. The mean baseline plasma HIV-1 RNA level was between 4.72 log₁₀ copies/mL and 5.03 log₁₀ copies/mL. The primary endpoint was time-weighted average plasma HIV-1 RNA level reduction over 2 weeks of dosing.

The viral load change was greater in both the 50-mg and 150-mg GS-7340 recipients than in the tenofovir group (−0.95 log₁₀ copies/mL and −1.07 log₁₀ copies/mL for GS-7340 doses vs −0.54 log₁₀ copies/mL for tenofovir; P = .03, and P = .001, respectively). The first-phase decay in plasma HIV-1 RNA level was statistically significantly greater in the 2 GS-7340 groups than in the tenofovir group. Both GS-7340 groups had lower plasma levels of tenofovir and higher intracellular tenofovir diphosphate levels in peripheral blood mononuclear cells (PBMCs). There were no safety concerns identified in this small study with limited follow-up. The authors noted that the lower dose of GS-7340 may allow for coformulations that are not possible with tenofovir and may reduce manufacturing costs, which could expand access to tenofovir in resource-limited settings (RLS).

Zinc-finger nucleases. Lalezari and colleagues presented data on 6 participants who received autologous CD4+ T cells that had been treated with a zinc-finger nuclease targeting the CC chemokine receptor 5 (CCR5) gene for disruption (Abstract 46). The participants underwent leukapheresis to collect a large volume of PBMCs, and the monocytes and CD8+ T cells were depleted. The remaining CD4+ T cells were treated with an adenoviral vector to introduce the zinc-finger nuclease that targeted the CCR5 gene for disruption. These cells were expanded in vitro and then infused back into the participant as a single dose.

The authors presented data on 2 dosing cohorts of 3 participants each. The participants were all men with longstanding HIV infection, were receiving antiretroviral therapy, had a plasma HIV-1 RNA level below the limit of detection, and had a CD4+ cell count in the range of 269/µL to 450/µL. There were no serious adverse events related to the infusion, but milder, infusion-related events such as fever, chills, and sweats were common. The CD4+ T-cell count increased in all 6 participants by amounts ranging from 100/µL to 500/µL. These changes generally persisted throughout follow-up, which ranged from 3 months to 12 months. The modified cells appeared to engraft and expand after infusion in 4 of the 6 participants. One participant who had high adenoviral antibody levels before infusion had modified cells that were detectable but did not appear to expand in vivo. These modified CD4+ T cells were also found in the rectal mucosa and persisted in 5 of the 6 participants.

CXC chemokine receptor 4 (CXCR4)-tropic HIV-1 is found commonly in patients with HIV infection, especially those with longstanding infection who have been treated with several different antiretroviral regimens.1 Potential gene therapies targeting CCR5 alone would not be sufficient to treat patients with CXCR4-tropic HIV-1. Small-molecule CXCR4 antagonists have not been developed successfully for treatment of HIV-1 infection. Wilen and colleagues presented data on using zinc-finger nucleases to disrupt the CXCR4 gene in CD4+ T cells (Abstract 47). They were able to disrupt the CXCR4 gene in vitro, and this did not appear
to adversely affect cell growth. They showed that these cells were protected from infection by CXCR4-tropic strains. Using a humanized mouse model, they found that mice receiving the CXCR4-disrupted cells were protected from CXCR4-tropic HIV. Dual-tropic HIV-1 species eventually emerged in these mice, suggesting that a strategy targeting CXCR4 and CCR5 was needed.

Oral Attachment Inhibitor

Nettles and colleagues presented data on the pharmacodynamics of BMS-663068 (Abstract 49). This compound is a prodrug of BMS-626529, which binds to gp120 and interferes with the attachment of HIV to the CD4 receptor. This was an open-label trial of 5 different dosing schemes of BMS-663068 with and without ritonavir. Each cohort enrolled 10 HIV-1-infected adults who were not receiving other antiretroviral therapy for at least 8 weeks before dosing. Two subjects were found to be ineligible after dosing began and were excluded from the analysis.

The median maximal decline in plasma HIV-1 RNA level ranged from 1.2 log_{10} copies/mL to 1.8 log_{10} copies/mL over 8 days of dosing, including all 48 subjects. There were 7 participants who were found to have HIV-1 strains that required more than 1 µmol of BMS-626529 (the active drug) to inhibit 50% of the growth and 2 additional subjects who did not have a baseline sample for analysis. When excluding these 9 subjects, the median maximal decline in plasma HIV-1 RNA level was 1.6 log_{10} copies/mL to 1.8 log_{10} copies/mL. The addition of ritonavir raised the area under the curve (AUC) and minimum plasma concentration (C_{min}) values moderately but did not appear to improve antiviral activity. There were no serious adverse events. The most common adverse events were headache and rash, which were mild to moderate. This study establishes the short-term efficacy of this compound but suggests that there are subpopulations of HIV-1 strains that are somewhat resistant to this compound. Nowicka-Sans and colleagues further characterized these subpopulations by examining the in vitro activity of BMS-626529 in various clinical isolates (Abstract 518). They found that 27% of HIV-1 subtype B, 58% of subtype C, and 72% of subtype A isolates had 50% effective concentrations greater than 1 µmol.

Nonnucleoside Analogue Reverse Transcriptase Inhibitors

GSK2248761 is a nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) that is currently in phase IIB clinical trials. Vavro and colleagues compared the in vitro activity of this compound with that of efavirenz, etravirine, and rilpivirine (Abstract 520). The compound appeared more potent than the other NNRTIs. The highest 50% inhibitory concentration (IC_{50}) was 41 nM for a strain with K103N, Y181C, and G190A mutations in reverse transcriptase. This compound was additive or synergistic with other antiretroviral medications tested.

Integrase Inhibitor

Fenwick and colleagues presented data on BI-C, an HIV-1 integrase inhibitor that prevents the processing of the 3' end of the viral DNA but not the strand-transfer reaction (Abstract 523). BI-C was among a series of compounds the investigators identified in a high-throughput assay. X-ray crystallography showed that these compounds bind a pocket on integrase targeted by lens epithelium-derived growth factor (LEDGF). BI-C has promising in vitro activity against a variety of isolates, including ones highly resistant to other integrase inhibitors that target the strand-transfer reaction (the integrase strand-transfer inhibitors, or INSTIs). The authors reported that this compound was moving into phase I trials.

Clinical Trials of Antiretroviral Therapy in Treatment-Naive Patients

AIDS Clinical Trials Group Study A5175

Campbell and colleagues presented data from AIDS Clinical Trials Group (ACTG) study 5175 (Abstract 149LB). Prior presentations reported on the inferiority of once-daily administrations of atazanavir, didanosine, and lamivudine. This analysis reported on the comparison of efavirenz plus zidovudine/lamivudine versus efavirenz plus tenofovir/emtricitabine. The primary endpoint was time to treatment failure, defined as death, virologic failure (plasma HIV-1 RNA level > 1000 copies/mL at week 16 or later), or HIV disease progression. HIV-1-infected adults with a CD4+ cell count less than 300/µL and naive to antiretroviral therapy were eligible. Participants were enrolled from 12 sites in 8 RLS in addition to the United States. There were 526 and 519 participants enrolled in the tenofovir/emtricitabine and zidovudine/lamivudine groups, respectively. The study population consisted of 46% women and had extensive racial and ethnic diversity. The median baseline CD4+ cell count was 162µL and 169µL for the tenofovir/emtricitabine and zidovudine/lamivudine groups, respectively. The median plasma HIV-1 RNA level was 5.0 log_{10} copies/mL and 5.1 log_{10} copies/mL, respectively. There was no difference between groups in the primary endpoint or any of the 48 subjects, and the CD4+ cell counts were similar between groups. At 3 years of follow-up, approximately 20% of subjects in both groups reached the primary endpoint.

There were statistically significant differences between groups in the safety analyses. The zidovudine/lamivudine group was more likely to have grade 3 or grade 4 laboratory abnormalities and more likely to require a drug substitution. The reason for drug substitution was almost entirely because of grade 3 or grade 4 anemia and neutropenia: 59 cases occurred in the zidovudine/lamivudine group compared with 0 cases in the tenofovir/emtricitabine group. These differences were more pronounced in women than in men. The authors concluded that both regimens are efficacious and that tenofovir/emtricitabine has safety advantages over zidovudine/lamivudine. Furthermore, they asserted that this safety advantage should prompt use of tenofovir/emtricitabine in popu-
tions at higher risk of adverse events, including women.

**Once-Daily Raltegravir**

Eron and colleagues presented data from the QDMRKK study, which compared once- and twice-daily dosing of raltegravir as initial antiretroviral therapy in HIV-1-infected adults (Abstract 150LB). This was a randomized, double-blind, active-controlled clinical trial. Participants were randomly assigned to receive tenofovir/emtricitabine with raltegravir either 400 mg twice daily or 800 mg once daily. The primary objective was to show the non-inferiority of once-daily to twice-daily dosing of raltegravir. The study included 770 participants (median age, 38 years; >80% men; >30% nonwhite).

The proportions of participants with plasma HIV-1 RNA level less than 50 copies/mL (noncompleters = failures) were 88.9% and 83.2% in the twice- and once-daily groups, respectively (overall difference between once-daily and twice-daily dosing, −5.7%; 95% confidence interval [CI], −10.7% to −0.83%). This did not exclude the noninferiority margin of −10%. In addition, the 95% CI excluded zero and established the statistical inferiority of the once-daily arm. Among those with a baseline plasma HIV-1 RNA level greater than 100,000 copies/mL, 84.2% of the twice-daily group and 74.3% of the once-daily group had levels less than 50 copies/mL (−9.9%; 95% CI, −19% to −0.8%). Among those with a baseline plasma HIV-1 RNA level of 100,000 copies/mL or less, 91.9% and 89.1%, respectively, had levels of less than 50 copies/mL (−2.7%; 95% CI, −8.3% to 2.7%). Virologic failure and development of resistance was more common in the once-daily group. These trends were similar across strata of plasma HIV-1 RNA level.

**Dolutegravir**

Eron and colleagues presented data from dolutegravir (S/GSK1349572), an investigational INSTI (Abstract 151LB). This study enrolled participants who had current or prior virologic failure with raltegravir and evidence of resistance. A prior cohort in this study received dolutegravir 50 mg once daily; this cohort received 50 mg twice daily. The results of both cohorts are presented for comparison. Participants were divided into 2 groups based on their INSTI resistance pattern (Q148H/K/R plus ≥ 1 secondary mutation, or other mutational patterns).

Subjects added dolutegravir to their existing antiretroviral therapy regimen for 11 days followed by optimization of the background regimen. They must have had 1 or more active drugs to add into the optimized background regimen to be eligible for the twice-daily cohort. The primary endpoint was a 0.7-log_{10} copy/mL reduction in plasma HIV RNA level or achievement of a plasma HIV-1 RNA level less than 400 copies/mL after 11 days. There were 27 and 24 subjects in the once- and twice-daily groups, respectively. The mean plasma HIV-1 RNA levels were 4.5 log_{10} copies/mL and 4.3 log_{10} copies/mL, respectively. The median baseline fold-changes to dolutegravir were 1.5 and 2.7, respectively.

Among subjects with the mutation pattern of Q148H/K/R plus at least 1 secondary mutation, 3 of 9 (33%) receiving once-daily dolutegravir achieved the primary endpoint, compared with 11 of 11 (100%) receiving twice-daily dosing. Among subjects with other mutational pathways, 18 of 18 (100%) receiving once-daily dosing and 12 of 13 (92%) receiving twice-daily dosing achieved the primary endpoint. The twice-daily dose has been selected for future phase III studies of dolutegravir in INSTI-experienced patients.

**Clinical Trials of Antiretroviral Therapy in Treatment-Experienced Patients**

**Dolutegravir**

Mambule and colleagues randomly assigned 202 participants with failure of an initial regimen of only nucleoside analogue reverse transcriptase inhibitors (nRTIs) to receive ritonavir-boosted lopinavir plus a NNRTI with either didanosine, lamivudine, or a regimen with no nRTI (Abstract 541). The CD4+ cell count increases after 24 weeks were similar among the 3 groups, with increases of 143/µL, 124/µL, and 148/µL after 24 weeks, respectively. At week 24, 66%, 76%, and 68%, respectively, achieved a plasma HIV-1 RNA level less than 50 copies/mL.

**Second-Line Therapy After Failure of 3 Nucleoside Analogue Reverse Transcriptase Inhibitors**

Two studies examined results of mono-therapy with lopinavir as second-line therapy. Bartlett and colleagues presented 24-week results from ACTG 5230, a pilot study of 123 patients from 3 sites in Africa and 2 in Asia with documented virologic failure, defined as plasma HIV-1 RNA levels between 1000 copies/mL and 200,000 copies/mL,
after at least 6 months of continuous, NNRTI-based initial antiretroviral therapy (Abstract 583). At baseline, median age was 39 years, median plasma HIV-1 RNA level was 164/µL, and 76% of patients had received nevirapine-based antiretroviral therapy. These patients, having met criteria for failure of their initial regimen, were switched to lopinavir/ritonavir monotherapy as second-line treatment.

After 24 weeks of lopinavir/ritonavir 400 mg/100 mg twice daily, 107 (87%; 95% CI, 80%–92%) remained virologically suppressed with plasma HIV RNA levels less than 400 copies/mL. HIV-1 genotypes were available for 11 of 15 participants meeting criteria for virologic failure, and 4 new major mutations were observed (2 A71T and 2 V82F). Thirteen participants for whom monotherapy was failing intensified their antiretroviral therapy with the addition of tenofovir/emtricitabine/ritonavir, and 11 (85%) achieved virologic suppression. Grade 3 or grade 4 adverse events were observed in 31 participants (25%). The authors note that the lack of a comparator group limits the utility of the findings. Long-term follow-up of the study participants will continue through antiretroviral therapy week 104, which will determine durability of the treatment response as well as outcomes for those who intensify failing monotherapy with tenofovir/emtricitabine.

Bunupuradah and colleagues presented a needed corollary to the above findings by comparing lopinavir/ritonavir monotherapy with tenofovir/lamivudine plus lopinavir/ritonavir in a randomized controlled trial of 200 patients with documented virologic failure (plasma HIV-1 RNA levels > 1000 copies/mL) of an initial NNRTI-based regimen in Thailand (Abstract 584). In an intention-to-treat analysis of 48-week outcomes, for which missing or adding tenofovir/lamivudine was treated as failure, the proportion of participants achieving virologic suppression (plasma HIV RNA level < 400 copies/mL) in the monotherapy group was 75%, compared with 86% in the tenofovir/lamivudine plus lopinavir/ritonavir group (P = .053). A statistically significantly lower percentage of participants receiving monotherapy had plasma HIV-1 RNA levels less than 200 copies/mL (69% vs 86%, respectively; P = .01) and less than 50 copies/mL (61% vs 83%, respectively; P < .01). Major protease inhibitor (PI) mutations (M46I, I50V) at failure were detected in 1 participant receiving monotherapy. The authors conclude that lopinavir/ritonavir alone should either not be recommended as a second-line regimen or used with caution.

**Darunavir/Ritonavir, Raltegravir, Etravirine**

Fagard and colleagues presented the long-term results of the TRIO (Efficacy of Darunavir/Ritonavir, Etravirine, and Raltegravir in HIV Patients with Resistant Viruses) study (Abstract 549). This was a single-arm, open-label trial enrolling patients for whom several antiretroviral regimens had failed. All participants received darunavir/ritonavir, etravirine, and raltegravir plus an investigator-selected background regimen. No participants discontinued the study regimen except for 1 participant, who discontinued raltegravir because of an adverse event at week 8. One participant died before week 96 and 2 participants withdrew consent. At week 96, 88% of participants had a plasma HIV-1 RNA level less than 50 copies/mL. Although 19 participants experienced virologic failure before week 96, failure generally occurred with low-level viremia, and virus was resuppressed without the participants changing regimens. This study supports the long-term efficacy of this combination of antiretroviral drugs in patients with prior virologic failure.

**Predictors of Antiretroviral Therapy Response From Large Cohort Studies**

Many presentations used existing cohort studies to examine potential determinants of treatment outcomes. Althoff and colleagues determined trends in plasma HIV-1 RNA levels in HIV-1-infected patients from 13 clinical cohorts participating in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) (Abstract 548). Investigators determined antiretroviral therapy usage at the time of the highest plasma HIV-1 RNA level per individual per year and found that, of 91,569 patients receiving care between 1997 and 2007, 77% used antiretroviral therapy at some point. The proportion of patients receiving antiretroviral therapy who achieved virologic suppression, defined as plasma HIV RNA level of 500 copies/mL or less, increased each year and reached more than 50% by 2005 to 2007.

For those receiving antiretroviral therapy, initial disparities in median plasma HIV-1 RNA level by HIV transmission group narrowed over time,
with injecting drug users having statistically significantly higher annual median levels from 1997 to 2006, and converged at a median below 500 copies/mL for all groups in 2007. Similarly, black patients consistently had a higher annual median plasma HIV-1 RNA level from 1997 to 2006 than that of white patients (P < .01), but disparities by all racial or ethnic categories (black, white, Hispanic, other/unknown) converged in 2007. These are encouraging data in terms of the potential for decreasing median community plasma HIV-1 RNA levels and in the diminishing disparities of those achieving virologic success during antiretroviral therapy.

Data from 18 cohorts in Europe participating in the Antiretroviral Therapy Cohort Collaboration (ART-CC) were examined by Jarrin and colleagues for differences in mortality among treated patients according to race or ethnicity and geographic origin (Abstract 558). Data on geographic origin were available for European and Canadian cohorts; origins were classified as Europe; Northern Africa and Middle East; sub-Saharan Africa; Asia; and Caribbean, South, and Central America. Data for race or ethnicity were available for Canadian and US cohorts. Thus, the investigators conducted separate analyses for Europe (n = 54,614), Canada (n = 1387 for geographic origin, and n = 1710 for race or ethnicity), and the United States (n = 7928). In Europe, HIV-infected migrants from sub-Saharan Africa and Asia had lower mortality than HIV-infected nationals, in unadjusted analysis (odds ratio [OR], 0.52; 95% CI, 0.44–0.61 for sub-Saharan Africa; and OR, 0.52; 95% CI, 0.33–0.81 for Asia). These associations remained statistically significant after adjustment for sex, age, transmission group, AIDS status, CD4+ cell count, and pre–antiretroviral therapy plasma HIV-1 RNA level. In the United States, black race was associated with higher mortality than white race (OR, 1.18; 95% CI, 1.07–1.31). None of the racial or ethnic categories in Canada (black, Hispanic, Asian, or indigenous) had statistically significantly different mortality from that of white Canadians in the cohort.

Two presentations examined switches to second-line antiretroviral therapy in non-RLS. The first, presented by Abraham and colleagues, used data from the ART-CC to determine antiretroviral therapy outcomes after transition to second-line therapy for those at least 16 years of age who started antiretroviral therapy after 2002 using either PI/r or NNRTI plus at least 2 nRTIs (Abstract 578).

Of 15,008 patients, 40% switched and 16.5% interrupted initial treatment. The hazard ratio (HR) for AIDS-defining illness or death was 2.49 (95% CI, 2.21–2.81) for those who interrupted treatment compared with those who switched antiretroviral therapy regimens. This association remained statistically significant after adjustment for risk-transmission group, age, AIDS diagnosis, calendar year, duration of initial regimen, and many other potential confounders. Those who switched regimens for treatment failure had a higher risk of death or AIDS event (HR, 5.91; 95% CI, 3.38–10.33) than those who switched for regimen simplifications. Those who switched because of a physician’s decision, side effect, or patient’s decision also had higher risks of AIDS or death than those who switched for regimen simplification in the adjusted analysis. The investigators also found that more than 50% of switches were exchanging or adding drugs within the same antiretroviral therapy class and that most of the switches, discontinuations, or deaths occurred within the first year of antiretroviral therapy.

Hull and colleagues determined the effect of fixed-dose combination formulations of antiretroviral therapy on switches to second-line therapy among 2144 HIV-1-infected adults initiating antiretroviral therapy between 2000 and 2010 with efavirenz, atazanavir, or lopinavir-based regimens in the Canadian Observational Cohort Collaboration (CANOC) (Abstract 579). They examined the following 3 associations: (1) fixed-dose abacavir/lamivudine for patients receiving abacavir and lamivudine, (2) fixed-dose lamivudine or emtricitabine/tenofovir for those receiving tenofovir plus lamivudine or emtricitabine, excluding those taking efavirenz, and (3) fixed-dose emtricitabine/tenofovir/efavirenz for those receiving tenofovir, efavirenz, and either lamivudine or emtricitabine.

For all 3 analyses, the use of a fixed-dose combination was inversely associated with regimen switch compared with those not using fixed-dose combinations after adjustment for age, sex, history of injection drug use, year of antiretroviral therapy start, pre–antiretroviral therapy plasma HIV-1 RNA level, and geographic location. For comparison 1, the adjusted odds ratio (aOR) for the inverse association was 0.20 (95% CI, 0.10–0.40); for comparison 2, aOR was 0.40 (95% CI, 0.24–0.68); and for comparison 3, aOR was 0.20 (95% CI, 0.15–0.44). Virologic suppression was also more likely when using fixed-dose combinations of abacavir/lamivudine and emtricitabine/tenofovir/efavirenz. Although this study is limited by the fact that data are derived from an observational cohort with the potential for unmeasured confounders, the findings imply that the use of fixed-dose combinations may lead to less regimen switching and, in some cases, increased likelihood of virologic suppression.

Three different cohorts determined causes of death in treated HIV infection. Ruppik and colleagues examined 459 deaths between 2005 and 2009 among 9053 Swiss HIV Cohort participants observed during that period (Abstract 789). They were able to determine cause of death in all but 11 of these individuals and found that non–AIDS-defining malignancies were the most common cause of death (19%), including hepatocellular carcinoma (2.8% of total deaths), followed by AIDS-defining illnesses (16.4%) and liver diseases excluding hepatocellular carcinoma (15%).

Kowalska and colleagues determined risk of cause-specific death over time in relationship to antiretroviral therapy exposure among HIV-1-infected patients in the EuroSIDA cohort (Abstract 790). They found that the risk of non–AIDS-related deaths (non–AIDS-related infections, liver disease, non–AIDS-defining malignancies, cardio-
vascular disease, other, and unknown) increased with cumulative exposure to antiretroviral therapy. Among 11,982 patients in antiretroviral therapy, the adjusted incidence rate ratio (aIRR) for non–AIDS-related death was lower in the first 2 years after antiretroviral therapy initiation than in years 2 to 4 of antiretroviral therapy (aIRR, 0.64; 95% CI, 0.52−0.80). This relationship was driven by those initiating antiretroviral therapy before 2002. The trend remained statistically significant after controlling for age when examined for the following specific causes of death: cardiovascular disease, liver-related disease, other, and unknown but not for the other causes of death.

Zhang and colleagues used data from the AIDS Therapy Evaluation Project (ATHENA) cohort to determine the association between CD4+ cell count and plasma HIV-1 RNA level before and after antiretroviral therapy initiation and non–AIDS-related endpoints: cardiovascular disease, renal failure, liver disease, and a combined endpoint incorporating all 3 (Abstract 791). Incidence of non–AIDS-related events was lower before than after antiretroviral therapy initiation for cardiovascular disease (0.18/100 person-years vs 0.49/100 person-years, respectively; P < .001) and for the combined endpoint but not for renal failure or liver disease. The investigators found that higher CD4+ cell counts were inversely associated with non–AIDS-related events both before initiation (adjusted relative risk [aRR], 0.60; 95% CI, 0.53−0.68) and after initiation (aRR, 0.40; 95% CI, 0.35−0.47). There was no statistically significant association between plasma HIV-1 RNA level before antiretroviral therapy initiation and non–AIDS-related events.

Several studies applied genome-wide association analysis to existing longitudinal cohorts, including one by McLaren and colleagues, who used samples from subjects in ACTG studies (A5202, A5142, A5095, and ACTG 384) to assess genetic influence on virologic outcomes of patients taking efavirenz or abacavir (Abstract 477). Genotypic testing was performed using whole-genome single-nucleotide polymorphism (SNP) arrays on 1622 samples from individuals taking efavirenz and 792 samples from people using abacavir. Samples were stratified by ethnicity, and approximately 500,000 SNPs were examined for association with the following 3 outcomes: (1) early virologic response (defined as plasma HIV-1 RNA level ≤ 50 copies/mL at or before 16 weeks of antiretroviral therapy), (2) virologic relapse (plasma HIV-1 RNA level > 200 copies/mL after achieving a level < 200 copies/mL), and (3) virologic response (plasma HIV-1 RNA level < 50 copies/mL at or before 48 weeks). All subanalyses included only those individuals who did not report missed doses, and they specifically interrogated SNPs within 100 kilobases of a selected group of drug-absorption, distribution, metabolism, and elimination (ADME) genes.

Results did not show any SNP that met criteria for genomewide statistical significance (P< 5 × 10−8) for association with any of the outcome categories. The authors reported approximately 80% power to detect OR value greater than 2.1 for virologic failure in the efavirenz group and approximately 80% power to detect OR value greater than 3.7 for virologic failure in the abacavir group. They concluded that there were no large-effect (OR > 2) common variants found to contribute to virologic failure in this combined cohort but that common variants with modest effects or rare variants would not be discovered in this analysis and could contribute to the outcomes tested.

### Treatment Outcomes Among Young Adults

A themed discussion (Session 14) covered 4 poster presentations on antiretroviral therapy use and outcomes in youth. Rudy introduced the session with an overview of epidemiology in this important group of approximately 10 million people living with HIV who are between the ages of 15 years and 24 years. In North and Latin America and in Central and Western Europe, this epidemic is driven by men who have sex with men (MSM), and in Eastern Europe and some parts of Asia, it is driven by injection drug use. In southern Africa, data suggest that the highest HIV infection risk is in women in their 20s, driven by heterosexual risk. There are also many perinatally infected adolescents who are now “aging up” into this group and who face additional challenges because of their extensive treatment experience. The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that there are 1 million new infections each year in young adults.

Agwu and colleagues examined disparities in antiretroviral therapy utilization in a cohort of 247 non–perinatally HIV-infected youth aged 12 years to 24 years receiving care at 14 different treatment sites between 2002 and 2008 (Abstract 692). Inclusion criteria for the cohort were being antiretroviral therapy-naïve and having at least 2 CD4+ cell count measurements of no more than 350/µL. The median age of the cohort was 21 years (interquartile range [IQR], 20 – 23 years), 72% were boys or men, and 68% were black. The majority (78%) were receiving care at adult HIV treatment sites. A total of 198 (69%) of the cohort initiated antiretroviral therapy.

In multivariate analysis, antiretroviral therapy initiation was associated with CD4+ cell count less than 200/µL (adjusted hazard ratio [aHR], 2.02; 95% CI, 1.40 – 2.90) and attending 4 or more outpatient HIV practitioner visits in the year after meeting treatment criteria (aHR, 2.23; 95% CI, 1.50 – 3.31). Potential predictors that were not statistically significant in the multivariate analysis included race or ethnicity, HIV acquisition risk, insurance coverage, year meeting treatment criteria, and being at an adult treatment center.

The investigators also examined risk of discontinuing first antiretroviral therapy regimen, which occurred in 117 individuals in the cohort (41%): 50 switched antiretroviral therapy regimens, and 67 discontinued antiretroviral therapy. Discontinuation of the initial antiretroviral regimen occurred statistically significantly more rapidly (within 297 days; IQR, 18 – 896 days) among those cared for at adult clinic
sites than among those cared for at pediatric sites (within 594 days; IQR, 229–999 days). The overall aHR for discontinuation was 2.06 (95% CI, 1.20–3.55) for those receiving care at adult sites compared with pediatric sites. Of those who discontinued, 67% remained in care the year following discontinuation; all 15 who received care at pediatric sites were receiving antiretroviral therapy, compared with only 78% of the 49 patients receiving care at the adult sites (P = .04).

Saavedra-Lozano and colleagues determined the clinical status of 74 members of the Madrid Cohort of HIV-infected children at the time of their transfer to an adult clinic (Abstract 693). The mean age at transfer was 18.9 years (range, 13–22 years), the mean absolute CD4+ cell count was 710/μL; 54% had plasma HIV-1 RNA levels less than 400 copies/mL; and 54% received a clinical diagnosis of lipodystrophy. The majority of the patients were receiving 1 PI and 2 nRTIs (28%) or 1 NNRTI and 2 nRTIs (27%), and 75% had received 2 or more antiretroviral regimens at the time of transfer. Thirty-nine (53%) of these patients underwent HIV-1 genotyping testing, although criteria for genotypic testing in the cohort were not provided. Of these, 21 had PI- and reverse transcriptase inhibitor–associated resistance mutations, and 3 had only PI-associated resistance mutations. The authors concluded that the patients had relatively well-preserved clinical and immunologic condition after many years of antiretroviral therapy but that prevalence of lipodystrophy and drug resistance mutations were high in the cohort.

Ryscavage and colleagues conducted a retrospective, matched case-control study comparing 46 HIV-1-infected young adults aged 17 years to 24 years with adults aged 25 years to 40 years, all newly receiving care in an adult-oriented, university-based clinic (Abstract 694). The adult control group was randomly selected from the clinic and matched 1:1 with the young adults for ethnicity, sex, pregnancy during the study period, pre–antiretroviral therapy plasma HIV-1 RNA level, and HIV genotypic susceptibility score. The young-adult population was 54% black, 61% women, and 59% pregnant patients. The primary endpoint was achievement of virologic suppression (plasma HIV-1 RNA level < 400 copies/mL) 6 months after antiretroviral therapy initiation or after establishment of care in the clinic for those already receiving antiretroviral therapy.

The investigators found that 58.7% of young adults achieved virologic suppression at 6 months compared with 78.2% of adults (P = .025), and the young adults had a 6-fold higher likelihood of being lost to follow-up (LTU, also indicates loss to follow-up) than did the adults, defined as no clinic attendance for 12 months or longer. These differences were particularly dramatic in black patients. Young-adult black patients had a statistically significantly lower probability of virologic suppression than either young nonblack patients (44% vs 77%, respectively) or nonblack adults (91%).

Lowenthal and colleagues determined the ability of a screening tool for pediatric psychosocial dysfunction, the Pediatric Symptom Checklist (PSC), and of age at antiretroviral therapy initiation to predict virologic failure of antiretroviral therapy in a cohort of HIV-infected children in Botswana (Abstract 695). They conducted a cross-sectional analysis of 8- to 16-year-old, HIV-infected children receiving care at a single site, and they translated, culturally adapted, and validated the PSC, using receiver operating characteristic (ROC) analysis to determine optimal cutoff scores. The study enrolled 635 children who had been receiving antiretroviral therapy for more than 6 months, 24% of whom met criteria for virologic failure and 17% of whom had PSC scores of more than 20, the threshold for positivity determined in the ROC analysis.

The OR for virologic failure among those with PSC scores of 20 or higher was 1.64 (95% CI, 1.04–2.57) compared with those with PSC scores less than 20. Initiating antiretroviral therapy at age 10 years or older was also statistically significantly associated with virologic failure (HR, 3.08; 95% CI, 2.01–4.71). Neither of the 2 associations varied statistically significantly after adjustment for sex, age, school grade, baseline or current CD4+ cell count, orphan status, or the other of the 2 predictors.

**Acute Infection**

**Treatment of acute HIV infection.** The benefit of treatment for acute HIV infection remains unclear. The following studies focused on the impact of treatment during acute or recent HIV infection in terms of treatment outcomes, viral load set point, or immune activation. Grijsen and colleagues reported results of a multicenter, open-label, randomized control trial comparing no treatment with 24 weeks or 60 weeks of temporary 4-drug antiretroviral therapy during primary HIV infection (Abstract 161). Only those patients for whom treatment was indicated were randomly assigned to 1 of the 2 treatment groups. There were 36 patients in the untreated group, 40 patients in the 24-week treatment group, and 59 in the 60-week treatment group. Patients were treated with 2 nRTIs, an NNRTI, and a PI. Primary endpoints were plasma viral load at 36 weeks after randomization or treatment interruption and total time off therapy. Subjects had serologic test results consistent with acute HIV infection in 73% of cases, and symptoms were present in 83% of cases. Antiretroviral therapy was initiated for subjects with an incident AIDS diagnosis or a CD4+ cell count less than 350/μL.

At 36 weeks after randomization or treatment interruption, the mean viral set point was statistically significantly higher in the untreated group: 4.8 log10 copies/mL in the untreated group compared with 3.9 log10 copies/mL and 4.2 log10 copies/mL in the 24- and 60-week treatment groups, respectively (P < .001). Authors also analyzed time off treatment and found that the median was 0.7 years (95% CI, 0.2–1.2 years) in the untreated group and 3.1 years (95% CI, 2.3–5.8 years) and 2.1 years (95% CI, 0.4–3.8 years) in the 24- and 60-week groups, respectively (P < .001). There was no statistically significant difference in time off treatment.
between the 2 treatment groups. The authors suggested that temporary antiretroviral therapy during primary HIV infection lowers the setpoint and defers the start time for continuous antiretroviral therapy for chronic HIV infection.

Markowitz and colleagues sought to understand whether antiretroviral therapy initiated during early HIV infection and targeting entry, reverse transcriptase, integrase, and protease would improve outcomes compared with a 3-drug, PI-based regimen (Abstract 148LB). The authors presented 48-week data from a randomized, open-label trial of a 5-drug regimen compared with a 3-drug standard PI-based antiretroviral regimen initiated during acute and early HIV-1 infection. Patients were randomly assigned 1:2 to receive 3 drugs or 5 drugs. Both treatment groups received tenofovir/emtricitabine and either atazanavir/r or darunavir/r; the 5-drug group also received maraviroc and raltegravir. Data were available from 11 patients in the 3-drug group and 23 patients in the 5-drug group.

At week 48 of treatment, there were no statistically significant differences in percent of subjects with plasma HIV-1 RNA levels below detection using the single-copy assay, increase in CD4+ T cell count, or immune activation markers. There were 3 individuals in the 5-drug group for whom treatment failed to suppress viral load at 48 weeks by standard assay; this result was unexpected but not statistically significant. Researchers noted that additional studies are under way to compare the effects of the 3-drug regimen with those of the 5-drug regimen on acute HIV infection and targeting entry, reverse transcriptase, integrase, and protease.

The authors highlighted the finding that patients with infection classified as Feibig stage III (classified as detectable HIV-1 RNA, p24 antigen positive, HIV seropositive on enzyme-linked immunosorbent assay, and negative on HIV Western blot testing) at enrollment had statistically significantly reduced numbers of CD4+CCR5+ T cells in the mononuclear mucosal cells compared with both healthy individuals and with persons with disease in Feibig stage I (defined as HIV-1 RNA detectable, p24 antigen negative, and HIV-antibody negative). The authors suggested that 5-drug treatment in early-Feibig-stage, acute HIV infection may prevent CD4+ cell depletion in the sigmoid colon and render gut and peripheral HIV RNA undetectable, thereby reducing the viral burden and promoting immune restoration.

Investigators from the University of California San Francisco (UCSF) Options Project compared the effect of antiretroviral therapy initiation during acute or early HIV infection with later antiretroviral therapy initiation on various immunologic and virologic outcomes (Abstract 517). There were 34 participants in the early-treatment group and 32 in the later-treatment group. Participants were included in the analysis if they maintained at least 2 years of viral suppression after initiation of either early or late antiretroviral therapy. The authors analyzed markers of CD4+ and CD8+ activation and found that the late-antiretroviral therapy group had statistically significantly higher levels of activated CD4+ and CD8+ T cells, statistically significantly higher proviral DNA levels, and statistically significantly higher viral reservoirs than the early-treatment group. They suggested that earlier antiretroviral therapy initiation may be associated with lower T-cell activation and smaller HIV reservoirs.

**Resistance and acute HIV infection.** The relevance of minor resistance variants at the time of acute infection is unclear. Liegler and colleagues studied minor resistance variants in 6 patients from the UCSF Options Cohort who were found to have the M184V transmitted drug resistance mutation during primary HIV infection (Abstract 513). Results of population-based sequencing and quantitative minor variant assays were observed over time in individuals enrolled within 6 months of infection whose transmitted drug resistance mutation M184V had reverted to wild type after discontinuation of antiretroviral therapy.

The sensitive polymerase chain reaction (PCR)-based minor variant assay detected reversion at an average of 18 weeks compared with 28 weeks using population-based sequencing. Loss of detectable M184V (less than 0.5%) occurred at a mean of 36 weeks from infection and persisted for up to 5 years of monitoring. After M184V detection by population sequencing, loss of detectable M184V occurs rapidly at a mean of 10 weeks. The authors suggested that the rapid overgrowth of wild-type virus may indicate that reverse transcriptase 184 declines to levels that are not clinically important 1 year after reversion.

Gianella and colleagues also looked at minority resistance variants during early HIV-1 infection and compared bulk sequencing with ultra-deep sequencing on baseline blood samples of 23 recently infected individuals (Abstract 514). Several findings suggested that such minority mutants are unlikely to be transmitted to, and maintained in, the recipient host. The authors showed that ultra-deep sequencing revealed a higher frequency of resistance mutations (93.7%) than found through bulk sequencing (12.5%). Furthermore, 60% of the drug resistance mutations in the ultra-deep sequencing group were present at less than 1% (mean 0.56%; 95% CI, 0.43% – 0.69%), and there was wide variability in the drug resistance mutations with repeated runs. There was no correlation between minority drug resistance mutations and negative clinical outcomes with initial antiretroviral regimens. The authors suggested that the majority of detected low-frequency
drug resistance mutations are likely to be the consequence of HIV-1 within-host diversification or evolution, or of methodology-related error.

**Antiretroviral Treatment in Resource-Limited Settings**

**Overview**

The opening session N’Galy-Mann Lecture, delivered by Harries, focused on the history of the HIV epidemic in Malawi, where HIV infection prevalence reached 14% of the general population by 1995 (Abstract 18). Harries reminded the audience that, before antiretroviral therapy availability in Malawi, 90% of adults receiving a diagnosis of stage 4 HIV disease were dead within 12 months, and half of all children receiving an HIV infection diagnosis were dead within 2 years of diagnosis. Harries and his colleagues envisioned a directly observed-therapy–like strategy for antiretroviral treatment in Malawi in August 2001, and they received resources from the Global Fund to Fight AIDS, Tuberculosis, and Malaria for antiretroviral therapy scale-up in 2002. Scale-up emphasized simplicity and standardization of regimens to ensure ease of delivery and equity of access throughout the country, with 1 initial and 1 second-line regimen available. Monitoring and evaluation procedures were built into the efforts early on and included quarterly, in-person site visits within that program. Data from the program showed that Harries and colleagues achieved 60% coverage for antiretroviral therapy by September 2010, and the percentage of patients initiating antiretroviral therapy at World Health Organization (WHO) clinical stage 4 diminished from 25% in 2005 to 10% in 2010. The efforts have yielded results at a population scale, with overall mortality declining dramatically, whether measured by traditional registers or by nontraditional mortality measurements such as coffin sales and church funerals.

Harries argued that the future will require a focus on prevention of new HIV infections, expansion of programs for prevention of mother-to-child transmission (PMTCT) of HIV infection, which reach only 35% of HIV-infected mothers and children, and LTFU of patients with HIV infection who have not yet initiated antiretroviral therapy. The 2010 WHO guidelines for antiretroviral therapy and PMTCT will help with these endeavors, but the lack of access to CD4+ cell count monitoring remains a major obstacle to progress.

Harries proposed universal HIV testing and immediate antiretroviral therapy initiation, as promoted by Granich and colleagues in 2009. Malawi recently adopted a policy of “antiretroviral therapy for life” with tenofovir, lamivudine, and efavirenz for all HIV-infected pregnant women regardless of CD4+ cell count. Harries acknowledged that such a program will require careful monitoring of the safety, acceptability, feasibility, and outcomes of the program, but he believes that this intervention, combined with targeted prevention interventions such as microbicides, preexposure prophylaxis (PrEP), and male circumcision should form the next salvo in the battle against the HIV epidemic in Malawi.

Sow gave a “Global Antiretroviral Therapy Update” during a workshop for new investigators and trainees (Abstract 6). She emphasized the unprecedented success of global antiretroviral therapy scale-up and highlighted challenges to continued success. These challenges include high mortality after antiretroviral therapy initiation, difficulty managing HIV infection in patients with tuberculosis coinfec-
tion, retention in care, lack of laboratory monitoring, and lack of access to second-line regimens or regimens for repeated antiretroviral therapy failure.

Sow selected 4 “top” papers of the past year, 2 that highlighted the mortality benefits of early initiation of antiretroviral therapy, even in patients receiving tuberculosis treatment, that demonstrated the importance of generic antiretroviral therapy to cost savings achieved within President’s Emergency Plan for AIDS Relief (PEPFAR)-supported programs, and 1 that described factors associated with increased mortality in patients receiving second-line antiretroviral therapy in a cohort of 27 Médecins Sans Frontières (Doctors Without Borders, MSF)-sponsored programs. Sow also emphasized the importance of the 2010 WHO guidelines for the initiation of antiretroviral therapy at CD4+ cell counts less than 350 µL and the need for treatment of HIV-associated comorbidities, such as cardiovascular disease, in RLS.

Walensky discussed several issues relevant to the cost-effectiveness of antiretroviral therapy in RLS (Abstract 74). She discussed the limitations of cost-effectiveness literature in general and the application of WHO cost-effectiveness standards to RLS. The economic value of antiretroviral therapy in RLS was first addressed in a 2006 publication, which examined the cost-effectiveness of antiretroviral therapy in Côte d’Ivoire by WHO Gross Domestic Product comparison standards. Subsequent studies examined cost-effectiveness of CD4+ cell count monitoring, plasma HIV-1 RNA level monitoring, and initial and second-line antiretroviral therapy. These showed that antiretroviral therapy costs, rather than laboratory-monitoring costs, were higher in regions offering plasma HIV-1 RNA monitoring, as the viral load monitoring led to transitions to more costly second-line regimens.

Walensky and colleagues also applied clinical efficacy and cost-effectiveness analysis to the 2010 WHO treatment guidelines, which recommended antiretroviral therapy initiation at CD4+ cell counts less than 350 µL, increased number of sequential antiretroviral regimens (ie, availability of second-line therapy), and replacement of stavudine with tenofovir. The clinical impact model determined that the initiation of antiretroviral therapy at CD4+ cell counts less than 350 µL conferred the greatest survival benefit, followed by the availability of second-line antiretroviral therapy, followed by replacement of stavudine by tenofovir. The cost-effectiveness analysis showed that earlier initiation of antiretroviral therapy and replacement of stavudine by tenofovir would be important first steps, followed by access to second-line therapy. Overall, the introduction of all 3 WHO-recommended measures.
was shown to be very cost effective, even for many RLS, with a ratio of US $2370 per life-year saved.

**Advances in Antiretroviral Therapy Scale-Up and Care Delivery in Resource-Limited Settings**

Several presentations highlighted new strategies for antiretroviral therapy scale-up and care delivery in RLS. Vitoria of the WHO gave an overview of current and future strategies for antiretroviral therapy optimization at the global level, and began by highlighting the dramatic success of the past decade of antiretroviral therapy scale-up (Abstract 108). He noted the 13-fold increase in access to antiretroviral therapy over the past 6 years and that 5.25 million people now receive antiretroviral therapy in low- and middle-income countries.

Antiretroviral therapy has been shown to impact country-level health indicators. Notable examples include antiretroviral therapy–associated reductions in overall mortality in South Africa and antiretroviral therapy–associated declines in tuberculosis incidence in Botswana. However, global coverage of antiretroviral therapy remains at 36% for adults with respect to the 2010 WHO guidelines criteria, 28% for children, and 53% for PMTCT in 2009, and stark inequalities in terms of drug price compared with national incomes persist. The joint UNAIDS/WHO “Treatment 2.0” initiative advocates specific strategies to catalyze the next phase of scale-up in HIV disease treatment.15

The strategies proposed by this initiative include (1) the promotion of fixed-dose combinations, which bring programmatic, clinical, and economic benefit; (2) potential dose reductions in antiretroviral therapy based on data from phase II trials indicating virologic outcomes were similar for several doses of many drugs;14 (3) reformulation of existing drugs to make them easier to take and less toxic; (4) improvements in bioavailability of drugs, including alterations of crystalline forms and the potential use of nanopharmaceuticals; (5) the potential role of new antiretroviral drugs in RLS, such as rilpivirine in a fixed-dose combination or long-acting tenofovir; and (6) new treatment strategies including induction or maintenance of monotherapy with ritonavir-boosted PIs, which have mixed results in early trials but deserve more investigation. Vitoria concluded that a combination of innovative strategies can help antiretroviral therapy scale-up move into its second decade and achieve further success.

Long and colleagues used results from a recent randomized control trial showing non inferiority of nurse versus physician management of HIV-infected patients receiving antiretroviral therapy as background for an examination of the impact of shifting the management of patients on stable antiretroviral therapy from physicians to nurses in South Africa in a routine care setting (Abstract 43). The study included patients initially managed by physicians and eligible for nurse management, as determined by stable antiretroviral therapy for longer than 6 months, undetectable plasma HIV-1 RNA level, CD4+ cell count greater than 200/µL, and less than 5% weight loss over the past 3 clinic visits. The patients were divided into 2 groups: those managed by doctors (n = 1620) and those managed by nurses (n = 540); the groups were matched for age, sex, CD4+ cell count, time on antiretroviral therapy, and antiretroviral regimen. Baseline characteristics were comparable across the 2 groups: subjects had been receiving antiretroviral therapy for a mean of 13.2 months and were receiving either stavudine/lamivudine/efavirenz or zidovudine/lamivudine/efavirenz.

Primary outcomes—LTFU, mortality, virologic rebound, and mean CD4+ cell count response—did not differ statistically significantly between the 2 groups. The cost savings were modest: a US $48 reduction per year per patient in care and responding to treatment. However, when extrapolated to the approximately 25% of South Africa’s current population receiving antiretroviral therapy and eligible for nurse-managed care, this shift in care would represent a savings of more than US $12 million annually. Long acknowledged that the study’s limitations included lack of generalizability and confounding by unmeasured variables that differ between study groups, but he concluded that shifting care to nurses could result in increased treatment capacity without compromise of patient outcomes.

Bendavid and colleagues estimated the contributions that the decreasing price of initial antiretroviral therapy and increasing foreign assistance for HIV care had on antiretroviral therapy coverage in RLS (Abstract 568). The authors used data from the WHO Global Price Reporting Mechanism and the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) Economics of AIDS and Access to HIV/AIDS Care in Developing Countries Project to create a price index for initial antiretroviral therapy for 13 countries in sub-Saharan Africa. The index described costs per country per year and represented 84% of Africa’s estimated total number of people living with HIV or AIDS. Foreign assistance was measured as disbursements from the World Bank, the Global Fund to Fight AIDS, Tuberculosis, and Malaria, and PEPFAR, and data on antiretroviral therapy coverage was obtained from UNAIDS.

The authors found that the mean annual price of initial antiretroviral therapy dropped from US $1177 in 2003 to $96 in 2008, and antiretroviral therapy coverage increased from 5.7% to 51.2% over the same time period. Multivariate analysis, adjusting for public health expenditures, gross domestic product, HIV prevalence, and government effectiveness, showed that antiretroviral therapy coverage was associated more closely with price reductions at lower prices and that, together, price reductions and foreign assistance for HIV care explained half of the increase in antiretroviral therapy coverage observed between 2003 and 2008. The authors concluded that price reductions, even to very low levels, are unlikely to be associated with substantial additional gains in antiretroviral therapy coverage and that achievement of universal coverage...
will require a substantial increase in foreign assistance and national public health expenditures for HIV care.

Retention in Care and Adherence to Antiretroviral Therapy in Resource-Limited Settings

Bangsberg discussed adherence and resistance to antiretroviral therapy (Abstract 111). He began his presentation by reminding the audience of a 2006 meta-analysis of 228 studies, which demonstrated that adherence in RLS was 77% (95% CI, 67%–86%), a level statistically significantly greater than in resource-rich countries (55%; 95% CI, 48%–61%).16 He stressed the positive-feedback loop of social capital and its promotion of adherence as proposed by Ware and colleagues,17 and he emphasized that the major barriers to treatment adherence in RLS—primarily structural and economic factors—can be neutralized by the protective effects of social capital.

Unfortunately, adherence does decline over time, a phenomenon well known in resource-rich settings and shown in RLS as well.18 Recently, 2 adherence interventions in RLS showed the potential for text-message reminders to substantially increase adherence. Adherence was increased from 48% to 57% in one study and from 47% to 63% in a second study, both comparing those receiving text messages to those not receiving text messages, respectively.19,20 Bangsberg highlighted a new monitoring technology, in which a medication dispenser records when it is opened and sends a wireless message to a central server, which then can send appropriate reminders to either patients or caregivers.21 He noted the potential limitation to this technology is that an intervention must be made quickly because treatment interruptions longer than 3 days to 4 days are associated with loss of virologic control.22 However, given that pharmacy-refill data can be better than CD4+ cell count monitoring at detecting virologic failure, Bangsberg speculated that the costs of more effective adherence monitoring and support devices could be covered by the cost savings of improved adherence.

Bangsberg concluded with a reminder that the most important challenge in sustaining adherence success in RLS is posed by restriction in funding sources. If the time to treatment increases, which Geng and colleagues showed occurs when funding sources are unstable, then those taking antiretroviral therapy are likely to share their medications with ill family and friends.29 This practice could erode treatment success for those undergoing antiretroviral therapy and lead to the emergence of resistance in those not “officially” receiving antiretroviral therapy but with whom the medications are shared.

Nachega introduced Session 16, “Retention and Adherence to Care in Resource-Limited Settings,” with an overview of how adherence fits into the larger framework of HIV care outcomes and the demonstrated cost savings of antiretroviral therapy adherence.30 He highlighted differences in methods of measuring adherence and mentioned the effectiveness and scalability of some of the interventions, particularly a pill-monitor and text-messaging intervention described above by Bangsberg; he noted that retention in care is also essential. Although much of the LTFU in RLS, up to 40% in some scenarios, is because of death, Nachega emphasized the need for improved methods of tracking and retention in care to improve the current situation, in which up to 50% of people can be LTFU by 24 months of antiretroviral therapy.31

Ahonkhai and colleagues presented results from a retrospective cohort study of 11,397 patients initiating antiretroviral therapy in South Africa between 2004 and 2008 (Abstract 1014). Median follow-up within the cohort was 2.4 years, and at study conclusion 63% of patients remained in care, 11% interrupted care but returned within 1 year, 17% were LTFU with no appointments within a year, and 9% died within the first 7 months of antiretroviral therapy. Of those who interrupted care, 84% had plasma HIV-1 RNA levels less than 400 copies/mL, and median CD4+ cell count was 257/µL upon return. Early death was predicted by low pre-antiretroviral therapy CD4+ cell count (median, 48/µL), and male sex predicted all outcomes other than maintenance in care. Interestingly, LTFU decreased over time as the program expanded. Ahonkhai also noted that baseline risk factors did not distinguish interrupted care from LTFU, but these 2 events had strikingly different outcomes.

Braitstein and colleagues presented data from an evaluation of LTFU in programs participating in the IeDEA (International Epidemiologic Databases to Evaluate AIDS) cohort collaboration (Abstract 1015). They included data from 29 antiretroviral therapy clinics in East Africa with 43,175 eligible patients (age ≥ 18 years, and receiving antiretroviral therapy at last visit) and used a Weibull survival model with the fixed covariates of age, sex, CD4+ cell count at antiretroviral therapy initiation, and WHO stage at antiretroviral therapy initiation to explore program characteristics associated with LTFU.

The authors determined that clinics using only telephone to reach lost patients and without dedicated outreach staff have an aHR for risk of LTFU, defined as absence from the clinic for 6 months or longer, of 3.36 (95% CI, 1.72–6.57) compared with clinics using dedicated staff for LTFU-prevention outreach. Furthermore, clinics that used only public means for outreach, defined as outreach by bicycle or foot, had an aHR for LTFU of 3.12 (95% CI, 1.41–6.88) compared with those that used all available means for outreach, including the use of a private vehicle. Clinics that waited more than 30 days after a missed visit were more likely to have LTFU than those who did not (aHR, 2.52; 95% CI, 1.26–4.24).

Matovu and colleagues showed results from a randomized, controlled noninferiority trial comparing patients receiving an intervention using nurses and peer educators to support adherence to antiretroviral therapy after initiation to those receiving standard care from a physician and counselor (Abstract 1016). They randomly assigned 92 antiretroviral therapy–naive patients eligible for initial antiretroviral therapy, 50 to the intervention group and 42 to the standard-counseling...
group. The authors found that the proportion of patients achieving the primary outcome, plasma HIV-1 RNA level less than 400 copies/mL, was similar in the 2 models: 91% in the standard group and 88% in the intervention group, \( P = .73 \). There was also no difference in a pill-count adherence measure, CD4+ cell count, or weight change over the 6-month to 12-month follow-up period, suggesting that task-shifting of follow-up care visits to nurses and peers could be effective for patients initiating antiretroviral therapy. These task-shifting findings are similar to those of Long and colleagues (Abstract 43), discussed above.

Geng and colleagues examined failure to initiate antiretroviral therapy, LTFU, and mortality among patients during the pre–antiretroviral therapy initiation period at a single site in Uganda (Abstract 1017). They assessed outcomes in the clinic and used a random-sample tracking method for 89 of the 514 patients LTFU before antiretroviral therapy initiation. Updated outcomes were ascertained for 80% of those originally LTFU in the subsample. Overall, a total of 1772 patients (58% women) met immunologic criteria for antiretroviral therapy initiation, with a median CD4+ cell count of 121/µL.

The cumulative incidence of antiretroviral therapy initiation rose slowly over the first 90 days from 20.6% at 30 days (95% CI, 18.6% – 21.9%) to 63.4% at 90 days (95% CI, 61.4% – 66.0%) but tapered off with a total cumulative incidence of antiretroviral therapy initiation at 365 days of 67.5% (95% CI, 65.1% – 69.7%). A total of 21% (95% CI, 19.3% – 22.6%) were LTFU before antiretroviral therapy initiation at 1 year, and the mortality in the subsample for whom patient tracking was implemented was 30.8% (95% CI, 22.9% – 40.6%). Extrapolating data from the subsample to the entire clinic of all antiretroviral therapy–eligible patients, 9% died before antiretroviral therapy initiation, 7% disengaged from care, 16% were in care awaiting antiretroviral therapy, and 69% initiated antiretroviral therapy. If these data can be extrapolated to the antiretroviral therapy scale-up in RLS to date, this implies that more than 1 million eligible patients who presented to care have failed to initiate antiretroviral therapy.

Kohler and colleagues analyzed the results of a program change in a single site in Kenya where free trimethoprim/sulfamethoxazole prophylaxis began to be offered to all patients, regardless of CD4+ cell count (Abstract 1018). They compared 1-year retention rates among 610 individuals enrolled before the free regimen was available with retention rates among 414 subjects enrolled after. The 2 groups had no statistically significant differences in age, sex, tuberculosis prevalence, body mass index, or CD4+ cell count.

They found a statistically significantly higher retention rate (84% vs 63%, respectively) for patients ineligible for antiretroviral therapy who enrolled after the free prophylaxis was available compared with those ineligible for antiretroviral therapy who enrolled before free prophylaxis was available (\( P < .001 \)). No statistically significant difference was observed in LTFU for those receiving antiretroviral therapy during the same time periods. The authors speculated that the improved retention rates could be the result of decreased morbidity, the perception of receiving treatment, lower costs of care, or the establishment of care-seeking habits.

Somi and colleagues presented a retrospective review of results from the Tanzanian national HIV treatment program, which scaled up from managing the care of 11,363 patients in 2004 to 197,412 patients in 2009 (Abstract 1019). The investigators used a multistage, random-sampling model to achieve a nationally representative sample of antiretroviral therapy–naïve patients at least 15 years of age who initiated antiretroviral therapy between October 2004 and August 2007 in 43 health facilities. They found that young adults, 15 years to 29 years of age, were more likely to have poor baseline clinical status (CD4+ cell count <50/µL or WHO clinical stage 4) with an OR of 1.63 (95% CI, 1.35 – 1.97) after adjustment for sex and location.

Retention in care for the cohort was 70% at 12 months and 63% at 24 months. By 24 months, 8% were reported dead, 4% were alive but had discontinued antiretroviral therapy, and 25% were LTFU. Poor retention was associated with being a young adult, male sex, having poor baseline clinical or functional status, or having a CD4+ cell count less than 50/µL. Notably for a program in the midst of a greater than 1000% scale-up, retention and clinical outcomes did not vary by initiation period.

Achieng and colleagues conducted an observational study to determine which components of a comprehensive clinic and community adherence and retention program were most effective in an antiretroviral therapy program in central Kenya (Abstract 1020). The study prospectively enrolled 301 patients and collected data on participation in home visits, support groups, postpharmacy counseling, and physician-conducted pill counts over the first 6 months of antiretroviral therapy, as well as the outcomes of virologic failure, antiretroviral therapy discontinuation, death, and LTFU for the first 12 months of antiretroviral therapy.

Time to treatment failure (virologic rebound, death, or LTFU) was determined by Kaplan-Meier survival analysis and was associated with participation in support groups, postpharmacy counseling, accurate pill counts, and home visits. However, in the multivariate analysis, statistically significant reductions in risk of treatment failure were observed only for accurate pill counts (aHR, 0.19; \( P < .001 \)) and participation in support groups (aHR, 0.43; \( P < .005 \)). The authors concluded that these 2 components are the most essential to maintain in their adherence structure and noted during the question period that the physician-conducted pill count traditionally takes less than 1 minute and is effective without requiring many resources.

Leisegang and colleagues conducted a retrospective cohort study of women receiving antiretroviral therapy in a private managed care program in South Africa to determine the impact of pregnancy on antiretroviral therapy adherence (Abstract 1021). Women were classified as never pregnant (n = 4549), pregnant at initiation of long-
term antiretroviral therapy (n = 293), or pregnant after initiating antiretroviral therapy (n = 128).

The authors found that for women who were never pregnant and women who became pregnant after initiation of antiretroviral therapy, improved treatment adherence as assessed by monthly pharmacy refills was associated with shorter time on antiretroviral therapy, older age, receiving second-line antiretroviral therapy, pregnancy, and the 6-month postpartum period. Median adherence was much lower in the group who were pregnant at antiretroviral therapy initiation (54%) than in those who were never pregnant (79%; P < .001). The time to antiretroviral therapy default, defined as no antiretroviral therapy claimed for at least 6 months, was also shorter in women who were pregnant at antiretroviral therapy initiation than in the never-pregnant group. The investigators concluded that adherence is improved during pregnancy and immediately postpartum for those who become pregnant while receiving antiretroviral therapy but that adherence is more difficult for women who initiate antiretroviral therapy while pregnant. They are expanding their analysis to include a larger sample to more thoroughly explore these interactions.

**Outcomes of Treatment for Adults in Resource-Limited Settings**

There were at least 23 presentations on treatment outcomes and predictors of response to therapy in RLS; here, we call attention to a few abstracts from the session on outcomes of second-line antiretroviral therapy in RLS. Fox and colleagues analyzed data from the iDEA cohort to determine rates and predictors of failure of initial antiretroviral therapy and switch to second-line antiretroviral therapy in 44,204 patients in South Africa (Abstract S80). They included antiretroviral therapy–naïve patients receiving NNRTI-based initial antiretroviral therapy with at least 24 weeks of follow-up. Virologic failure was defined as a plasma HIV-1 RNA level of at least 400 copies/mL to 10,000 copies/mL. At baseline, median CD4+ cell count was 121/µL (IQR, 55–184/µL); 57% initiated antiretroviral therapy with stavudine/lamivudine/efavirenz; and more than 65% had disease classified as WHO clinical stage 3 or stage 4.

Median time from antiretroviral therapy initiation to treatment failure was 16 months (IQR, 12–24 months) for the 10% of patients who met at least 1 failure definition. The threshold chosen for the second confirmatory plasma HIV-1 RNA level elevation affected cumulative estimates of failure, increasing levels by 1.4-fold and 1.6-fold if set at 5000 copies/mL and 1000 copies/mL, respectively, when compared with a threshold of 10,000 copies/mL. Failure was predicted by lower age, male sex, nevirapine use, year initiating antiretroviral therapy, a baseline CD4+ cell count less than 250/µL, and a baseline plasma HIV-1 RNA level of 1,000,000 copies/mL or higher. Only 33% of those with documented virologic failure switched to second-line antiretroviral therapy after a median of 5.5 months after the first elevated plasma HIV-1 RNA level. Switch was predicted by low CD4+ cell count at the time of switch and CD4+ cell count decline over time. Thus, there remains a substantial delay in switching, and many of those meeting criteria for antiretroviral therapy failure do not transition to second-line antiretroviral therapy.

Some of these studies of HIV-infected adults in RLS are summarized in Table 1, which includes studies in children. Other presentations of relevance to adult outcomes of antiretroviral therapy in RLS include Abstracts 537–539, 541, 552, 554, 555, 557, 559–567, 581, and 582.

**Outcomes of Treatment for Infants and Children in Resource-Limited Settings**

Although data on treatment outcomes for infants and children in RLS remain limited, there were several presentations of interest at the 2011 CROI. Kuhn and colleagues presented long-term outcomes of the NEVEREST (Nevirapine Resistance Study), a randomized, controlled trial of treatment strategies in which HIV-infected children with prior exposure to nevirapine for PMTCT were switched to nevirapine-based therapy after initial suppression with a PI-based regimen (Abstract 128). The 52-week results of this trial have already been reported, but Kuhn presented follow-up data for 18 months to 53 months postrandomization. Beginning at 18 months after randomization and continuing through 48 months, children who were in the group that switched back to nevirapine-based antiretroviral therapy were less likely to have a postrandomization plasma HIV-1 RNA level greater than 50 copies/mL, the primary endpoint of the study, than were children who continued treatment with lopinavir/r-based regimens. However, when the secondary endpoint of a confirmed plasma HIV-1 RNA level greater than 1000 copies/mL was assessed, more children in the nevirapine group than in the lopinavir/r group met this endpoint.

The authors pointed out that the patterns of failure differed between the 2 groups: by 6 months, 59% of the treatment failures, as determined by plasma HIV-1 RNA levels greater than 1000 copies/mL, were detected in the nevirapine group; by 12 months, all of the treatment failures had been detected. In contrast, by 12 months, only 60% of the failures had been detected in the lopinavir/r group. Pretreatment drug resistance genotypic testing data, determined by population sequencing, showed a clear relationship between treatment failure in the nevirapine group and the presence of NNRTI mutations in the baseline genotype. The authors concluded that a switch strategy to an NNRTI-based regimen for children exposed to nevirapine for PMTCT could be employed safely in settings where plasma HIV-1 RNA level monitoring is available. They also noted that pretreatment screening for drug resistance mutations would optimize the switch strategy by screening out those for whom an NNRTI-based regimen would likely fail, offering a novel way to integrate genotypic testing into treatment-strategy studies in children.
Table 1. Selected Studies on Failure to Initiate, Loss to Follow-Up (LTFU), and Switching to Second-Line Antiretroviral Therapy (ART) in Resource-Limited Settings

<table>
<thead>
<tr>
<th>Abstract No.</th>
<th>Study Description</th>
<th>Location Cohort</th>
<th>Study Design Participants Definitions</th>
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<tr>
<td>Abstract 1014</td>
<td>Early death, care interruption, and LTFU in adults from a large South African community treatment program</td>
<td>South Africa, South African Catholic Bishops Conference, Catholic Relief Services HIV treatment program (71 sites)</td>
<td>Retrospective cohort; n = 11,397; ≥ 15 years old; initiating ART 2004–2008; median follow-up, 2.4 years. <strong>LTFU</strong>: missing all appointments in first 12 months after ART start. <strong>Interruption</strong>: missing some appointments but returning to care by 12 months</td>
<td>• 63% remained in care, and 37% missed appointments in first year after ART start: 11% interrupted care, 17% were LTFU, 9% died. • Of interrupters: 84% had HIV-1 RNA ≤ 400 copies/mL, 88% had increase in median CD4+ count at return to care. • LTFU: decreased with increasing calendar year of enrollment. <strong>Conclusion</strong>: Baseline factors did not distinguish interrupted care from LTFU, despite very different clinical implications of these 2 outcomes.</td>
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<td>Abstract 1015</td>
<td>Association of program characteristics with patient LTFU in adults on ART in International Epidemiological Databases to Evaluate AIDS (IeDEA) East Africa Consortium</td>
<td>Uganda, Tanzania, Kenya IeDEA East Africa (29 clinics)</td>
<td>Retrospective cohort; n = 43,175; ≥ 18 years old; on ART at last visit; data from 2007–2009; 61% women; mean age, 38 years. <strong>LTFU</strong>: absent from clinic ≥ 6 months</td>
<td>• LTFU: 16.5/100 person-years (py) (95% confidence interval [CI], 16.2–16.9/100 py) varied widely between sites (1–7.9/100 py). • Clinics without dedicated staff or with telephone-only outreach had hazard ratio (HR) 3.36 (95% CI, 1.72–6.57) for risk of LTFU compared with clinics with dedicated staff for outreach. • Clinics with only public means for outreach (bicycle/walking): HR, 3.12 (95% CI, 1.41–6.88) for LTFU compared with clinics with private vehicles for outreach. • Clinics that searched for patients LTFU &gt; 30 days after a missed visit: HR, 2.32 (95% CI, 1.26–4.24) for LTFU compared with those that searched ≤ 30 days of a missed visit. <strong>Conclusion</strong>: Patients at sites with outreach programs with dedicated staff and vehicles and early tracking of LTFU patients had lower risk of LTFU.</td>
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<td>Abstract 1017</td>
<td>Failure to initiate ART, LTFU, and mortality among adult HIV-infected patients qualifying for ART in Uganda</td>
<td>Uganda Immune Suppression Syndrome Clinic, Mbarara (single site)</td>
<td>Retrospective cohort with intensive tracking of a random sample to assess outcome; n = 1772; enrolling in care and meeting criteria for ART; 2007–2009; 58% women; median CD4+ count, 121/μL <strong>LTFU</strong>: 60 days late for appointment</td>
<td>• ART start: 20.6% (95% CI, 18.6%–21.9%) at 30 days; 63.4% (95% CI, 61.4%–66.0%) at 90 days; 67.5% (95% CI, 65.1%–69.7%) at 365 days. • LTFU: 21% (95% CI, 19.3%–22.6%). • 1-year mortality in subsample (n = 134) of those LTFU with outcome tracking: 30.8% (95% CI, 22.9%–40.6%). • Extrapolating subsample results to cohort: 69% initiate, 16% in care awaiting ART; 7% disengaged from care, 9% died before ART initiation. <strong>Conclusion</strong>: Failure to initiate ART may be an important issue; more work is needed to determine and eliminate its causes.</td>
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<td>Abstracts 680, 681</td>
<td>Outcomes in ART-naive children in Abidjan, Côte d’Ivoire</td>
<td>Côte d’Ivoire Aconda Program</td>
<td>Retrospective cohorts Abstract 680: n = 1724; ART-naive; June 2004–November 2007; median age, 54 months. Abstract 681: n = 405; ART-naive; 2004–2009; median age, 4.5 years; median follow-up, 12 months; 28% met World Health Organization criteria for immunodeficiency.</td>
<td>Abstract 680: • 31% of children died, transferred out, or were LTFU before ART start. • Mortality rate: 13.2/100 child-years (cy) (95% CI, 10.0–13.4/100 cy). • Mortality correlated with pre-ART CD4+ count in all age strata. <strong>Abstract 681</strong>: • Observed risk of a serious morbid event: 17.8/100 cy at 18 months of follow-up. • Cumulative mortality: 3.62/100 cy at 18 months (95% CI, 3.5–8.1/100 cy). • LTFU: 6.36/100 cy (95% CI, 6.16–6.55/100 cy); highest for those 2–5 years of age (9.37/100 cy, 95% CI, 8.92–9.81/100 cy). <strong>Conclusion</strong>: Mortality is high among ART-naive children who qualify for treatment initiation, as are rates of LTFU and serious morbid events. These events may be preventable by earlier ART initiation.</td>
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Malaste et al. and colleagues described outcomes for children before antiretroviral therapy initiation in a large pediatric antiretroviral therapy program in Abidjan, Côte d’Ivoire (the Aconda Program). A retrospective cohort study examined morbidity, mortality, and LTFU in a cohort of 405 HIV-infected children in 2 health facilities who had a median age of 4.5 years. The study determined the relationships between absolute CD4+ cell count and percentage and risk of death in 1724 antiretroviral therapy–naive, HIV-infected children with a median age of 4.5 years. Risk was lower for children previously exposed to antiretroviral therapy for PMTCT and for children under 5 years of age. Cumulative mortality was 3.62 per 100 cy at 18 months (95% CI, 3.5–8.1 per 100 cy). Risk of LTFU was 6.36 per 100 cy (95% CI, 6.16–6.55 per 100 cy), and was highest for those between 2 years and 5 years of age (9.37/100 cy; 95% CI, 8.92–9.81 per 100 cy). Together, these results argue for earlier initiation of antiretroviral therapy for children in RLS, a strategy currently recommended by the WHO but still not available to many children.

Barlow-Mosha and colleagues reported on a cohort of 142 children in Uganda, aged 1 year to 12 years, who had been receiving initial antiretroviral therapy for at least 1 year and were enrolled in an ongoing, randomized controlled trial. The mean age of the children was 7.3 years, 44% were girls, all were on NNRTI-based regimens, the median duration of antiretroviral therapy was 50 months (IQR, 30–63 months), 37% were exposed to single-dose nevirapine for PMTCT, and 79% had disease in WHO clinical stage 2 or 3. The authors found that median CD4+ cell percentage was 55% (IQR, 29%–42%), and 65% had a plasma

### Table 1. Selected Studies on Failure to Initiate, Loss to Follow-Up (LTFU), and Switching to Second-Line Antiretroviral Therapy (ART) in Resource-Limited Settings (continued)

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<td><strong>Abstract 580.</strong> Rates and predictors of failure of initial regimen and switch to second-line ART in South Africa</td>
<td>South Africa. LeDIA Southern Africa (8 programs)</td>
<td>Retrospective cohort; n = 44,204 (96,937 py); NNRTI-based initial ART for ≥ 24 weeks; 59% women; pre-ART median CD4+ count, 121/μL; 57% on stavudine/lamivudine/efavirenz</td>
<td>• 10% of patients met at least 1 definition of treatment failure • Median time from ART start to failure, 16 months (interquartile range, 12–24 months) • Failure predicted by lower age, male sex, nevirapine use, year initiating ART, baseline CD4+ count &lt; 25/μL, and baseline HIV-1 RNA ≥ 1,000,000 copies/mL • 33% of those with virologic failure switched to second-line ART at a median 5.5 months after first elevated HIV-1 RNA • Switch predicted by low CD4+ count at time of switch and rapid CD4+ count decline over time <strong>Conclusion:</strong> A substantial delay in switching exists, and many of those meeting criteria for ART failure do not transition to second-line ART.</td>
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<td><strong>Abstract 684. Outcomes of HIV-infected and HIV-exposed children LTFU in Western Kenya</strong></td>
<td>Western Kenya. AIDSRelief-Kenya</td>
<td>Prospective tracking of random sample of children LTFU; n = 97 (of 308 meeting inclusion) LTFU: absent from clinic ≥ 6 months for children on ART who were HIV-exposed or had unknown HIV serostatus; absent from clinic ≥ 12 months for HIV-infected children not on ART</td>
<td>• Community health workers were able to locate or determine vital status for 82% of children: 11 died: 7 on ART, 2 HIV-exposed, 2 HIV-unknown serostatus • Primary reasons for LTFU for those with known HIV serostatus: fear of family/community discrimination or disclosure issues • For HIV-exposed LTFU: 14/46 never returned because guardians had not disclosed own serostatus or fear of family/community stigma <strong>Conclusion:</strong> Fear of family/community discrimination was an important cause of LTFU in this cohort and should be considered in future interventions</td>
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*Updated data provided in oral presentation differs from the published abstract.*

ART indicates antiretroviral therapy; HIV-1 RNA, plasma HIV-1 RNA level; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; nRTI, nucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor.
HIV-1 RNA level below 400 copies/mL. Children exposed to single-dose nevirapine had reduced odds of achieving an undetectable plasma HIV-1 RNA level (OR, 0.36; 95% CI, 0.17–0.74). There was poor correlation between CD4+ cell percentage and having a detectable plasma HIV-1 RNA level (r = 0.015). As one-third of the children receiving antiretroviral therapy had detectable plasma HIV-1 RNA levels despite good immunologic response, the authors concluded that plasma HIV-1 RNA monitoring is important for early detection of treatment failure, particularly for children with prior exposure to single-dose nevirapine who are receiving nevirapine-based initial antiretroviral therapy.

Braitstein and colleagues described the results of aggressive tracking of a random sample of children LTFU in western Kenya who were HIV-infected and receiving antiretroviral therapy, HIV-infected and not receiving antiretroviral therapy, HIV-exposed, or of unknown HIV serostatus (Abstract 684). LTFU was defined as absent from the clinic for at least 6 months for children who were receiving antiretroviral therapy, HIV-exposed, or of unknown HIV serostatus, and as absent from the clinic for at least 12 months for HIV-infected children not receiving antiretroviral therapy. A total of 308 children met these inclusion criteria, and of those, the investigators randomly selected 97 children (19 from a rural district hospital and 78 from an urban hospital) for aggressive tracking by community health workers equipped with detailed patient locator information collected on the last known visit.

The community health workers were able to locate 82% of the children in the sample. Of those, 11 (11%) had died: 7 (16%) receiving antiretroviral therapy, 2 (4%) HIV-exposed, and 2 (29%) of unknown HIV serostatus. The primary reason the majority of children did not return to the clinic, of those with known HIV infection or HIV exposure, was because of fear of family or community discrimination or disclosure issues. Of children with unknown HIV serostatus, 2 were not located and 2 were confirmed dead, making these the largest categories in this group of 7 children. The authors pointed out that the sampling of those LTFU more recently may have led to a higher rate of successful tracking than might occur when tracking children LTFU for a longer time.

Meyer-Rath and colleagues estimated the average outpatient cost of the first 2 years of outpatient antiretroviral therapy for pediatric patients in Zambia and South Africa. The investigators selected 120 children in Zambia and 148 in South Africa who were initiating therapy at up to 12 years of age between 2005 and 2008 and who remained in the same clinical setting for the first 24 months of antiretroviral therapy. They determined patient outcomes (HIV serostatus, CD4+ cell count, plasma HIV-1 RNA level, and clinical condition) and resource utilization at 12 months and 24 months of antiretroviral therapy. The median age at antiretroviral therapy initiation was 5.45 years (IQR, 2.21–8.28 years) in Zambia and 4.01 years (IQR, 1.62–7.16 years) in South Africa, and the median CD4+ cell percentages at initiation were 12.5% (IQR, 8.60%–16.40%) and 13.23% (IQR, 7.09%–17.58%) in Zambia and South Africa, respectively. The majority of patients in Zambia received either stavudine/lamivudine/nevirapine or zidovudine/lamivudine/nevirapine, and the majority of patients in South Africa received stavudine/lamivudine/efavirenz or stavudine/lamivudine plus lopinavir/ritonavir. Patients were classified as follows: in care and responding (undetectable plasma HIV-1 RNA level, acceptable CD4+ cell percentage and clinical condition); in care and not responding (detectable plasma HIV-1 RNA level, unacceptable CD4+ cell percentage or clinical condition); or no longer in care (died or LTFU).

Rates of retention in care were approximately 75% at both sites at 12 months. The average cost per year for a patient remaining in care was US$367 in year 1 and US$346 in year 2 in Zambia, and US$1068 in year 1 and US$707 in year 2 in South Africa. The higher costs in South Africa were attributed to the more expensive antiretroviral regimens and higher staff costs. The investigators highlighted that, although pediatric treatment costs approximately the same or less than adult treatment (average per adult per first year, US$448 in Zambia and US$699 in South Africa), very few young children have access to antiretroviral therapy in either country. Some of these studies of HIV-infected children in RLS are summarized in Table 1.

### Strategies for Laboratory Monitoring in Resource-Limited Settings

Hosseinipour gave an overview of laboratory and clinical monitoring strategies in Session 33, “Getting the Most From Global HIV Scale-Up” (Abstract 109). She emphasized issues specific to RLS, where the poor performance characteristics of clinical and immunologic criteria to determine antiretroviral therapy failure can lead to challenges at both ends of the spectrum: premature switch to second-line therapy for patients for whom virologic control has been achieved but is not recognized because of the lack of virologic monitoring versus prolonged treatment with suboptimal antiretroviral therapy followed by the emergence of resistant virus when clinical and immunologic criteria allow for prolonged treatment without virologic suppression. Hosseinipour reviewed data from the DART (Development of Antiretroviral Therapy in Africa) trial, which showed a small but statistically significant mortality benefit to immunologic monitoring over clinical monitoring after 5 years of antiretroviral therapy. A prior study of home-based antiretroviral care showed an increased risk of death or AIDS–defining events in the clinical group compared with the immunologic and virologic monitoring group but found no statistically significant difference between the immunologic- and virologic-monitoring groups for the same outcome at 3 years of follow-up.

Hosseinipour also mentioned data on monitoring strategies (Abstracts 44 and 45LB, reviewed below). She concluded that a moderate advantage to immune monitoring can be observed...
primarily beyond 2 years, and although no mortality benefit to virologic monitoring has been documented, virologic monitoring is associated with increased switch to second-line therapy and decreased duration of viremia. She then reviewed studies that evaluate the WHO immunologic criteria, all of which showed low sensitivity and low positive predictive value, and similar data for the WHO clinical criteria to identify failure. Data from the ART-LINC (Antiretroviral Therapy in Lower Income Countries) cohort collaboration have also shown that, of individuals who met WHO criteria for treatment failure, only 24% were switched to second-line antiretroviral therapy, and failure to switch was associated with mortality. Hosseinipour also discussed resistance in RLS (Abstracts 53 and 618, reviewed below under Resistance) and second-line treatment outcomes (Abstract 583, reviewed above under Clinical Trials of Antiretroviral Therapy in Treatment-Experienced Patients).

Lallemant presented data from a randomized controlled trial in Thailand, powered for noninferiority analysis, comparing the use of CD4+ cell count with the use of plasma HIV-1 RNA level monitoring to dictate changes in antiretroviral regimen (Jourdain et al, Abstract 44). Inclusion criteria were HIV-seropositive with CD4+ cell count between 50/µL and 250/µL, no coinfection with either hepatitis B virus (HBV) or hepatitis C virus (HCV), and initiating NNRTI-based antiretroviral therapy. A total of 716 people were randomly assigned to CD4+ cell count between the 2 groups—8.3% in the viral load monitoring group and 7.7% in the CD4+ cell count monitoring group—not was the risk of death (4.4% vs 3.5%, respectively). Anemia, CD4+ cell count less than 150/µL, plasma HIV-1 RNA levels over 10,000 copies/mL, and body mass index less than 18.5 kg/m² were associated with risk of clinical failure in an adjusted multivariate analysis. Median time to switch was lower in the viral load monitoring group (11.7 months) than in the CD4+ cell count monitoring group (24.7 months; P = .001 for comparison), but virologic and immunologic response at 3 years were similar in both groups. Of the 31 patients in the CD4+ cell count monitoring group, 15 switched to PI-based regimens while their HIV-1 RNA level was undetectable, and 7% of patients required a treatment substitution for toxicity, with no statistical difference between the 2 study groups. There was no statistical difference in future drug options between the 2 groups. The investigators concluded that the additional time spent using failing regimens in the CD4+ cell count monitoring group did not lead to a decrease in future drug options for those patients, but they emphasized the need for adherence support and third-line regimen availability in RLS.

Kouaafack and colleagues asked a similar question in Cameroon, using a randomized noninferiority trial to compare laboratory monitoring (plasma HIV-1 RNA level, CD4+ cell count) plus clinical monitoring every 6 months with clinical monitoring alone (Abstract 45LB). Inclusion criteria were as follows: HIV-infected, antiretroviral therapy–naive adults; WHO stage 3 or stage 4 disease or WHO stage 2 disease with total lymphocyte count less than 1200 cells/µL, and initiating antiretroviral therapy in 1 of 9 district hospitals. The primary outcome was the mean increase in CD4+ cell count after 2 years of antiretroviral therapy, and noninferiority was defined as a difference of no more than 25% in the mean increase in CD4+ cell count between the 2 groups. Switch to second-line therapy was required for the following scenarios: persistent plasma HIV-1 RNA level above 5000 copies/mL for the laboratory-monitoring group, and persistent WHO disease stage 3 or stage 4 or AIDS–defining event for the clinical-monitoring-only group. A total of 459 patients were randomly assigned, and characteristics were similar between the laboratory- and clinical-monitoring groups (median CD4+ cell count, 179/µL and 182/µL, respectively). Two-thirds of all patients in both groups received stavudine/lamivudine/nevirapine, and LTFU was 9% in the clinical-monitoring group and 8% in the laboratory-monitoring group.

The primary outcome analysis showed a difference in the mean change in CD4+ cell count between the 2 groups of a 31/µL decrease (clinical monitoring vs laboratory monitoring; 95% CI, 63/µL decrease to 2/µL increase). These results did not reach the noninferiority margin of a 52/µL decrease (95% CI, 58/µL decrease to 45/µL decrease), as the lower boundary of the 95% CI of the difference (62/µL decrease) was lower than that allowed to prove noninferiority (58/µL decrease). Thirteen patients in the laboratory-monitoring group were switched to second-line antiretroviral therapy because of treatment failure, compared with none switched to second-line antiretroviral therapy in the clinical-monitoring group (P < .001). There were comparable results in virologic suppression, HIV drug resistance, mortality, disease progression, adherence and toxicity between the 2 groups.

The investigators concluded that clinical monitoring was not noninferior to laboratory monitoring and that switch to second-line antiretroviral therapy was statistically significantly increased in the laboratory-monitoring group. Both conclusions support the WHO recommendation to use laboratory monitoring in RLS. However, the authors added the caveat that, because of the overall limited differences between the 2 strategies, clinical monitoring could be used within the first 2 years of scale-up to allow for financial and structural limitations in RLS.

Rawizza and colleagues used a Markov simulation model to assess the impact of CD4+ cell count monitoring compared with plasma HIV-1 RNA level monitoring to determine antiret-
The second DART presentation, by Kityo and colleagues, retrospectively determined virologic response to treatment in 1164 patients who continued initial antiretroviral therapy in the immunologic- or clinical-monitoring arms of the DART trial (Abstract 677). The investigators found that virologic suppression (plasma HIV-1 RNA level < 200 copies/mL) after a median of 46 months of therapy was common (933 participants, 80%) and was associated with older age, female sex, and higher pre-antiretroviral therapy CD4+ cell count. However, when a conservative estimate of overall rates of virologic suppression was used that assumed lack of suppression for those who died or switched to second-line antiretroviral therapy based on clinical or immunologic criteria, the estimated suppression rate at the end of the trial was 54.8% (95% CI, 52.5% – 57.0%). The authors argued that the low rates of virologic failure in this trial, which did not monitor virologic outcomes of antiretroviral therapy, prospectively call into question the need for virologic monitoring in RLS.

Keiser and colleagues used data from the IeDEA cohort collaboration to examine immunologic response to antiretroviral therapy and mortality in 18,706 South African patients receiving care in clinics where plasma HIV-1 RNA level monitoring is available and in 80,937 patients from sites in Zambia and Malawi where such monitoring is not available (Abstract 678). Patients at the virologic-monitoring sites had lower CD4+ cell counts at antiretroviral therapy initiation (93/µL) than patients at sites without virologic monitoring had (152/µL; P = .001). After 3 years of antiretroviral therapy, the median CD4+ cell count was 415/µL at sites with virologic monitoring and 372/µL at sites without (P < .001). At sites with virologic monitoring, the risks of death and LTFU were also lower among the patients, and the likelihood of switching to second-line antiretroviral therapy was higher (aHR, 4.44; 95% CI, 3.95 – 4.98). The authors concluded that these data, contrary to those from the DART trial reported in Abstract 677 above, support virologic monitoring in RLS. Table 2 summarizes these studies on monitoring strategies in RLS.

**Mother-to-Child Transmission of HIV Infection**

**Pregnancy and Prevention of Mother-to-Child Transmission**

Harries, as part of his N’Galy Mann Lecture discussed above, described a proposed 2011 Malawi initiative to test all pregnant women for HIV infection and treat all who tested HIV-seropositive for life, initially with once-daily tenofovir/lamivudine/efavirenz, in the hope of creating a “Born HIV Free” generation by 2015 (Abstract 18). The approach recognizes the nation’s weak health infrastructure, insufficient availability of and capacity for CD4+ cell count monitoring, and high total fertility rate, plus the desire to send a simple message to the community that antiretroviral therapy is to be taken for life. It is anticipated that this approach would be simple to implement, reduce mother-to-child transmission (MTCT), protect babies born in subsequent pregnancies, improve maternal health, reduce risk of tuberculosis, and provide treatment of HBV coinfection.

Session 146 was also dedicated to plans for PMTCT of HIV. Dryden-Peters and colleagues reported compelling data in support of maternal highly active antiretroviral therapy from a prospective observational study of HIV-infected women who participated in the Botswana PMTCT Programme (Abstract 740). Investigators observed 427 women during pregnancy. Women with CD4+ cell counts below 250/µL were treated with antiretroviral therapy, and those with CD4+ cell counts of 250/µL or above were treated with zidovudine starting at 28 weeks gesta-tion (and a single dose of nevirapine if the zidovudine was taken for less than 4 weeks). All HIV-exposed babies received single-dose nevirapine and zidovudine for 1 month.

Of 432 live-born babies, 262 infants were born to mothers taking antiretroviral therapy, and 170 infants were born to mothers taking zidovudine...
### Table 2. Selected Studies Addressing the Impact of Laboratory Monitoring Strategies to Determine Antiretroviral Therapy (ART) Treatment Response in Resource-Limited Settings (RLS)

<table>
<thead>
<tr>
<th>Abstract No. Study Description</th>
<th>Location Name of Study</th>
<th>Study Design Participants Definitions</th>
<th>Key Findings Conclusions</th>
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| **Abstract 44.** Randomized trial comparing CD4+ count vs virologic monitoring strategies | Thailand Perinatal HIV Prevention Trial-3 | Randomized, double-blind (preswitch) trial of CD4+ count vs HIV-1 RNA monitoring every 3 months; n = 716; initiating NNRTI-based ART; median pre-ART CD4+ count, 144/μL; mean age, 36 years Follow-up: 3 years | • Risk of clinical failure similar: 8.3% in HIV-1 RNA group; 7.7% in CD4+ count group (P = .74)  
• Risk of death similar: 4.4% in HIV-1 RNA group; 3.5% in CD4+ count group  
• Median time to switch: 11.7 months in HIV-1 RNA group; 24.7 months in CD4+ count group (P = .001)  
• 15/31 patients in CD4+ count group switched when HIV-1 RNA < 50 copies/mL  
• No statistical difference between groups in future drug options  
**Conclusion:** Rates of clinical failure were low at 3 years and did not differ between the 2 monitoring strategies, nor did CD4+ count monitoring diminish future treatment options. |
| **Abstract 45LB.** Randomized trial comparing virologic, CD4+ count, and clinical monitoring to clinical monitoring alone | Cameroon Strattall ANRS 12110/ESTHER Trial (9 rural district hospitals) | Randomized, non-inferiority trial of clinical monitoring vs CD4+ count and HIV-1 RNA monitoring every 6 months; n = 459; ART-naïve; World Health Organization (WHO) stage 3/4; loss to follow-up (LTFU): 9% in clinical arm, 7% in laboratory-monitoring arm Follow-up: 2 years | • Median CD4+ count after 2 years: 182/μL in clinical group, 179/μL in laboratory-monitoring group  
• Mean increase in CD4+ count between groups did not meet criteria for noninferiority (a difference ≤ 25% between groups)  
• 13 patients in laboratory-monitoring group switched to second-line ART, none in clinical-monitoring group  
• Otherwise, comparable results in virologic suppression, HIV drug resistance mutations, mortality, disease progression, adherence, and toxicity between groups  
**Conclusion:** Clinical monitoring was not noninferior to laboratory monitoring; laboratory monitoring was associated with higher rates of switch to second-line ART. Authors suggest the minimal overall differences make 2 years of clinical monitoring feasible, but longer follow-up period is needed. |
| **Abstracts 676, 677.** Examining virologic outcomes from a randomized trial of CD4+ count and clinical monitoring vs clinical monitoring alone | Uganda, Zimbabwe DART (Development of Antiretroviral Therapy in Africa) trial | Randomized, unblinded trial of clinical monitoring vs CD4+ count monitoring every 12 weeks; n = 3315; ART-naïve; CD4+ count < 200/μL Follow-up: 5 years **Clinical failure:** new WHO stage 4 event or ≥ 1 WHO stage 3 event **Immunologic failure:** CD4+ count < 100/μL | • At time of treatment failure determination: 15% of those with CD4+ count monitoring and 28% of those with clinical monitoring had HIV-1 RNA < 400 copies/mL  
• Only 7/82 (9%) of those with CD4+ count ≥ 250/μL at time of switch had HIV-1 RNA < 400 copies/mL  
• Of 1174 who remained on initial ART: 80% had HIV-1 RNA < 200 copies/mL after a median of 64 months of ART  
• Authors argue that rates of virologic failure were low, and that use of a CD4+ count tiebreaker at a level ≥ 250/μL could avoid switches in patients with undetectable HIV-1 RNA  
**Conclusion:** Although overall rates of virologic suppression are high in those remaining on initial ART, if patients who switched or died are included as failures, rates of virologic “success” drop to 55%. CD4+ count monitoring is a potential strategy in RLS, but pitfalls exist. |
| **Abstract 678.** Comparing CD4+ count response to ART and mortality in programs with and without virologic monitoring in southern Africa | South Africa, Zambia, Malawi (International Epidemiological Databases to Evaluate AIDS [iDEA] cohort collaboration) | Retrospective cohort South Africa (virologic monitoring); n = 18,706; pre-ART median CD4+ count, 132/μL Zambia and Malawi (no virologic monitoring); n = 80,937; pre-ART median CD4+ count, 93/μL (P = .011 for difference with virologic monitoring) Follow-up: 3 years | • After 3 years: median CD4+ count, 415/μL at sites with virologic monitoring and 372/μL at sites without (P < .001)  
• Risk of death and LTFU were lower at sites with virologic monitoring  
• Adjusted hazard ratio for switch to second-line ART was higher at sites with virologic monitoring than those without: 4.44; 95% CI, 3.95–4.98  
**Conclusion:** These data differ from those presented above in that they support a role for virologic monitoring in RLS but are limited by the fact that they are drawn from an observational cohort, albeit a very large one. |

ANRS indicates French National Agency for Research on AIDS and Viral Hepatitis; ESTHER, Ensemble pour une Solidarité Thérapeutique Hospitalière En Réseau (Network for Therapeutic Solidarity in Hospitals); HIV-1 RNA, plasma HIV-1 RNA level; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor.
alone. A total of 10 infants were infected with HIV. Only 1 HIV-infected infant (0.4%; 95% CI, 0.01%–2.3%) was born to a woman taking antiretroviral therapy, compared with 9 HIV-infected infants (5.9%; 95% CI, 2.7%–10.9%) born to women taking zidovudine alone (P < .001). Thai investigators Phanuphak and colleagues also reported excellent safety and efficacy of maternal triple-drug antiretroviral therapy regardless of maternal CD4+ cell count from the Thai Red Cross PMTCT Program from 2004 to 2010. The transmission rate to babies was 1% (Abstract 742).

Ciaramello and colleagues modeled combinations of treatment options within the context of scale-up of antenatal care that could result in virtual elimination of MTCT in Zimbabwe and predicted that an approach stratified by CD4+ cell count could reduce MTCT to near or less than 5% (Abstract 739). Mothers who have a CD4+ cell count less than 500/µL would be treated with antiretroviral therapy, and mothers who have a count greater than 500/µL would receive short-course zidovudine during pregnancy and extended nevirapine treatment for the infant during breastfeeding. In a talk dedicated to applying principles of cost-effectiveness to HIV care programs, Walensky addressed the issue of PMTCT and cost-effectiveness, reporting that effective programs for PMTCT are often associated with cost savings (Abstract 74).

Ekouevi and colleagues reported on maternal HIV disease progression after the interruption of triple-drug antiretroviral therapy or short-course antiretroviral treatment for PMTCT using data from 13 programs in Africa and Thailand from the MTCT-Plus Initiative (Abstract 753). Among 1027 HIV-infected pregnant women with CD4+ cell counts greater than 400/µL, investigators compared rates of CD4+ cell count decline according to PMTCT treatment: antiretroviral therapy (n = 113; 11%), single-dose nevirapine (n = 444; 43.2%), short-course antiretroviral prophylaxis (n = 355; 34.4%), or no prophylaxis (n = 117; 11.4%). After adjusting for age, country, CD4+ cell count, and WHO stage of disease at enrollment, women who received antiretroviral therapy were 3 times as likely to become antiretroviral therapy–eligible within 24 months as women receiving short-course antiretroviral prophylaxis (HR, 3.37; 95% CI, 1.96–5.79; P < .001). The authors urged consideration of lifelong antiretroviral treatment for pregnant women with CD4+ cell counts less than 500/µL.

**Mother-to-Child Transmission and Breast-feeding**

Maldonado presented HIV Prevention Trials Network (HPTN) 046 data comparing an extended course of daily nevirapine for infants through age 6 months with 6 weeks of nevirapine for postnatal prevention of HIV infection acquired through breastfeeding (Coovadia et al, Abstract 123LB). After 6 weeks of daily nevirapine, 1522 breast-feeding infants were randomly assigned to either continuation of daily nevirapine or placebo until 6 months postpartum. At randomization, 29% of mothers in each group were receiving antiretroviral therapy for their own health; at 6 months, this amount increased to 31% in the extended-nevirapine group and 32% in the placebo group.

At 6 months, the rate of HIV infection was statistically significantly lower in the extended-nevirapine group (1.1%) than in the placebo group (2.4%; P = .048); however, this difference was not observed at 9 months or 12 months. Stratification by maternal antiretroviral therapy status showed a very low rate of infant transmission (0.2%) at 6 months for the mothers receiving treatment compared with the mothers not receiving antiretroviral therapy (2.4%; P = .027). For mothers not receiving antiretroviral therapy, there was a statistically significant difference in infant HIV infection at 6 months (1.4% for infants receiving extended nevirapine vs 3.4% for infants receiving placebo; P = .027). There were no differences in mortality or serious adverse events between the extended-nevirapine- and placebo-treated infants.

Nielsen-Saines, on behalf of the HPTN 040/PACTG (Pediatric AIDS Clinical Trials Group) 1043 study, presented compelling data in support of postexposure prophylaxis (PEP) with 2- or 3-drug antiretroviral regimens instead of zidovudine alone for prevention of intrapartum HIV transmission to infants born to women not receiving antiretroviral therapy before labor (Abstract 124LB). Babies of mothers not receiving antiretroviral drugs were identified at labor or postpartum. In this international study, babies were randomly assigned within 48 hours of birth to 1 of 3 groups: zidovudine alone for 6 weeks; zidovudine for 6 weeks plus nevirapine for 3 doses in the first week; or zidovudine for 6 weeks plus lamivudine and nelfinavir for 2 weeks. All babies were formula-fed, and follow-up continued until 6 months.

Of the 1684 babies included in the analysis, 8.3% overall were infected, with 5.5% infected in utero and 2.8% infected intrapartum. Intrapartum infection in the zidovudine-alone group occurred in 4.9%, compared with 2.2% in the zidovudine-plus-nevirapine group (P = .045) and 2.5% in the zidovudine-plus-lamivudine-and-nelfinavir group (P = .034). In addition to the association with treatment regimen, maternal viral load was associated with transmission on multivariate analysis. There was statistically significantly more neutropenia in the zidovudine-plus-lamivudine-and-nelfinavir group (15%; P < .0001) than in the other 2 groups. For infants born to HIV-infected mothers not receiving antiretroviral drugs, investigators suggested administering 2- or 3-drug antiretroviral treatment within 48 hours of birth for infants rather than zidovudine alone.

In an effort to identify maternal antiretroviral regimens that would still prevent infection to infants but would possibly be less toxic to the mother and child during treatment, the Primeval ANRS 135 trial studied maternal treatment with lopinavir/ritonavir monotherapy compared with lopinavir/ritonavir plus zidovudine/lamivudine (Abstract 125LB). A total of 105 women were randomly assigned in a 2:1 ratio to begin lopinavir/ritonavir monotherapy (n = 69) or treatment with lopinavir/ritonavir plus zidovudine/lamivudine (n = 36; control group) at 26 weeks’ gestation; follow-up continued...
up until 12 weeks postpartum. All babies were treated postpartum with 4 weeks to 6 weeks of zidovudine and observed for 24 months. Changes of antiretroviral drugs because of intolerance were statistically significantly less frequent in the monotherapy group (1.4%) than in the control group (11.1%; \( P = .046 \)).

Based on an intention-to-treat analysis, the primary endpoint of plasma HIV RNA level below 200 copies/mL at week 8 of treatment was achieved at comparable rates in both groups: 88.4% of women receiving monotherapy and 94.4% of control women (\( P = .5 \)). Monotherapy patients had statistically significantly less viral suppression (plasma HIV RNA level < 50 copies/mL) at delivery (79.7% vs 97.2% in controls; \( P = .01 \)). Of the 105 children born, there was 1 case of transmission in the control group and none in the monotherapy group. Studies of genotoxicity, mitochondrial toxicity, cardiac toxicity, and hematologic toxicity in infants are ongoing.

Risk of HIV Transmission During Pregnancy

John-Stewart gave a presentation on transmission risk in pregnancy in which she discussed risk of acquiring HIV infection during pregnancy and postpartum, specific issues related to the pregnancy and postpartum periods, and strategies for HIV prevention during and after pregnancy (John-Stewart et al., Abstract 67). Biological changes associated with pregnancy may put pregnant women at higher risk of HIV infection. Examples include hormonal changes, immune activation, and changes in the genital mucosa. In some studies, pregnancy and lactation have been identified as cofactors influencing risk of HIV infection. John-Stewart reported historical data from Rwanda, which indicate that the risk of transmission to infants from mothers with acute HIV infection (up to 29%) is higher than transmission rates for women with chronic HIV infection (16%). As PMTCT becomes more effective, the proportion of HIV infections in children of mothers with acute HIV infection is expected to rise substantially.

Eshleman and colleagues reported on the use of a multiasay algorithm to determine recency of HIV infection in pregnant women in the PEPI (Postexposure Prophylaxis for Infants)-Malawi trial (Abstract 737). Subjects were 2561 women enrolled in the PEPI-Malawi trial who were in labor, their infants were randomly assigned to 1 of 3 postnatal infant regimens. A multiasay algorithm was performed within 3 days of delivery on samples from all women; 73 women were identified as having been recently infected. The risk of in utero transmission of HIV was found to be 17.9% among women recently infected and 6.7% in women whose infection was not recent.

Several other abstracts examined risk factors for MTCT. Tubiana and colleagues reported extremely low risk of MTCT of HIV in women starting antiretroviral therapy before pregnancy in the French Perinatal Cohort (Abstract 735). Nearly 6000 women enrolled in the ANRS French Perinatal Cohort were included in the analysis of HIV transmission risk and stratified according to whether their antiretroviral treatment was initiated. The HIV transmission rate was 0.5% if treatment had begun before conception, 0.6% if initiated in the first trimester, 1.2% if initiated during the second trimester, and 2.6% if initiated after 28 weeks. When the maternal plasma HIV-1 RNA level was less than 50 copies/mL at delivery, the transmission rates dropped to 0%, 0%, 0.5%, and 0.8% in the 4 strata, respectively.

French and colleagues looked at the effect of subsequent pregnancies on MTCT risk (Abstract 736). In reviewing 9807 pregnancies in HIV-infected women in the United Kingdom and Ireland, monitored through the National Study of HIV in Pregnancy and Childhood, they found no evidence of an increased risk of MTCT in subsequent pregnancies. Khamduang and colleagues presented data on the interrelated transmission of HIV-1 and cytomegalovirus (CMV) during gestation and delivery in the children of HIV-infected mothers (Abstract 122). Investigators sought to understand the timing of CMV transmission and its relationship to HIV transmission, compare the risk of CMV infection in HIV-infected and -uninfected mothers, and examine risk factors for CMV transmission in HIV-infected infants. Women and infants who had participated in a clinical trial for PMTCT in Thailand were included in the study. Ninety-seven HIV-infected infants were matched 1:2 with HIV-uninfected infants by baseline maternal viral load. CMV infection was determined by CMV IgG antibody testing at 18 months and timed by CMV IgM antibody testing or CMV DNA detection in plasma or blood at birth and thereafter.

CMV infections were more common in HIV-infected infants than in HIV-uninfected infants: congenital (14% vs 3%, respectively), intrapartum (41% vs 28%, respectively), acquired (80% vs 63%, respectively), and overall (84% vs 63%, respectively). CMV infection in utero was associated with increased odds of intrauterine HIV infection (OR, 8.1; \( P = .01 \)). Intrapartum HIV infection was associated with both congenital and intrapartum CMV infection (OR, 2.5; \( P = .04 \)). Overall, HIV infection was associated with CMV infection (OR, 2.9; \( P = .001 \)). In HIV-infected infants, the risk of CMV infection was statistically significantly associated with prematurity, intrapartum HIV infection, and vaginal delivery.

Effects of Antiretroviral Therapy During Pregnancy on Infant Health

Sessions 147 and 148 were dedicated to understanding the effect of antiretroviral exposure during the perinatal period on infant health. Two studies reported on PI use and perinatal delivery. Sibiude and colleagues reported findings from a retrospective analysis of 13,957 singleton pregnancies in HIV-infected women of the ANRS French Cohort from 1990 to 2009 (Abstract 743). The authors reported steadily increasing rates of perinatal delivery from 9.2% (1990–1993: no antiretroviral therapy available) to 9.6% (1994–1996: zidovudine available), 12.4% (1997–1999: double-nRTI therapy and some multiclass antiretroviral therapy available), and 14.3%
Statistically significantly more deaths occurred in mothers and infants after weaning and antiretroviral therapy cessation at 6 months than occurred during treatment. The authors urged a higher threshold for continuous maternal antiretroviral therapy and further evaluation of optimal weaning strategies.

Storfer and colleagues examined the risk of birth defects in children exposed to nevirapine according to the trimester of first exposure in the Antiretroviral Pregnancy Registry and compared risks to those of external control subjects from 1989 to 2010 (Abstract 749). Investigators reported on 2327 nevirapine-exposed pregnant enrollees in the Registry, of whom 970 were exposed to nevirapine in the first trimester (1001 babies) and 1182 were exposed starting in the second or third trimester (1201 babies). There was no association of birth defects with first-trimester exposure or with nevirapine exposure in general.

Two abstracts looked at the effects of antiretroviral drug exposure on HIV-uninfected children of HIV-infected mothers. Noguera-Julian and colleagues reported lower mitochondrial-encoded complex IV activity in antiretroviral drug–exposed, HIV-uninfected healthy infants from a prospective observational study of 135 HIV-uninfected, antiretroviral drug–exposed babies (Abstract 750). Mitochondrial DNA was measured using quantitative real-time PCR, and mitochondrial respiratory chain enzymatic activity of complex IV and mitochondrial mass were assessed from PBMCs obtained at 6 weeks and at months 3, 6, and 12. The control group included healthy infants of women with HCV infection (n = 32). A total of 87% of study women received antiretroviral therapy during pregnancy through the breastfeeding period with use of zidovudine plus single-dose nevirapine treatment stopping at delivery. The rate of resistance mutations present at follow-up was 25% in the zidovudine plus single-dose nevirapine group and 0% in the triple-drug antiretroviral therapy group. Additional analysis of resistance in infants is planned.

WHO guidelines recommend a brief course of antiretroviral treatment (a “tail”) for women after single-dose nevirapine treatment for PMTCT. Two abstracts presented data in favor of this practice. McMahon and colleagues found a trend toward superior outcomes in prevention of emergence of resistance after single-dose nevirapine administration for PMTCT with a 21-day tail compared with a 7-day tail of either tenofovir/emtricitabine, zidovudine/lamivudine, or lopinavir/ritonavir (Abstract 759). Ngo-Giang-Huong and colleagues showed that 1 week of treatment with zidovudine plus lamivudine after exposure to single-dose nevirapine virtually eliminated the emergence of nevirapine resistance mutations at 7-day, 10-day, and 1-month follow-up analysis of 117 women who participated in the Thai PHPT (Perinatal HIV Prevention Trial)-5 (Abstract 760).
Resistance

Resistance in Resource-Limited Settings

As part of global antiretroviral therapy scale-up, the WHO recommends programmatic assessment informed by surveillance of acquired drug resistance (ADR) and transmitted drug resistance (TDR) to help inform best practices and minimize emergence of HIV drug resistance. Bertagnolio, on behalf of the WHO, reported on 2 major surveillance initiatives from RLS (Abstract 52). The ADR report consisted of surveys from 16 resource-limited sites from 2002 to 2010. The survey results represent 2150 patients who initiated antiretroviral therapy (and were either treatment naive or experienced at initiation) at 15 sites in Burundi, India, Malawi, Mozambique, and Nigeria. Nearly three-fourths of patients were taking stavudine/lamivudine/NRTI (74%), 22% were taking zidovudine/lamivudine/NRTI, 5.2% were taking tenofovir/lamivudine/NRTI, and 0.8% used other regimens. A total of 90% of patients had virologic suppression (HIV RNA level <1000 copies/mL) at 12 months. There were 128 patients (10%) in whom genotypic analysis was performed because of a plasma HIV RNA level greater than 1000 copies/mL at 12 months. Analysis of patients with baseline genotypic testing results (n = 1503) revealed the following resistance pattern: 6% any resistance, 5% NNRTI resistance, 2.7% nRTI resistance, 2% double-class resistance, and 0.5% PI resistance; 77% had subtype-C HIV. The most common mutations were Y181/C/I, K103NS, and M184I/V. Of the 128 individuals for whom antiretroviral therapy failed at 12 months, 67% had any drug resistance, 65% had NNRTI resistance, 55% had nRTI resistance, 55% had double-class resistance, and 3% had any PI resistance. The most common mutations conferred resistance to nevirapine, efavirenz, and lamivudine.

The authors noted that a statistically significant proportion of patients also had 3 or more thymidine analogue-associated mutations (TAMs) (4.7%) and the K65R mutation (5%). Such mutations would negatively impact effectiveness of the second-line regimen that contain tenofovir or zidovudine. Of patients who were retained in care and alive, 90% had viral load suppression (plasma HIV RNA level <1000 copies/mL), which dropped to 70% when including LTFU and patients discontinuing treatment in the analysis. A total of 75% of clinics were able to meet a goal of having 70% of patients suppressed at 12 months. These results are similar to resource-rich-setting cohorts. The authors pointed out that, given the patterns of resistance, a second-line regimen including PI/r plus tenofovir or zidovudine should be effective at the population level.

Bertagnolio and colleagues also reported surveys of TDR in recently infected, antiretroviral therapy-naive populations. Age less than 24 years, first pregnancy, first HIV risk-defining event within the past 3 years, and CD4+ cell count greater than 500/µL were used as surrogates for recent infection. Results represent geographic areas as opposed to specific clinics or nations. There were 41 surveys from 20 countries during 2005 to 2007. The majority of surveys were from sites in Africa, Asia, and Mexico. Truncated sequential sampling was used to classify prevalence of TDR as low (less than 5%), moderate (5%–15%), or high (>15%). The results showed that 81% of sites had low levels of TDR and 17% of sites showed moderate levels of TDR, mainly to NNRTIs (12%) and some to nRTIs (7%). No surveys showed moderate levels of PI resistance, but all reported low levels. Bertagnolio pointed out those geographic areas with moderate resistance that warrant additional attention.

Additional abstracts dedicated to understanding resistance across the globe were presented in Session 119 (Abstracts 619–626). Dross and colleagues illustrated the impact of TDR on antiretroviral efficacy, reporting on nevirapine- and lamivudine-resistant HIV-1 detected in antiretroviral therapy–naive Kenyans initiating NNRTI-based antiretroviral therapy (Abstract 620). Of 400 treatment-naive adults who began nevirapine-based antiretroviral therapy, 42 had virologic failure at follow-up. Genotypic testing of baseline blood samples showed mutations associated with nevirapine resistance or with lamivudine resistance in 26% of patients with virologic failure.

Yang and colleagues reported on the global surveillance of TDR in 530 plasma or dried blood spot samples from PEPFAR-supported countries including Botswana, China, Kenya, Malawi, Tanzania, and Vietnam (Abstract 619). All sites showed TDR of less than 5% except for the site in Ho Chi Minh City, which had a moderate level of resistance (5%–15%). The authors urged further understanding of this concerning trend.

Rates of TDR in Kampala, Uganda (Abstract 621), and Mexico City (Abstract 623) were also reported to be moderate at 5% to 15%, whereas investigators from Brazil reported rates of TDR ranging from moderate to high (>15%) in some areas (Abstract 624). Hamers and colleagues compared rates of drug resistance to year of antiretroviral therapy scale-up in sub-Saharan Africa. Earlier year of scale-up was more strongly associated with prevalence of drug resistance (Abstract 622).

Viral Load Monitoring in Resource-Limited Settings

Reynolds and colleagues reported on the effect of routine viral load monitoring on the rate of accumulated...
genotypic evidence of resistance to commonly used antiretroviral drugs in Uganda (Abstract 53). A cross-sectional, observational study in infectious diseases clinics of Kampala, Uganda, compared a cohort of 559 antiretroviral-naive patients who had CD4+ cell count and viral load monitoring every 6 months with 998 clinic patients who had been receiving antiretroviral therapy and had CD4+ cell count monitoring only. Viral load monitoring was performed at the end of 36 months in all patients in the CD4+ cell count-only group, and genotypic analysis was also performed if the plasma HIV RNA level was greater than 2000 copies/mL. In the viral load–monitoring group, viral loads were assessed at months 12, 24, and 36, with genotypic testing of patients with levels exceeding 2000 copies/mL. Mutations were classified according to the IAS–USA panel listing6 and the Stanford University HIV Drug Resistance Database (www.hivdb.stanford.edu).

At 36 months, the viral load–monitoring group showed 57% resistance to NNRTI; 43% had the M184V mutation, 7% had K65R, and 7% had a single TAM. The immunologic-monitoring group showed 90% resistance to NNRTI; 87% had the M184V mutation, 1% had the K65R mutation, 43% had a single TAM, 23% had 2 TAMS, and 10% had 3 or more TAMS. Viral load monitoring was associated with reduced resistance in all categories. The most dramatic reduction in resistance mutations in the viral load–monitoring group was in the TAMs. Only 23% of the participants in the viral load–monitoring group had 4 or more etravirine mutations, compared with 40% in the immunologic-monitoring group.

The additional resistance that accumulated during immunologic monitoring has implications for the effectiveness of second-line regimens. Gupta and colleagues echoed these findings, showing a rapid accumulation of TAMs in the absence of viral load monitoring with nevirapine-based or triple-nRTI regimens. This information has serious implications for the use of zidovudine, abacavir, or tenofovir in second-line antiretroviral regimens (Abstract 618).

**Nonnucleoside Analogue Reverse Transcriptase Inhibitor Resistance**

Session 114 was dedicated to new insights in resistance to NNRTIs. In an effort to explain the association of the E138K rilpivirine-associated mutation with the M184I mutation (rather than M184V), Hu and Kuritzkes created recombinant viruses carrying E138K plus M184I or M184V mutations and compared relative infectivity and fitness profiles (Abstract 594). The E138K/M184I virus had higher relative infectivity than the E138K/M184V recombinant in the presence of a second-generation NNRTI. Drug-susceptibility data showed that the E138K/M184I virus also had a greater fold-increase in the IC50 for etravirine, efavirenz, and lamivudine than the E138K/M184V virus. The authors concluded the E138K/M184I combination confers a meaningful replication advantage and higher levels of resistance to etravirine and lamivudine compared with the E138K/M184V double-mutant. This may explain why the E138K/M184I combination was observed in patients with virologic failure in trials of rilpivirine.

Mackie and colleagues examined the prevalence and clinical importance of baseline polymorphisms in antiretroviral-naive subjects initiating NNRTI-based antiretroviral therapy (Abstract 595). Baseline genotypic testing results were obtained from the UK HIV drug resistance database and linked to clinical cases. There were 2058 subjects included in the analysis, of whom 1704 initiated efavirenz-based antiretroviral regimens and 354 initiated nevirapine-based therapy. Reverse transcriptase polymorphisms of interest included those on codons 90 to 108, 135 to 138, 179 to 190, and 225 to 348. A total of 40% of subjects were identified as having at least 1 polymorphism at baseline. Neither single nor double polymorphisms had an effect on plasma HIV RNA level reduction at week 4 or on achieving a plasma HIV RNA level less than 200 copies/mL at week 24 compared with wild-type virus.

Geretti and colleagues analyzed the virologic outcomes of patients who interrupted and restarted NNRTI-based antiretroviral therapy in the SMART (Strategies for the Management of Antiretroviral Therapy) study (Abstract 596). They compared virologic outcomes with respect to the modality of treatment interruption, Cytochrome P450 2B6 constitutive androstane receptor (CYP2B6/CAR) host genotype, NNRTI clearance rates, and presence of drug resistance mutations as detected by allele-specific PCR and ultra-deep sequencing. Of the 132 subjects who underwent interruption of an NNRTI-based regimen (60.6% with efavirenz, 38.6% with nevirapine, and 0.8% with delavirdine), 63 discontinued nRTIs and the NNRTI simultaneously, and 69 either continued nRTIs alone or switched to nRTIs plus a PI. Median plasma nevirapine levels were 0.96 ng/mL (IQR, 0.5−3.2 ng/mL) after a median of 52 days and 16 ng/mL (IQR, 9−55 ng/mL) for efavirenz after a median of 30 days.

The CYP2B6/CAR genotype was predictive of efavirenz concentrations, with the highest levels observed in the TT/CC profile (P = 0.02). Major nRTI resistance was detected in 20% of patients and major NNRTI resistance was detected in 11% of patients by bulk sequencing and slightly more by allele-specific PCR, 24% and 16%, respectively. Although 81% of patients with suppressed viremia who interrupted and then restarted NNRTI-based antiretroviral treatment regained viral suppression, 19% did not. Predictors of virologic suppression at 12 months to 18 months after restarting antiretroviral treatment included simultaneous interruption of antiretroviral therapy (as opposed to stagger-switch), longer duration of treatment interruption, and older age. The authors issued caution regarding the risk of resistance with treatment interruptions, suggesting the use of stagger-switch methods rather than simultaneous interruption. They proposed additional studies to better understand the possible utility of CYP2B6/CAR genotypic testing as a predictor of delayed NNRTI clearance.

Cozzi-lepri and colleagues reported an analysis of predictors of virologic response to etravirine-containing antiretroviral regimens in the EuroSIDA
Protease Inhibitor Resistance

Novel insight into the emergence of drug resistance mutations in protease was the subject of Session 115 (Abstracts 599–605). Fun and colleagues presented data on how the genetic barrier to resistance is decreased by gag polymorphisms (Abstract 603). The investigators performed in vitro selections with molecular clones of HIV subtypes B, C, and AG in the presence of increasing darunavir concentrations, and they monitored gag and protease genes over time. The investigators reported that in 5 of 5 cultures with HIV subtype AG, a mutation occurred at the NC/p1 cleavage site at gag codon 437. The gag 437 mutation corresponds with a 5- to 7-fold decreased susceptibility to darunavir compared with the parental AG virus.

Larrouy and colleagues reported on the positive impact of the HIV-1 gag CS A431V mutation on virologic response to darunavir/r in treatment-experienced patients (Abstract 604). The A431V gag CS mutation was associated with short-term virologic response. The investigators hypothesized that a specific gag CS mutation might not have the same impact on virologic outcome, according to the PI used, and could have a direct impact on PI susceptibility in an inhibitor-specific manner.

Depatureaux and colleagues reported on protease-region resistance mutations in the highly diverse HIV-1 group O in both treatment-naive and on-treatment individuals infected with HIV-1 group O virus (Abstract 605). Logistic regression analysis revealed a statistically significant association with lopinavir/r treatment and the following mutations: 115I, G48M, L63K, and T74S (P < .005).

CC Chemokine Receptor 5 Antagonist Resistance

Session 113 was dedicated to coreceptor usage and resistance to CCR5 inhibitors. Putcharoen and colleagues described kinetics and mechanism of resistance of vicriviroc-resistant HIV-1 subtype B clinical isolates from subjects in the ACTG 5211 trial (Abstract 589). Pseudoviruses were constructed that expressed cloned or uncloned HIV-1 envelope obtained at baseline and at virologic failure in 3 subjects in whom resistance to the investigational drug vicriviroc emerged. Resistant viruses had slower entry kinetics than wild-type virus, and in the presence of the investigational small-molecule coreceptor antagonist TAK-779, the entry kinetics were restored to wild-type level, suggesting that vicriviroc-resistant viruses use drug-bound CCR5 for entry. Vicriviroc-resistant virus was also shown to be cross-resistant to maraviroc and TAK-779. Additionally, the authors showed how vicriviroc-resistant viruses are inhibited by monoclonal antibodies directed against the CCR5 N-terminal domain and second extracellular loop (ECL2), suggesting that the resistant envelope may have adapted to utilize drug-bound receptor by more efficient utilization of the N-terminal and ECL2 regions of the CCR5.

Similarly, Jubb and colleagues also described how maraviroc-resistant viruses use the ECL2 and the N-terminal domain of CCR5 (Abstract 590). Svircher and colleagues showed an association between dual tropism and signature mutations in the V3 bridging sheet domain of HIV-1 gp120 and how these mutations modulate the interaction at the CCR5 N-terminus (Abstract 591). The study analyzed 498 V3 and 242 gp120 sequences from 740 HIV-1 subtype B–infected patients from the Los Alamos Database. Three V3 determinants—T2M, I26R, and I12V—were statistically significantly associated with phenotypically defined dual tropism. These determinants occurred in negligible amounts in pure R5 and X4 viruses (0%, 0%, and 2%, respectively) but at much higher rates in dual-mixed virus (9.3%, 4.9%, and 14.2%, respectively; P < .001). The mutations I12V and I26R both decreased N-terminus binding affinity for gp120.

Other mutations associated with dual-mixed virus outside the V3 loop include T102S, M105V, and R398Q, all of which are in the gp120 bridging domain. These mutations were present at 15.8%, 16.7%, and 33.3%, respectively, in dual-mixed virus, compared with less than 3% in pure R5 or X4 virus. The authors pointed out that dual-tropic viruses represent HIV species that are structurally different from pure R5 and X4 viruses, as opposed to being just a mixture.

Coakley and colleagues described a comparison between V3-sequencing-based prediction and coreceptor tropism as determined by an enhanced-sensitivity coreceptor tropism assay (Monogram Biosciences) (Abstract 592). Both tests were performed on 4 distinct patient groups: an HIV acute-seroconversion cohort (n = 69), an early-treatment-naive cohort (n = 271), a treatment-naive cohort of participants in ACTG 384 (n = 221), and a late-treatment-experienced group
(n = 587). Compared with the enhanced-sensitivity tropism assay, V3 sequencing showed increasing sensitivity with disease stage: 18%, 34%, 43%, and 62%, respectively, in the 4 patient groups. There was also a strong inverse correlation of average sensitivity compared with CD4+ cell count ($R^2 = −.98; P = .01$). The authors concluded that V3 sequencing for prediction of CXCR4 virus in treatment-naive individuals is inadequate, given its lack of sensitivity in this group.

The role of ultra-deep sequencing in the use of maraviroc was explored by Heera and colleagues (Abstract 593). Ultra-deep sequencing was performed on specimens from treatment-experienced patients who participated in the combined maraviroc-treated groups of the MOTIVATE (Maraviroc Versus Optimized Therapy in Viremic Antiretroviral Treatment–Experienced Patients) trials, of whom 674 patients had been identified as having R5 virus and 215 as having non-R5 virus by the original coreceptor tropism assay (Monogram Biosciences). Both the relative percentage of X4 virus and the absolute count of virus were determined via ultra-deep sequencing. Multivariate analysis of predictors of achieving a plasma HIV RNA level of less than 50 copies/mL of sensitivity in this group.

Of those tested, 58 seroconversions occurred in the placebo group and 33 in the emtricitabine/tenofovir (PrEP)-treated group. The majority of HIV subtypes were B. Minor resistance-associated mutations were detected in 2 samples from the placebo group: 1 with K65R and the other with M184V. There were no minor variant mutations in any of the seroconversions from the treatment group. Most of the seroconversions in the PrEP group did not have positive PrEP-drug levels, and the 3 subjects with detectable drug had extremely low levels and did not show minor drug-resistant variants. There were 3 individuals who were HIV-seronegative at entry but later found to be undergoing acute HIV infection, of whom 2 were from the PrEP arm: 1 found to have an M184V mutation and the other an M184I mutation. In these 2 individuals, the mutant subpopulations became undetectable by population sequencing by 9 weeks and 12 weeks after discontinuing PrEP.

Viral Load Monitoring and Resistance Testing

Metzner discussed the current state-of-the-art and future directions for viral load assays, drug resistance mutations testing, and the goal of expanded access to technology for RLS (Abstract 72). With regard to viral load detection, the increasing sensitivity of commercially available assays to a detection level of 20 copies/mL, or perhaps in the future to 1 copy/mL, raises questions about the importance of low-level viremia at different levels in relation to risk of resistance, need for antiretroviral drug adjustment, and immune activation.

Session 124 provided insight into novel HIV quantification methods by nucleic acid amplification. Yuki and colleagues explored modification of a well-known commercial real-time PCR assay to detect plasma HIV-1 RNA levels less than 1 copy/mL (Abstract 656). Investigators reported that mean plasma viral load correlated inversely ($R = −0.78; P = .028$) with total duration of viral suppression (plasma HIV RNA levels < 40 copies/mL) and suggested that residual viremia may
decay slowly over years of treatment (Abstract 656).

Innovations in genotypic drug resistance testing were also discussed, such as testing of other areas of the HIV genome, or even whole HIV-1 genome sequencing. At this point, there is no evidence that whole-genome sequencing is superior to sequencing of protease and reverse transcriptase; however, whole-genome sequencing could offer increased options for combining of antiretroviral drugs and enhance current methods of epidemiology. Whole-genome sequencing would require effective algorithms to be developed for the prediction of the clinical relevance of various mutations.

The role of minority drug resistance mutation assays compared with bulk sequencing was also emphasized. Metzner described data comparing the presence of minority drug resistance mutations in the Zurich Primary HIV Cohort with that of a chronically infected group from the Swiss Cohort Study. Results showed that minority variants with the K103N mutation were detected at equal rates in both groups (4%) but that M184V variants were present at higher rates in the primary-HIV-infection cohort (8%) than in the chronically HIV-infected cohort (2.5%), suggesting that the M184V virus is less fit and less likely to persist over time.

The impact of NNRTI-associated minority resistance variants on virologic success for treatment-naïve patients beginning initial NNRTI-based regimens was illustrated in a meta-analysis of 10 studies and 985 subjects covered by Li and colleagues (Abstract 614). Patients with baseline NNRTI-associated minority resistance variants had a statistically significantly higher risk of viral failure, regardless of adherence, than patients without such variants. The importance of minority resistance variants appears to vary by drug class. Further study will be needed to understand their impact on clinical care.

The design and application of feasible resistance mutations testing methods for use in RLS is of crucial importance. Several abstracts at the conference illustrated methods for resistance mutation analysis in RLS (Session 125, Abstracts 662–664).

**Pharmacokinetic Considerations**

**Tenofovir/Emtricitabine for Preexposure Prophylaxis**

Anderson and colleagues evaluated drug concentrations in plasma and PBMCs in 16 HIV-uninfected adults given a single tablet of fixed-dose tenofovir/emtricitabine (Abstract 641). They found that the tenofovir diphosphate concentrations in PBMCs were approximately 35% of those achieved in primate models of HIV transmission and that the tenofovir diphosphate concentrations in plasma were similar to those in the primary models. As expected, concentrations of both drugs were much lower than steady-state concentrations in HIV-1-infected patients receiving long-term therapy. The authors note that the low concentrations of tenofovir diphosphate are concerning for episodic administration of tenofovir/emtricitabine as used for PrEP of HIV-1 transmission.

**Raltegravir-Based Antiretroviral Therapy**

Miro and colleagues reported on the antiviral and pharmacokinetic properties of raltegravir-based regimens for HIV-1-infected, solid-organ transplant recipients (Abstract 644). There were 15 subjects whose regimens were switched to raltegravir plus tenofovir/emtricitabine or abacavir/lamivudine. All participants had continued virologic control, and this regimen switch allowed for standard dosing of immunosuppressant medications. The authors found no statistically significant pharmacokinetic interactions between raltegravir and cyclosporine or mycophenolic acid.

**Pharmacokinetic Properties of Newly Available and Investigational Compounds**

The compound TBR-652 is an investigational antagonist of CCR5 and CC chemokine receptor 2 (CCR2) virus that has demonstrated in vivo antiviral activity. Martin and colleagues reported on the pharmacokinetic profiles in several animal models (Abstract 627). There was good bioavailability and a long plasma half-life (approximately 35 hours) in all the species examined.

Telaprevir is a nonstructural protein 3 (NS3)/4A protease inhibitor that was recently approved by the US Food and Drug Administration (FDA) for the treatment of HCV infection. It is both a substrate and an inhibitor of cytochrome P450 3A (CYP3A). The current dose is 750 mg every 8 hours. Garg and colleagues attempted to enhance the pharmacokinetic profile of telaprevir by adding ritonavir (Abstract 629). Two dosing schemes, telaprevir 250 mg/ritonavir 100 mg twice daily and telaprevir 750 mg/ritonavir 100 mg twice daily, were administered to healthy volunteers, and the pharmacokinetic properties were compared with those of the standard dose. Neither of the ritonavir regimens achieved adequate trough levels of telaprevir. Moreover, the addition of ritonavir did not appear to change the pharmacokinetic profile of telaprevir.

Rilpivirine is a NNRTI recently approved by the FDA for the treatment of HIV infection. Cauwels and colleagues evaluated the pharmacokinetic profiles of rilpivirine after switching from efavirenz (Abstract 630). They found that rilpivirine concentrations were reduced after switching from efavirenz compared with a control period of rilpivirine administration before efavirenz dosing. This effect lessened over time but was still somewhat apparent up to 28 days after efavirenz administration. The authors concluded, however, that none of the observed drug concentrations was low enough to be concerning for virologic breakthrough and that this switch should be safe in clinical practice.

**Once-Daily Maraviroc Dosing**

Taylor and colleagues investigated the pharmacokinetic profile of maraviroc dosed once daily with darunavir/r (Abstract 636). They compared the maximal concentration and trough concentration of 20 subjects receiv-
ing maraviroc 300 mg once daily plus once-daily darunavir/r with those of 13 subjects receiving maraviroc 300 mg twice daily plus fixed-dose tenofovir/emtricitabine. They found that maximal concentrations (at 2 hours post–maraviroc dosing in both groups) and trough concentrations (at 24 hours and 12 hours post–maraviroc dosing, respectively) were similar in the 2 groups.

**Neuroleptic Drugs**

Okulicz and colleagues evaluated the virologic outcomes of 21 patients receiving antiepileptic drugs that induce the CYP3A4 enzymes: phenytoin, carbamazepine, and phenobarbital (Abstract 646). Their comparison included 85 patients receiving other neuroleptic drugs as a control group. The authors found the risk of virologic failure was much higher for patients receiving the enzyme-inducing antiepileptic drugs; 10 of 17 patients (59%) had virologic failure compared with 20 of 75 patients (27%) taking other neuroleptic drugs. They noted that this difference has important implications for RLS, where, in general, only enzyme-inducing antiepileptic drugs are available for treatment of seizure disorders.

**Efavirenz in the Second and Third Trimesters of Pregnancy**

Efavirenz is teratogenic when taken early in pregnancy but is recommended as initial therapy by the WHO for HIV-1-infected women after the first trimester. Cressey and colleagues compared the pharmacokinetics of efavirenz in HIV-1-infected women during the third trimester of pregnancy with pharmacokinetics at 6 weeks to 12 weeks postpartum (Abstract 754). They found slightly higher efavirenz clearance and lower trough concentrations during the third trimester than at the postpartum points. The authors felt that the magnitude of this change was enough to warrant a change in efavirenz dosing during pregnancy. It is important to note the majority of the women in this study were Thai and these results may not generalize to other populations.

**Antiretroviral Therapy and Breast-feeding**

Liotta and colleagues presented data on drug concentrations in infants being breast-fed by HIV-1-infected women receiving antiretroviral therapy (Abstract 757). They had 38 paired maternal and infant samples from patients at 1 month to 6 months postpartum. Nevirapine was present at therapeutic concentrations in all infant samples tested. Lamivudine was detectable in most infant samples. Lopinavir, stavudine, and zidovudine were detected much less commonly. The authors concluded that direct administration of nevirapine to infants during breast-feeding was likely not necessary.

**Rifabutin and Lopinavir/Ritonavir**

Naiker and colleagues evaluated 2 dosing schemes for rifabutin when administered with lopinavir/r (Abstract 650). They enrolled 16 HIV-1-infected patients being treated for tuberculosis. All patients received rifabutin 300 mg daily for 4 weeks along with other standard initial tuberculosis drugs, after which a lopinavir/r-based regimen was added. Patients were randomly assigned to a reduced dose of rifabutin (either 150 mg daily or 150 mg 3 times per week). Participants receiving 150 mg 3 times weekly had rifabutin drug levels that were appreciably lower than levels before the initiation of lopinavir/r. The group receiving rifabutin 150 mg daily had levels that were similar to or slightly higher than those observed before lopinavir/r dosing, and they had peak rifabutin concentrations that were within the therapeutic range. There were no safety concerns in any of the groups. The authors suggested that rifabutin should be administered at 150 mg daily when dosed with lopinavir/r, not at the currently accepted dosage of 150 mg 3 times weekly.

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A list of all cited abstracts appears on pages 99–106.

**References**


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<table>
<thead>
<tr>
<th>Location</th>
<th>Date</th>
<th>Venue</th>
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<tbody>
<tr>
<td>Atlanta, Georgia</td>
<td>Monday, March 14, 2011</td>
<td>Renaissance Waverly Hotel</td>
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<tr>
<td>Washington, DC</td>
<td>Wednesday, May 4, 2011</td>
<td>Capital Hilton</td>
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<td>Los Angeles, CA</td>
<td>Monday, March 28, 2011</td>
<td>California Endowment Center</td>
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<td>San Francisco, CA</td>
<td>Monday, May 16, 2011</td>
<td>Grand Hyatt San Francisco</td>
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<tr>
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<td>Tuesday, April 5, 2011</td>
<td>New York Marriott Marquis</td>
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<tr>
<td>Chicago, IL</td>
<td>Monday, June 13, 2011</td>
<td>Marriott Chicago Downtown</td>
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<tr>
<td>New York, NY - Fall</td>
<td>Friday, October 14, 2011</td>
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Conference Abstracts Cited in This Issue

The full text of all abstracts is available online at www.retroconference.org
HIV env and VSV-G Overcome an Entry Restriction in Naïve CD4+ T Cells. Matthew Pace, L Agosto, and U O’Doherty.

181. Resistance of HIV-1 Virologic Synapse-mediated Infection to Neutralization is Regulated by the gpr41 Cytosolic Tail. Natasha Durham, P Chen, and B Chen.


191. Residual HIV-1 Replication Is Observed in the Absence of LENS/Pr75 but Remains Sensitive to Inhibition by LEDGIN. Rik Schrijvers, R Gipsers, J De Rijck, B Desimie, F Christ, K Ronen, F Bushman, and Z Debayer.


304. No Evidence of CD4 Cell Recovery in Patients at Higher Risk of Death following IL-2 Administration. Clifford Lane and INSIGHT, ESPRIT Network.


375. Baseline D-dimer Levels Identify a Subset of Patients at Higher Risk of Death following IL-2 Administration. Clifford Lane and INSIGHT, ESPRIT Network.


528. A Comparison of Neuropsychological and Neurological Effects of 3 Antiretroviral Regimens in Diverse RLS. ACTG Study ASI99, the International Neuropsychological Study. Kevin Robertson, J Jiang, J Nunnaka, W Kappurapati, S Evans, T Campbell, R Price, S Tripathi, N Narumarsamy, A LaRoza, and ACTG 5199.

517. Baseline D-dimer Levels Identify a Subset of Patients at Higher Risk of Death following IL-2 Administration. Clifford Lane and INSIGHT, ESPRIT Network.

518. Baseline D-dimer Levels Identify a Subset of Patients at Higher Risk of Death following IL-2 Administration. Clifford Lane and INSIGHT, ESPRIT Network.


539. ART Initiation during Acute/Early HIV Infection Compared to Later ART Initiation is Associated with Improved Immunologic and Virologic Parameters during Suppressive ART. Vivek Jain, W Hartogensis, P Hitchon, P Hunter, J Morris, S Sinclair, TH Lee, M Busch, F Hecht, and S Deeks.


541. Progressive Atrophy of the Corpus Callosum in HIV-infected Patients on Stable ART. David Tate, J Harelazik, E Daar, M Taylor, G Schifitto, E Singer, T Campbell, C Yannoutsos, C Gutmann, and B Nava.


545. 2D-LCOSY of the Brain in HIV Youths by Prof-Quantitation. R Nagarajan, A Thomas, M, Sarama, J Hayes, H Nielsen-Sanders, P Lewis, J Church, J Deville, L Chang, and Margaret Keller.

546. Whole Genome Association Study of Viral Failure with EFV- and ABC-containing Regimens in ACTG Studies. Paul McLaren, H Ribaudo, E Daar, G Comrie, R Haubrich, E Acosta, G Morse, P de Bakker, D Haas, and ACTG.


NNRTI Resistance Mutants and Is Additive to Syner-
gistic Combination with Other ART. Cindy Vavro,
R Ferris, M Edelstein, D Standring, and M ScIair.
523. Identification of Bi-C, a Novel HIV-1 Non-
catalytic Internal Inhibitor. Craig Fenwick, R
Bethell, P Bonneau, J Duan, A-M Faucher, S Mason,
M-A Poupart, B Simonou, Y Tsiantrios, and C Voa-
la.
524. Long-term Efficacy of DRV/r Monotherapy in
Patients with HIV-1 Viral Suppression in the MONO-
ANRS 136 Study. Results at 96 weeks. Marc-Antoine
Valantin, C Duvivier, S Lambert-Niclot, P Flandre, A
Cabin, J-M Molina, L Cuzin, L Slama, A-G Marcellin,
and T Li.
525. ZDV/3TC vs d4T/3TC Outcomes among HIV-
1-infected Adults Receiving First-line Combination
ART in Botswana: Results from a Clinical Trial. Wil-
liam Wester, P Blencowe, H Bussmann, S Moy, M
Farahani, B Shepherd, J Makhema, M Essex, V de-
Gruttola, and R Marlink.
526. Predictors of Suboptimal CD4 Response
among Women Achieving Viral Suppression in a Ran-
donized ART Trial. Africa. A Amedealth, Y Zheng,
K Wools-Kaloustian, D Shaffer, F Sawe, R Salata,
E Stringer, J Currier, M Hughes, and Shahnuk
Lockman.
527. Second-line Boosted Protease-Containing Ther-
apy: Assessing the Impact of Maintaining 3TC vs
Switching to d4T in Addition to 2 Drugs from New
Classes in a Randomized Comparison. Ivan Mambele,
S Walker, A Reid, F Ssali, P Munderi, H Grosskurth,
D Gibb, J Hakim, P Mugyenyi, C Gilks, and DART Trial
Team.
528. Trends in HIV Viral Load among Adults in
Keri Althoff, P Rebeiro, J Gill, M Horberg, J Eron,
S Napravnik, K Anastos, R Bosch, R Moore, S Gange,
and North American AIDS Cohort Collaboration on
Res and Design.
529. Long-term Follow-up of Patients Receiving
RALT, ETV, and DRV/r in the ANRS 159 TRO1 Trial.
Catherine Fagard, F Descamps, C Colin, A-M Tabu-
ret, J-M Molina, C Katlama, F Raffi, F Jeannel, G Chene,
Y Yazdanpanah, and ANRS 139 TRO1 Trial Group.
530. Results from a Single Arm Study of DRV/r +
RALT in Treatment-naive HIV-infected Patients
(ARTG A5262). Babafemi Taiwo, S Zheng, S Gallien,
W Koffi, P Kim, J Eron, and ACTG A5262 Team.
531. Comparison of Durability and Patient Survival
between NVP-based and EFV-based First-line ART
Regimens in China’s National Free ART Program.
Yao Zhang, Y Ma, R Zhang, Z Dou, Y Zhao, E Geng,
H Zhu, and T Li.
532. Use of Computational Models to Predict HIV
Treatment Outcomes in Rwanda. Luminita Ene, D
Wagner, Y Acosta, P Kim, J Eron, and ACTG
A5262 Team. Babafemi Taiwo, S Zheng, S Gallien,
W Koffi, P Kim, J Eron, and ACTG A5262 Team.
533. Examining the Interaction between Current CD4
Cell Count, Current Viral Load Suppression, and
Time on ART and Mortality. Alana Brennan, M
Masquel, P MacPhail, I Sanne, and M Fox.
534. Hb Levels at 6 Months and Their Association
with Subsequent Mortality among Adults on ART in
Lusaka, Zambia. Mohammed Lumba, M Gugani,
A Mwangi, L Mulenga, C Bolton-Moore, P Mulenga,
J Stringer, and B Chi.
535. Differences in Mortality Rates among Treated
Patients According to Geographical Origin and Eth-
nicity/Race: The ART Cohort Collaboration. I Jarrn,
Julia Del Amo, and ART-CC.
536. Gender Differences in Long-term Immune
Response to ART and Mortality: A Cohort Analysis
in 4 Sub-Saharan HIV Programs. David Marwan,
M Pujades-Rodriguez, F Subil, L Pinoges, M Mcguire,
E Rochard, and J-F Eurd.
537. Delay Art Initiation and Risk of Death
Christopher Hoffmann, J Lewis, S Charalamouis,
G Churchyard, N Martinson, and R Chaisson.
538. Long-term Survival of HIV-infected Adults
Starting HAART in Thailand. Risk Factors for Early
and Late Mortality. F Gregonne, J Collins, G Jou-
dain, S Le Coeur, T Cressy, N Ngo-Giang-Huong,
S Banchongti, A Chutanunta, M Techapoomrong,
Marc Lallemand, and Prgm for HIV Prevention and
Treatment. P Murenzi, O Nwanevu, V Kinyunhu,
M Xu, and R Murenzi.
539. Service Delivery Site Factors Are Associated
with ART Cohort Outcomes—Analysis of National
Assessment Data to Inform Public Health Action. N
Do Thi, T Nguyen Thi Minh, H Do Mai, Masaya Kato,
T Cao Thi Thany, V Nguyen Thi Thuy, K Nguyen
Van, D Bui Duc, L Nguyen Thanh, and M Fujita.
540. Modular HIV Patient Education: Impact of
Learning Outcomes on ART Outcomes. Development
of Diphtheria with Protective Antigen Receptors
and Tumour Necrosis Factor. C Duvivier, A Peeters,
I Mcleans, and HIV A5262 Study Team.
541. Effect of Previous NVP Failure on Subsequent
Suboptimal Failing Association. Mark Alkhatib,
and C Muzoora, P Hunt, J May, J Sterne, and ART-CC.
542. First ART Regimen: The ART Cohort Collaboration.
543. Localized Spatial Distribution of Early Vi-
rable Response: Population Structure and HIV
Amongst Urban and Rural Populations. M Etienne-
Mesubi, Anthony Amoroso, M Kneen, C Duvivier,
C Duvivier, S Lambert-Niclot, P Flandre, A
Masquel, K Wools-Kaloustian, D Shaffer, R Salata,
A Ayde, and E Stringer.
544. Comparison of Durability and Patient Survival
between NVP-based and EFV-based First-line ART
Regimens in a Large European Cohort.
545. Income Decline Is Associated with Viologic
Rebound among HIV+ ART-treated Individuals in
Rural Uganda. Marcella Alsan, F Bajurnirwe, S
Tolbert, P Moore, J Makhema, M Essex, and North
American AIDS Cohort Collaboration on Res and
Design.
546. Predicting MVC Responses According to Ab-
solute Number vs Proportion of CXCR-4 Using
Virological Endpoints among Patients treated with
Second-line ART. T Binsz, S Wajant, J Aouani,
J Trabado, and C Muzoora.
547. Use of Computational Models to Predict HIV
Treatment Outcomes in Zambia and Switzer-
land. Franziska Schon-Affolter, O Reiser, A Mi-
wan-go, B Chi, B Ledergerber, L Mulenga, A Westfall,
N Chintu, M Egger, and J Stringer.
548. Clinical and Epidemiological Characteristics of
HIV-1 Disease Stage Significantly Correlates with
Sensitivity to V3 Sequence-based Predictions of
CXC4R4 Use. Eoin Coakley, E Stawski, J Toma,
M Haddad, L Napolitano, J Whitcomb, R Ledde,
G Snowman, V Mule, and W Karma.
549. Predicting NRTI Resistance: Do Polymor-
phisms Matter? Nicola Mackle, I Garvey, AM Geretti,
L Harrison, P Tilston, C Sabir, D Dunn, and UK HIV
Drug Resistance Database and UK Collaborative
HIV Cohort Study.
550. NNRTI Clearance Rates, Drug-resistance Pro-
files, and Virologic Outcomes of Patients Stopping
and Restarting NNRTI-based cART in SMART. Anna
Maria Geretti, Z Fox, J Johnson, A Owen, L Stuyver,
A Phillips, and INSIGHT Study Group.
551. Predictors of Viral Response to ETR-
based cART Regimens in a Large European Cohort
of HIV-infected Patients: Alessandro Cozzi-Lepri,
P Paredes, A Phillips, J Kjaer, A Lazzarin, J van Lanzen,
A Karlsson, M Johnson, J Lounden, and EuroSIDA
Study Group.
552. Non-active Site Mutations Contribute to Drug
Resistance in HIV-1 Protease by Potentially Alter-
ing the Dynamics of Substrate Processing. Seema
Mittal and C Schiffer.
553. Key Mutations Maintain Protein Stability dur-
ing the Evolution of Drug Resistance in HIV-1 Prote-
ase. Max Chiang and Troppmair.
554. TPV-resistant HIV-Lacks both Protease Enzym-
ic Inhibition and Dimersization Inhibition Activ-
ity. Manabu Aoki, K Ide, M Danish, Y Koh, H Aoki-
ogita, and H Mituya.
555. Co-evolution of p1-p6 Results in Altered Inter-
actions with FVRI-resistant D50N/R53K HIV-1 Prote-
ase: Madhavi Kollu and C Schiffer.
556. Genetic Barrier of DRV Is Decreased by Gag
557. Positive Impact of HIV-1 gag CS A431 Muta-
tion on Virologic Response to DRV Boosted with
Ritonavir. A Larroyo, S Lambert-Niclot, C Charpen-
tier, M Wirden, C Katlama, P Yeni, F Brun-Vezinet,
V Calvez, A-G Marcellin, and Diane Descamps.
558. Protease Associated Resistance mutations.
in HIV-1 Group O Agnès Departuareaux, M Leoz, C Charpentier, A Vessières, D Roussel, J Jadrier, J-C Planier, and RESO.


607. Identification of Alternative Amino Acid Substitutions at HIV-1 Integrase Codon 143 that Confer Reduced Susceptibility to RAL. Wei Huang, S Fransen, A Frantzell, and C Petropoulos.


626. MCV 300 mg Once Daily + DRV/RTV 800/100 mg Twice Daily Provides MCV Trough Concentrations Comparable to Trough Concentrations in HIV-1 Patients Taking MCV 300 mg Twice Daily + TVD: Implications for Phase 3 Studies. Stephen Taylor, N Dufly, J Watison, D White, G Gillieron, S Barrett, C Robertson, K Gandhi, and E Smit.


637. MVC 300 mg Once Daily + DRV/RTV 800/100 mg Twice Daily Provides MCV Trough Concentrations Comparable to Trough Concentrations in HIV-1 Patients Taking MVC 300 mg Twice Daily + TFD: Implications for Phase 3 Studies. Stephen Taylor, N Dufly, J Watison, D White, G Gillieron, S Barrett, C Robertson, K Gandhi, and E Smit.

638. Warning Indicators in 21 Countries. Michael Jordan, R Kasirye, I Mambule, B Goodall, P Kaleebu, D Pillay, C Gihks, D Pillay, B Gihks, and APIN PEPFAR Team.

639. A Single CD4 Test with Threshold > 250 Cells/mm³ Can Markedly Reduce Switching to Second-line ART in African Patients Managed without CD4 or Viral Monitoring. Charles Gilks, S Walker, P Munderi, C Kirby, A Reul, E Katabira, H Grosskurth, P Mugyenyi, D Gibbs, J Hakim, and DART Trial Team.

640. High Rates of Virologic Suppression among Patients Not Receiving Routine Virologic Monitoring after 5 Years of First-line ART. Cisiy Kityo, D Dunn, R Kasiyente, I Mambule, B Goodall, P Kaleebu, D Pillay, C Gihks, D Pillay, B Gihks, and APIN PEPFAR Team.


645. Viremopaigne [They have become lost]: Outcomes of HIV-infected and HIV-exposed Children Lost to Follow-up from a Large HIV Treatment Program in Western Kenya. Patricia J Songok, R Veenman, K Woololls, Kuszstian, S Ayay, N Yandikl, C Yiannousos, and iDE East Africa Consorium.


649. Clinical Outcomes of HIV-1+ Adolescents and Young Adults in Adult-oriented Care. Patrick Ryscavage.
age, S Sutton, E Anderson, B Armbruster, and B Taiwo.


707. 2-Year Bone Mass Accrual in HIV+ Children and Adolescents after Bi-monthly Supplementation with Oral Cholecalciferol and Calcium. Stephen Ar-Muñoz, L Prieto, B Soto, B Fraile, T del Rosal, M de Cohort for the Study of HIV MTCT.


763. Seroreivalence of HPV Vaccine Types 6, 11, 16 and 18 in HIV+ Women from South Africa, Brazil, and Botswana. Cynthia Finharher, D Evans, R Khaldi Friedman, S Williams, K Mah alliance, C Wester, B Grinsztejn, and S Lockman.


790. Risk of Cause-specific Deaths over Calendar Time and According to Cumulative Exposure to cART, CD4 Count, and Exposure to BAZ. R Hoffmeyer, D Fries, P Reiss, B Ledergberger, J Gaell, A Armanino Monforte, J Lundgren, O Kirk, for EuroSIDA Study Group.


804. Association of Müllerian Inhibiting Substance, a Marker of Ovarian Reserve, with Surrogates of Ath erosclerosis in HIV+ Women. Christopher LaCross, C Wanke, C Cu-Uvin, S Skinner, and A Mangili.


806. Associations between Visceral and Subcutaneous Fat Depots with Total and Calculated Coronary Plaque. The MACS. Frank Palella, X Li, L Jacobson, D Monte, J Sleasman, G Aldrovandi, and PHPT-5 Study Team.


815. ABC Induces Leukocyte Adhesion in Arteri oles. C de Pablo, S Orden, N Apostolova, J Espu las, and Angeles Alvarez.


959. Kinetically Guided pegIFN and RBV Therapy for HIV+ Adults Co-infected with Acute HCV. B Hare, Kristen M Davis, L Randolph, E Yarborough, C Charlesbois, G Cloherty, M Glesby, A Talal, D Hadrir, and M Peters.

966. Liver-related Mortality Risk is Greater from Chronic HBV than from Chronic HCV. MACS. Olawuse Sanai-Fawole, E Seaberg, C Rinaldo, S Badri, M Witt, and C Thio.


1015. Not All Are Lost: Early Death, Care Interruption, and Loss to Follow-up in a Large South African Community Treatment Program. Aima Ahonkhai, F Vidal, J Dombrowski, and Tanzania Natl PHI and SPOT Cohorts.


Posttest Questions

Check the box next to the single best answer to each question below from information presented in this issue. To earn CME credit, you must receive a passing score of 80% or more correct.

1. MicroRNAs regulate gene expression by:
   - A. Introducing double-stranded breaks into the DNA
   - B. Promoting proteasomal degradation of the protein product
   - C. Impairing messenger RNA translation and stability
   - D. Preventing splicing of the RNA transcript

2. Tetherin/BST2 inhibits HIV-1 replication by:
   - A. Preventing virion detachment from the infected cell
   - B. Inhibiting reverse transcription of viral RNA
   - C. Inhibiting processing of viral Gag polyproteins
   - D. Preventing interaction of the viral envelope with coreceptor molecules

3. Aberrant immune activation in patients with HIV-1 infection reflects:
   - A. Stimulation of cell activation following binding of the virus to the cell surface
   - B. Damage to mucosal integrity and translocation of microbial products such as lipopolysaccharide
   - C. Adverse effects of antiretroviral drugs on the immune system
   - D. Destruction of T cells by virus replication

4. HIV-specific neutralizing antibodies:
   - A. Are found in the acute phase of infection
   - B. Take more than 2 years to develop and require extensive hypermutation
   - C. Do not protect monkeys from simian human immunodeficiency virus infection
   - D. Can easily be induced by vaccination

5. Cytolytic CD4+ T cells against HIV:
   - A. Are found during the acute phase and may be involved in control of HIV replication
   - B. Likely do not play a role in controlling HIV replication
   - C. Are mostly directed against Env
   - D. Select for viral variation in the acute phase

6. According to data from 1990–2006, one risk group in the United States had increasing HIV infection rates; rates for other groups were level or decreasing. Which risk group had increased rates?
   - A. White MSM
   - B. Injection drug users
   - C. Men who have sex with men (MSM)
   - D. Heterosexuals with HIV-seropositive partners

7. Rates of HIV infection in black MSM are higher than in other subgroups of MSM. According to recent data, an explanation for the difference is that:
   - A. Higher levels of sexual risk-taking behavior are present in black MSM than white MSM
   - B. White MSM have lower rates of drug use than black MSM
   - C. The reasons for the differences are unclear
   - D. White MSM have higher HIV testing rates than black MSM

8. In extended follow-up from the iPrEx (Chemoprophylaxis for HIV Prevention in Men) study of oral preexposure prophylaxis (PrEP) with emtricitabine/tenofovir, overall efficacy (ie, reduction in new HIV infections) was:
   - A. 92%
   - B. 72%
   - C. 42%
   - D. No efficacy was observed with extended follow-up

9. In the iPrEx PrEP study, participants receiving tenofovir/emtricitabine were statistically significantly more likely than placebo recipients to experience:
   - A. Nausea
   - B. Bone fractures
   - C. Renal failure
   - D. Tenofovir-resistant HIV infection

10. HIV-associated neurocognitive disorder (HAND) is defined based primarily on:
    - A. Patient symptoms and signs from neurologic history and examination
    - B. Neuropsychological testing performance
    - C. Laboratory markers derived from blood and cerebrospinal fluid (CSF) testing
    - D. Brain-imaging results

11. Which of the following biomarkers has been found in association with early HIV infection?
    - A. Relatively low levels of plasma HIV-1 RNA
    - B. An increase in CSF chemokine ligand 2/monocyte chemoattractant protein 1 level
    - C. A decrease in basal ganglia choline:creatine ratios
    - D. Consistent absence of CSF HIV-1 RNA until the stage of chronic infection

12. All of the following biomarkers have been associated with HAND except:
    - A. CSF level of hyperphosphorylated Tau protein (pTau)
    - B. CSF level of neurofilament protein
    - C. Neurofibrillary tangles in the brain
    - D. Increased carotid intima media thickness

13. Compared with HIV-uninfected control subjects, individuals with untreated HIV infection may have brain-imaging results characterized by:
    - A. Elevations in levels or ratios of the neuronal integrity cerebral metabolite marker N-acetyl acetate (NAA)
    - B. Enlarged caudate volume even in the early stages of infection
    - C. Decreases in white matter integrity as measured by diffusion tensor imaging
    - D. No association between CSF inflammatory markers and magnetic resonance spectroscopy markers of inflammation

14. The new oral hepatitis C virus (HCV) protease inhibitors, telaprevir and boceprevir, may have drug-drug interactions with antiretroviral medications based on their roles as:
    - A. Cytochrome P450 (CYP450) inducers
    - B. CYP450 inhibitors and CYP450 substrates
    - C. P-glycoprotein inhibitors
    - D. Inhibitors of gastric acid production

Continued on next page
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15. Increased visceral fat was associated with all of the following except:
   - A. Subclinical atherosclerotic plaque
   - B. Increased mortality
   - C. Initiation of antiretroviral therapy with efavirenz and atazanavir/ritonavir
   - D. Vitamin D deficiency

16. Treatment of HCV infection during the first year of infection (acute HCV infection) is associated with what rate of sustained virologic response (cure)?
   - A. 15%
   - B. 40%
   - C. 65%
   - D. 90%

17. Beginning antiretroviral therapy within 2 weeks to 4 weeks of tuberculosis (TB) treatment initiation was associated with decreased mortality and AIDS progression for HIV/TB-coinfected patients with CD4+ cells counts below:
   - A. 50/µL
   - B. 200/µL
   - C. 350/µL
   - D. 500/µL

18. Compared with twice-daily dosing, once-daily raltegravir dosing was associated with:
   - A. Increased resistance to raltegravir
   - B. Fewer adverse events
   - C. Higher proportions of participants with plasma HIV-1 RNA levels below 50 copies/mL
   - D. Decreased adherence

19. Data on laboratory monitoring in resource-limited settings from the DART (Development of Antiretroviral Therapy in Africa) trial showed:
   - A. A mortality benefit for immunologic (CD4+ cell count) monitoring compared with clinical monitoring
   - B. A mortality benefit for virologic monitoring compared with immunologic monitoring in resource-limited settings
   - C. No difference among the 3 monitoring strategies tested
   - D. A mortality benefit for virologic monitoring compared with immunologic monitoring for participants with pre–antiretroviral treatment CD4+ cell counts above 200/µL

20. Data from the HIV Prevention Trials Network 046 study of mother-to-child transmission of HIV showed that:
   - A. The rate of HIV transmission from HIV-infected mothers to their breast-feeding infants was not associated with maternal antiretroviral therapy status
   - B. Breast-feeding infants of HIV-infected mothers who received an extended course (through age 6 months) of daily nevirapine had more serious adverse events than infants who stopped receiving daily nevirapine at 6 weeks postpartum
   - C. The rate of HIV infection was statistically significantly lower at 6 months in infants receiving extended daily nevirapine than in infants receiving 6 weeks of nevirapine postpartum
   - D. Mortality was higher in the infants receiving nevirapine for 6 weeks postpartum than in infants receiving nevirapine for 6 months postpartum

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108
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The IAS–USA publishes Topics in Antiviral Medicine as a resource for physicians and other health care practitioners who are actively involved in the care of patients with HIV or other viral infections. The journal is indexed in Index Medicus/MEDLINE and is distributed to approximately 12,000 national and international subscribers.

The following guidelines describe the types of articles and contributions published in the journal, outline its policies, and provide instructions for authors. For further information, contact Topics in Antiviral Medicine at topics2011 “at” iasusa.org.

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

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**Editorials.** Topics in Antiviral Medicine and its editors invite submission of editorials. Editorials should be approximately 500 to 1500 words (excluding references) and should include numbered references.

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