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Highlights of the 16th Conference on Retroviruses and Opportunistic Infections

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About This Issue

This issue features highlights of the 16th annual *Conference on Retroviruses and Opportunistic Infections,* held in Montreal, Canada, from February 8 to 11, 2009. Mario Stevenson, PhD, reviews recent advances in basic HIV science and pathogenesis, including mechanisms of viral attack and cellular defense, cellular restrictions, and viral replication and pathogenicity. David I. Watkins, PhD, discusses issues in HIV vaccine development, including HIV variants that initiate infection, lessons learned from negative vaccine trials, and a novel use of an adeno-associated virus as a gene therapy agent in monkey studies. Susan Buchbinder, MD, reviews testing and prevention strategies, including new approaches to preexposure prophylaxis, the epidemiology of HIV infection in specific global populations, and strategies to improve the rate of HIV testing. Neurologic complications of HIV disease and their management are reviewed by Scott Letendre, MD, and colleagues, including the prevalence of distal sensory polyneuropathy and neurocognitive disorders, resistance testing of cerebrospinal fluid, and management of neurologic opportunistic infections. Judith S. Currier, MD, and Diane Havlir, MD, review updates on the complications of HIV disease and therapy such as coinfections, serious non–AIDS-related events, and long-term complications of antiretroviral therapy. The final conference review article by Timothy J. Wilkin, MD, and colleagues addresses new information on investigational drugs, antiretroviral drug resistance, the use of drugs to prevent mother-to-child transmission, the considerable information on therapy from resource-limited settings, and results of ongoing trials of interleukin-2 treatment.

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Reviews

Announcements

Basic Science Summary

Mario Stevenson, PhD

The 16th Conference on Retroviruses and Opportunistic Infections featured a strong and balanced program that showcased exciting research into cellular restrictions that defend the cell against viral infection as well as cellular cofactors that regulate central steps in viral replication. Immunopathogenesis presentations continued to reveal some surprises such as evidence for pathogenicity in natural simian immunodeficiency virus infection. The identification of novel cellular restrictions and cellular cofactors of viral replication indicate the possibility of numerous opportunities for the development of novel therapeutic agents for the treatment of HIV and AIDS.

Viral Attack and Cellular Defense, Update on Cellular Restrictions

In addition to *gag, pol,* and *env* genes that are common to all retroviruses, primate lentiviruses contain additional small open reading frames. Four of these small open reading frames, namely *vif, vpu, nef,* and *vpr/vpx,* are referred to as accessory genes. For many years, the function of these accessory genes in viral replication has remained elusive, but it is now becoming apparent that they may share a common purpose, that is, to protect the virus from the antiviral effects of cellular restrictions.

Pioneering studies in the laboratories of Malim and Kabat were the first to reveal that the Vif protein of primate lentiviruses counteracted a dominant cellular restriction. This was eloquently demonstrated when researchers generated heterokaryons between cells in which Vif was dispensable for infectious virus production and cells in which Vif was necessary for production of infectious virus. The fact that the resultant heterokaryons produced noninfectious virus indicated that cells in which Vif was required for viral replication harbored a dominant antiviral restriction and that Vif neutralized this restriction.[1,2] Research by Malim and colleagues subsequently revealed the identity of the dominant restriction, a cellular cytidine deaminase known as APOBEC 3G.[3]

In the past year, it has been revealed that the accessory protein Vpu, which is expressed by HIV-1 and certain simian immunodeficiency virus (SIV) lineages such as chimpanzee SIV (SIV_{cpz}), counteracts a cellular restriction that has been independently identified by research groups led by Bieniasz and Guatelli as tetherin (also known as BST-2 or CD317).[1-5] Presentations at the conference this year described evidence that the Vpx protein of HIV-2 and sooty mangabey SIV (SIV_{sm}) and the Nef protein also play roles in neutralizing cellular restrictions of retrovirus infection. Previous studies suggested that Vpx and Vpr may play specific roles in viral replication of myeloid-lineage cells. Heterokaryons formed between macrophages, in which Vpx is necessary for viral infection, and COS cells, in which Vpx is dispensable, were resistant to infection by Vpx-deleted viruses.[6] This evidence suggests that myeloid-lineage cells harbor a restriction that is neutralized by the Vpx protein. Two presentations (Abstracts 25, 238) suggested that this restriction is also active against simple retroviruses including murine leukemia virus (MLV) and may restrict infection of quiescent monocytes by HIV-1.

A central characteristic that distinguishes lentiviruses from simple retroviruses is the ability to infect terminally differentiated, nondividing cells. Whereas retroviruses transduce cells during mitosis, lentiviruses appear to have the capacity to transduce cells at all stages of the cell cycle (with the exception of quiescent cells, see below). For this reason, lentivirus vectors have been exploited for the transduction of nondividing cells including neurons, macrophages, muscle cells, and dendritic cells.

What governs the ability of lentiviruses to transduce nondividing cells is a matter of some debate. A popular model is that the relative abilities of retroviruses and lentiviruses to transduce nondividing cells is dictated by the ability of these viruses to circumvent the nuclear envelope. Upon infection of a cell, viral cDNA is reverse transcribed within the context of a large nucleoprotein reverse transcription complex. In a nondividing cell, these complexes must traverse the nuclear envelope to integrate within chromatin. Therefore, it has been proposed that reverse transcription complexes of lentiviruses harbor nucleophilic determinants that allow the lentiviral reverse transcription complex to translocate across the intact nuclear envelope.

In retroviruses, however, it is generally believed that the reverse transcriptase complexes lack the nucleophilic determinants that permit translocation across the nuclear envelope and consequently, access the nuclear compartment only after the nuclear envelope dissipates during mitosis. Abstract 25 provided the alternative explanation that the relative abilities of retroviruses and lentiviruses to transduce nondividing macrophages are dictated by the ability of these viruses to neutralize a restriction operative in these cells. When HeLa cells permissive to MLV infection were fused with macrophages that are restricted for MLV infection, the resultant heterokaryons were resistant to MLV infection, indicating that nondividing macrophages harbor a restriction that antagonizes MLV. Macrophages harbor a dominant restriction that antagonizes lentiviral

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reverse transcription, and this restriction is counteracted by Vpx of HIV-2 and SIV_{sm}. Kaushik and colleagues suggested that this same restriction was operative against MLV, given that the block to macrophage infection by MLV was at the level of reverse transcription. Furthermore, infection of macrophages with an SIV variant that expressed Vpx rendered macrophages permissive to MLV infection, and an MLV variant that was engineered to package Vpx protein efficiently transduced nondividing macrophage.

Collectively, these results suggest the presence of a dominant restriction that is active against retroviruses and lentiviruses and that this restriction is the obstacle to transduction of nondividing, terminally differentiated cells by retroviruses. Therefore, to establish myeloid cell reservoirs, primate lentiviruses have evolved Vpx (and perhaps Vpr) proteins to neutralize a dominant restriction that otherwise prevents infection of these cells.

In Abstract 238, the same research group demonstrated that the macrophage restriction neutralized by Vpx might also be an obstacle to infection of quiescent monocytes by primate lentiviruses. Although macrophages and dendritic cells are permissive to lentivirus transduction, a large body of experimental evidence demonstrates that quiescent monocytes, which are the circulating precursors to tissue macrophages, are refractory to lentivirus infection. Infection of monocytes is blocked primarily at the level of reverse transcription, and the blocks have been attributed to rate-limiting levels of deoxynucleotide triphosphates that are required for optimal reverse transcription or to the presence of inhibitory complexes of APOBEC 3G. Using a heterokaryon approach, researchers uncovered evidence that monocytes harbor a dominant restriction and that expression of Vpx in these heterokaryons conferred the ability to support HIV-1 infection. Furthermore, packaging of Vpx within HIV-1 variants conferred the ability to infect quiescent monocytes. Susceptibility to infection did not reflect a change in the distribution of APOBEC 3G between low- and high-molecular-mass complexes; it appears that the restriction was unrelated to APOBEC 3G.

A prediction stemming from these observations is that lentiviruses that express a Vpx protein have a greater capacity to infect quiescent monocytes than, for example, HIV-1 does. Whether the ability to establish a reservoir of infected monocytes has an impact on the immunopathogenicity of infection remains to be determined.

Tetherin, or BST-2, is an interferon-inducible, cellular protein that inhibits the dissociation of progeny HIV-1 virions from the surface of the infected cell. To overcome this restriction, HIV-1 has evolved Vpu, which neutralizes tetherin by a poorly understood process. A long-standing question has been how members of the HIV-2 and SIV_{sm} lineages that do not have a *vpu* gene counteract the antiviral effects of tetherin. One study (Abstract 28LB) suggests that the Nef protein of SIV may have assumed this responsibility. Nef is an enigmatic, viral accessory protein required for efficient viral replication and pathogenicity in vivo, and many activities have been ascribed to it. Nef has been shown to down-regulate immunoregulatory molecules from the cell surface, inducing CD4 and major histocompatibility complex class I (MHC-I) receptors, and as a consequence, Nef is believed to play a general role in immune evasion.

Deletion mutants of SIV were tested for virion production in 293T cells that expressed either human or rhesus tetherin, and results revealed that SIV Nef could promote particle release by inhibiting rhesus tetherin. However, SIV Nef was not able to neutralize human tetherin. Conversely, HIV-1 Vpu specifically neutralized human tetherin but not rhesus tetherin. Jia and colleagues identified a 4-amino-acid motif in the cytoplasmic domain of tetherin that was required for its ability to be neutralized by SIV Nef. However, this domain was absent from human tetherin.

With these new findings on the role of Nef in neutralization of tetherin, it now appears that all 4 viral accessory proteins play a role in counteracting cellular antagonists of HIV and SIV replication. The fact that lentiviruses have evolved these counter-defense mechanisms supports the notion that these viral accessory proteins represent highly attractive targets for therapeutic intervention.

A number of presentations featured research aimed at improving understanding of how viral accessory proteins counteract cellular restrictions. Two (Abstracts 129LB, 130LB) presented nuclear magnetic resonance structures of the deaminase domain of APOBEC 3G. These structures have begun to reveal insight into loops within the active site that are directly involved in binding to substrate. Although the 2 structures presented very different orientations of the substrate groove, they are important first steps toward identifying elements in APOBEC 3G that can aid in the rational design of small molecules that enhance substrate binding and antiviral activity of APOBEC 3G.

Additional APOBEC Studies

Although considerable insight into the mechanism by which Vif counteracts the antiviral activity of APOBEC 3 proteins has been obtained, gaps remain in our understanding of the mechanisms by which APOBEC 3 proteins inhibit viral replication. APOBEC 3G is a cytidine deaminase that is packaged into viral particles, and the consensus is that it restricts viral replication by catalyzing deamination of cytosines in minus-strand viral cDNA. Whereas APOBEC 3G has 2 cytidine deaminase domains, only the C-terminal domain has catalytic activity.

Several studies provide evidence that the antiviral activity of APOBEC 3G is dependent upon cytidine deaminase activity. However, studies by Malim, Sheehy, and colleagues have provided evidence that APOBEC 3G may exhibit antiviral activity independent of APOBEC 3G enzymatic activity. For example, packaging of APOBEC 3G protein into Vif-deleted HIV-1 virions correlates with an inhibition of endogenous reverse transcription within the virion.[7] This would suggest that APOBEC 3G has the capacity to inhibit viral reverse transcription. Abstract 240 continued in this vein by describing a

large panel of APOBEC 3G proteins, some of which retain cytidine deaminase activity yet do not have antiviral activity. Studies presented in Abstract 233 reinforced the model that the extent of deamination of viral cDNA correlated inversely with viral infectivity and that packaging of a single molecule of APOBEC 3G was sufficient to affect HIV-1 infectivity, which further implicated that restriction is dependent upon enzymatic activity.

The level to which APOBEC 3G is expressed in cells also shapes the outcome of infection. At higher levels of APOBEC 3G expression, neutralization by Vif may be incomplete, which would create the scenario in which even wild-type viruses are suppressed by APOBEC 3G. Abstract 241 presented evidence that the differential expression of APOBEC 3G in T helper lymphocyte subsets (T_H1 or T_H2) correlated with their susceptibility to infection. APOBEC 3G was expressed at higher levels in T_H1 than T_H2 cells, and virus produced from T_H1 cells was less infectious than virus obtained from T_H2 cells. This suggests that strategies that augment APOBEC 3G expression in vivo may be effective in inhibiting the replication of HIV-1.

Abstract 26 employed biochemical procedures to evaluate the interaction between the cellular restriction TRIM5 and lentiviral capsid proteins. TRIM5α from rhesus monkeys potently inhibits HIV-1 infectivity at an early step in the viral life cycle. It has been hypothesized that TRIM5α interferes with retroviral uncoating. However, study of the uncoating process in the context of an infected cell has been a difficult challenge. Abstract 26 presented evidence that a recombinant form of TRIM5α, containing the RING domain of human TRIM21, formed monomers and dimers and bound directly to synthetic capsids of HIV-1 CA-NC proteins as well as to core particles of equine infectious anemia virus. Furthermore, TRIM5-TRIM21 chimeric proteins were able to autoubiquitylate in vitro. The ability to recapitulate ubiquitin ligase activity and Gag binding in vitro with recombinant TRIM proteins should allow a more detailed investigation into the mechanism by which TRIM5 proteins affect capsid function and viral uncoating.

Abstract 24 presented studies aimed at monitoring the uncoating process in vivo. The investigators incorporated a fluorescent label into the membranes of HIV-1 virions that had also packaged green fluorescent protein (GFP) through its association with Vpr. Cells were then infected and virions visualized with antibody to capsid. The investigators followed the timing of uncoating from the percentage of virions that had lost the membrane fluorescent signal. They observed that capsid remained associated with the viral core after fusion and gradually associated over the first 4 hours after infection. Curiously, when cells were treated with reverse transcriptase inhibitors, the percentage of capsid-associated virions increased with time. Collectively, these findings suggest that capsid can remain associated with the viral core for hours after infection and that reverse transcription may be important for HIV-1 uncoating because the process was delayed in the presence of reverse transcriptase inhibitors.

Cellular Cofactors and Viral Replication

Over the past year, considerable attention has focused on cellular cofactors that regulate early events in the retroviral life cycle and in particular, cellular proteins that aid in translocation of viral complementary DNA (cDNA) into the nucleus. Last year, a short interfering RNA (siRNA) screen by Brass and colleagues identified more than 200 potential HIV-1 cofactors required for viral replication.[8] Among these were nuclear pore proteins and nuclear shuttling proteins that may play a role in trafficking of viral reverse transcription complexes from the cytoplasm to the nucleus.

This aspect of retroviral replication has remained highly elusive. After infection of a cell and synthesis of viral cDNA, viral integrase remains associated with viral cDNA as it translocates to the host cell nucleus. Because these nucleoprotein reverse transcription complexes approach the size of a ribosome, some specialized mechanism must permit them to translocate across the nuclear envelope during infection of a nondividing cell. Abstract 23 presented evidence that transportin-SR2 binds to HIV-1 integrase but not MLV integrase. Upon siRNA-mediated knockdown of transportin-SR2, nuclear translocation of HIV-1 reverse transcription complexes was blocked. Interestingly, transportin-SR2 knockdown inhibited nuclear translocation of HIV-1 in cells that had not been growth arrested. This suggests that infection of the cell by HIV-1 may depend upon nuclear transport factors irrespective of the cycling state of the target cell.

In a plenary presentation, Debyser (Abstract 74) discussed ongoing studies aimed at developing small molecule inhibitors of the interaction between HIV-1 integrase and its cellular cofactor, lens epithelium-derived growth factor/p75 (LEDGF/p75). This cellular protein was originally identified in association with integrase complexes expressed in cells.[9] Subsequent studies using RNA interference (RNAi)-mediated knockdown of LEDGF indicated that it played an important role in viral integration. Crystallographic information on LEDGF/p75-integrase interaction has aided in the design of inhibitors of the interaction by computer modeling. Debyser discussed a lead compound that fits in the LEDGF binding pocket. This compound was antiviral and was active against viruses resistant to the integrase inhibitor raltegravir. Importantly, this small molecule appeared to act at the interface between LEDGF and integrase rather than the interface of LEDGF with cellular binding partners such as JPO2. Therefore, inhibition of LEDGF-integrase interaction may be possible without affecting the normal cellular function of LEDGF.

Studies were presented of HIV replication using analyses of single molecules aimed at visualizing the pathway that viruses use to navigate in and out of the cell (Session 44). Abstract 167 presented studies using virions in which integrase was fused to a fluorescent protein. This permitted analysis of the spatial and dynamic distribution of viral reverse transcription com-

plexes in the nucleus. This strategy indicated that viral reverse transcription complexes localized primarily to decondensed regions of chromatin but not to heterochromatin, suggesting the existence of a mechanism by which viral reverse transcription complexes are oriented toward particular integration sites. In a parallel presentation (Abstract 166), fluorescently tagged derivatives of Gag were used to follow the assembly of HIV-1 virions at the surface of the infected cell. Using a variety of fluorescent imaging approaches, virions were found to appear at the cell surface sequentially, and assembly of a single virion typically required 5 minutes to 6 minutes.

Studies of Nef

Abstract 258 presented research aimed at identifying small molecule inhibitors of HIV-1 Nef. As discussed above, of the myriad of activities that have been described for lentiviral Nef proteins, its ability to down-regulate MHC-I receptor expression on the surface of the infected cells is generally considered an important function of Nef because it would protect the infected cell from immune surveillance by cytotoxic T cells. A cell-based assay was described that screens for small molecules that stabilize surface expression of MHC-I in the presence of HIV-1 Nef. From a library of 70,000 compounds, 2 were identified that could prevent down-regulation of MHC-I on the cell surface in the presence of HIV-1 Nef. Studies are underway to determine whether these small molecules restore the sensitivity of HIV-1-infected cells to killing by cytotoxic T lymphocytes.

Although Nef plays a central role in viral replication, it is also implicated as a determinant of pathogenicity in HIV and SIV infection. Nef may be a determinant that contributes to an increased risk of cardiovascular disease in HIV infection (Abstract 147). There is an increased incidence of dyslipidemia and cardiovascular disease in HIV-1-infected individuals. Examining high-density lipoprotein (HDL) metabolism in SIV-infected macaques fed an atherogenic diet, Bukrinsky and colleagues observed an SIV-specific block in HDL remodeling in the liver and down-regulation of ABCA1 (adenosine triphosphate-binding cassette, subfamily A, member 1) activity in the liver. Soluble extracellular Nef was found in liver tissue and in plasma. In vitro, Nef inhibited ABCA1-dependent cholesterol efflux from macrophages and hepatocytes, suggesting a model in which Nef released from infected cells inhibits reverse cholesterol transport. This effect may lead to changes in HDL metabolism that may contribute to increased risk of cardiovascular disease.

Viral Replication and Pathogenicity

Pathogenic lentivirus infection (HIV-1 infection of humans and SIV infection of rhesus macaques) is associated with high-level viral replication and viremia, accelerated turnover of CD4+ lymphocytes and CD4+ cell depletion, and generalized immune activation. In contrast, primate lentiviruses are not considered pathogenic in their natural hosts (SIV_{cpz} infection, SIV_{smm} infection). Nonpathogenic infection exhibits most of the characteristics of pathogenic infection including efficient viral replication, high-level viremia, and accelerated CD4+ lymphocyte turnover. However, the CD4+ lymphocyte depletion and generalized immune activation characteristic of pathogenic infection are not apparent in nonpathogenic infection.

Abstract 80 presented the surprising finding that SIV_{cpz} may have a substantial impact on the health of infected chimpanzees as well as their survival and reproduction, indicating that SIV_{cpz} is pathogenic in its natural host. Because chimpanzees are a protected species, it has been difficult to study the natural history of SIV_{cpz} infection in these animals. However, the investigators exploited 50 years of observational data, combined with antibody and DNA polymerase chain reaction status, to study SIV_{cpz} infection in chimpanzees in Gombe National Park, Tanzania. SIV_{cpz} prevalence rates increased from 8% in 2001 to 17% in 2007. There was a higher mortality risk in infants born to SIV_{cpz}-infected mothers than in infants born to uninfected mothers, and infected chimpanzees had a 6- to 17-fold increased death hazard. CD4+ lymphocyte depletion was also evident in 2 of 3 SIV_{cpz}-infected animals but not in 4 uninfected controls. Thus, in terms of the extent of pathogenicity, mortality data in SIV_{cpz} infection in chimpanzees is lower than that of HIV-1-infected humans but higher than in SIV_{smm} infection. Whether the extent of pathogenicity in SIV_{cpz}-infected monkeys correlates with levels of generalized immune activation remains to be determined.

In a plenary presentation, Douek discussed the role of immune activation in pathogenic lentivirus infection as well as factors that may drive immune activation (Abstract 20). The mucosal barrier is damaged as a consequence of depletion of gut-associated lymphoid tissue (GALT), with the preferential loss of T_H17 cells in the gastrointestinal tract as a result of HIV infection. Translocation of microbial products from the gut lumen into the systemic circulation, as a consequence of this damaged mucosa, drives immune stimulation. In contrast, levels of T_H17 cells in the gastrointestinal tract of SIV-infected sooty mangabeys remain normal, and there is no evidence for increased translocation of immunostimulatory microbial products.

T_H17 cells may be selectively depleted in HIV-1 infection because the majority of T_H17 cells are CD4+ and are thus susceptible to infection (Abstract 78). Although the majority of T_H17 cells expressed both CC chemokine receptor 5 (CCR5) and CXC chemokine receptor 4 (CXCR4) coreceptors, CCR5 expression was higher in the T_H17 subset that secretes interleukin-17 and interferon-gamma (IFN-γ). These cells were highly susceptible to infection by X4-tropic and R5-tropic HIV-1 and to the cytopathic effects of infection in vitro. There was a substantial decrease in this IFN-γ-positive T_H17 population in HIV-1-infected individuals. This T_H17 subset was also decreased in HIV-1-infected individuals receiving suppressive antiretroviral therapy who have a CD4+ count greater than 200 cells/μL. Therefore, targeting of these cells by HIV-1 may occur even with effective

antiviral therapy, or this subpopulation of T_H17 cells may not recover if viral replication is subsequently controlled by antiretroviral therapy.

Rowland-Jones discussed features of HIV-2 infection and pathogenicity (Abstract 56). The majority of HIV-2-infected individuals do not show signs of disease, and as such, HIV-2-infected individuals share similar characteristics with HIV-1-infected long-term nonprogressors. About 20% of HIV-2-infected individuals develop a pathogenic infection similar to AIDS in HIV-1 infection. Rowland-Jones presented evidence that proviral DNA load in HIV-2 progressors and HIV-1-infected individuals at the same stage of disease are similar. However, HIV-2-infected nonprogresssors have lower plasma viremia. HIV-2-infected individuals with nonprogressive infection are more able to mount an effective immune response and preserve HIV-specific T-helper-cell responses and strong CD8+ cell responses. Low viral load correlated with the presence of T-cell responses to HIV-2 Gag.

Surprisingly, there are variations in HIV-2 Nef that affected its ability to down-regulate T-cell-receptor complex, and although this correlated with levels of systemic immune activation, there was no correlation with the extent of disease progression. It was previously hypothesized that down-regulation of the T-cell-receptor–CD3 complex from infected T cells by Nef may inhibit their response to activation and that this ability to down-regulate the T-cell receptor was lost in HIV-1 Nef.[10] The interpretation was that an inability to down-regulate the T-cell receptor and prevent infected cell responsiveness to activation may contribute to the extent of pathogenicity. Although the ability to down-regulate the T-cell receptor may not directly correlate with clinical outcome in HIV-2 infection, accumulating evidence suggests that Nef plays a role either in contributing to the state of immune activation or in regulating the ability of the infected cell to respond to immune stimuli.

As in some HIV-2-infected individuals, rare SIV_{sm}-infected sooty mangabeys show profound CD4+ lymphocyte depletion. This lymphocyte depletion is accompanied by emergence of SIV that is able to use several coreceptors for entry (R5/X4/R8/R2). To determine whether viral or host determinants defined the extent of lymphocyte depletion, plasma from sooty mangabeys with depleted CD4+ cells was used to infect additional animals. This led to a rapid depletion of CD4+ cells within 4 weeks of plasma transfer. In addition, virus recovered from 3 additionally infected monkeys retained its ability to infect cells by several coreceptors. Despite the profound depletion of CD4+ lymphocytes, levels of immune activation remained at levels observed in uninfected monkeys. Furthermore, plasma lipopolysaccharide levels remained low, which suggested that profound depletion of CD4+ lymphocytes was not accompanied by an impairment of gut epithelial integrity.

Collectively, these results indicate that SIV variants capable of using numerous coreceptors can induce severe systemic CD4+ cell loss in the natural host without inducing simian AIDS. This indicates that the natural host of SIV infection is able to maintain mucosal integrity and adaptive immune responses without the presence of high levels of CD4+ cells.

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A list of all cited abstracts appears on pages 89-95.

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HIV Vaccine Development

David I. Watkins, PhD

Several interesting new vaccine-related studies were presented at the 16th Conference on Retroviruses and Opportunistic Infections this year. Transmitted viruses appear to be derived from cell-free virus rather than cell-associated virus, at least in men who have sex with men. Follow-up studies from the Step (HIV Vaccine Trials Network 502) trial indicated that if individuals mounted certain vaccine-induced responses, they may control viral replication after infection. Finally, adeno-associated-virus-derived neutralizing antibodies completely protected macaques from infection, suggesting novel mechanisms of viral control.

Transmission

One of the highlights of the 2008 (15th) Conference on Retroviruses and Opportunistic Infections was the discovery that only a few HIV variants cross the mucosa to initiate viral infection. At the 2009 (16th) conference this year, data were presented suggesting that the origin of the infecting virus in semen is cell-free virus rather than viral DNA present in cells (Abstract 49LB). Four transmission pairs of men who have sex with men (MSM) were studied; sequences of the virus present in plasma of the infected recipient clustered with donor cell-free virus from semen rather than viral DNA in lymphocytes from semen. It will now be important to assess the origin of the transmitted virus in heterosexual transmission pairs and in men infected by genital secretions. Nonetheless, this result suggests that vaccines should target cell-free virus rather than cell-associated virus. Furthermore, the cell-free viral challenges employed in macaque challenge studies may be relevant to HIV transmission.

Step Trial Follow-Up

In a symposium on "Learning from Negative Trials," Hunter discussed possible reasons for the failure of the Step trial (HIV Vaccine Trials Network 502 study) (Abstract 119). It was suggested that despite relatively robust vaccine-induced T-cell responses, the breadth of these responses may not have been sufficient to protect against HIV infection or reduce postinfection viral loads in the majority of vaccinees. New T-cell vaccine approaches may, therefore, have to be qualitatively different or include an antibody component in the future.

In an attempt to explain why vaccinees in the Step trial with high adenovirus serotype 5 (Ad5) neutralizing antibodies were more susceptible to HIV infection, the immune response to Ad5 was monitored in individuals participating in phase I studies (Abstract 85). Approximately 73% of individuals already had Ad-specific T cells before receiving the vaccine. Only individuals given 3 injections of 3×10^{10} viral particles showed a statistically significant increase in the percentage of Ad-specific CD4+ and CD8+ T cells. These CD4+, Ad5-specific cells exhibited macrophage inhibitory protein (MIP)-1 alpha activity, which the authors speculated might make them resistant to HIV infection.

In a follow-up study of the Step trial, data suggest that if vaccinees show a response to a "good" epitope after vaccination, they will likely exert some measure of control over viral replication after infection (Abstract 86LB). Although this would be expected for epitopes bound by the "protective" alleles HLA-B*57 and -B*27, there were 9 individuals who showed a response to the HLA-A*02-bound epitope Nef LV10. The vaccinees who showed a response to this epitope before infection did better than those that did not.

Further evidence for the concept that CD8+ T-cell recognition of good epitopes results in control of viral replication was presented by Streeck and colleagues (Abstract 112). The authors showed that if individuals recognized frequently targeted immunodominant epitopes during the acute infection phase, they would control viral replication later. Preservation of this recognition pattern into the chronic infection phase also correlated with a slower CD4+ decline.

Finally, 2 studies (Abstracts 90aLB, 90bLB) presented the effects of interleukin-2 on clinical outcomes. Despite evidence of preservation of CD4+ cells and increases in some patients, there was no reduction in the rate of opportunistic infections or death.

Monkey Vaccine Studies Using Attenuated Simian Immunodeficiency Virus

Two studies (Abstracts 116, 117) shed light on protection induced by live attenuated simian immunodeficiency virus (SIV) $SIV_{mac239\Delta Nef}$. The first study examined the expansion of natural killer (NK) cells (CD3-, CD8+, NKG2A+) after vaccination and challenge. NK cells expanded by as much as 8-fold in 70% of the vaccinated animals. Similarly, NK expansion was observed in challenged vaccinated monkeys, in the absence of obvious anamnestic responses, implying that these NK cells may play a role in vaccine-induced protection.

The second monkey study involving $SIV_{mac239\Delta Nef}$ showed that depletion of B cells had little effect on vaccine-induced protection. Although not all of the vaccinated macaques exhibited adequate B-cell depletion, 5 of 10 anti-CD20-antibody-treated animals had no SIV-specific antibody at time of challenge. Of these, 4 of 5 showed no evidence of

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replication of the challenge virus, and the other showed only limited viral replication and subsequent control. Thus, B-cell responses likely play only a marginal role in vaccine protection induced by $SIV_{mac239\Delta Nef}$.

Vaccine Development

In a symposium titled "Vaccines—Back to Basics," several elegant antibody studies were described. The first presented an analysis looking at the first antibodies present after detection of virus (Abstract 162). At 8 days postinfection, antibody-virion complexes were present, followed by antibody to gp41 at 13 days. Anti-gp120-specific antibodies appeared at 28 days post-viral detection. Mathematical modeling suggested that these antibodies had little effect on reducing acute-phase viremia given the timing of their appearance during natural infection.

Mascola discussed approaches to generate broadly reactive neutralizing antibodies (brNAbs) (Abstract 163). These antibodies may be more common than previously thought, and new methods for developing additional brNAbs were described. This involved sorting of B cells from infected individuals with subsequent cloning of the immunoglobulin heavy and light chains. After transfection of these heavy and light chains, it was possible to produce neutralizing antibodies.

One of the most interesting and novel discoveries reported at this year's conference involved the use of adeno-associated virus as a gene therapy agent to express an SIV-specific neutralizing monoclonal antibody (Abstract 164). Three monkeys treated in this way resisted challenge with SIV_{mac316}, whereas 6 naive macaques became infected and developed sustained viral replication out to 12 months postinfection. This novel approach may well hold substantial promise as a method of controlling the HIV epidemic.

Encouraging news from the T-cell vaccine field closed this symposium (Abstract 165). Vaccination with a DNA/Ad5 regimen encoding all of the SIV proteins except Env induced high-frequency and broad T-cell responses in 8 macaques. Repeated low-dose mucosal challenge with a heterologous virus demonstrated that these vaccine-induced T-cell responses controlled replication of the challenge virus in 6 of 8 vaccinees. These data suggest that both acute- and chronic-phase viral replication can be controlled by T cells alone, in the absence of Env-specific antibody responses.

New HIV Vaccine Testing

Finally, encouraging immune responses were engendered in a safety trial of a protein vaccine adjuvanted (with AS01) and consisting of a recombinant fusion protein containing p17, p24 Gag, reverse transcriptase, and Nef (Abstract 87LB). Additionally, there were no vaccine-related serious adverse effects. At the highest doses of this vaccine, 80% of the human volunteers showed recognition of all 4 antigens in the vaccine, with a mean CD4+ cell reactivity of 1.2%. Interestingly, few CD8+ T-cell responses were seen in the vaccinees. Further human testing is planned for this vaccine approach.

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A list of all cited abstracts appears on pages 89-95.

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The Epidemiology of New HIV Infections and Interventions to Limit HIV Transmission

Susan Buchbinder, MD

After the disappointing news reported at the 2008 (15th) Conference on Retroviruses and Opportunistic Infections regarding HIV vaccines, microbicides, and herpes virus suppression trials, the 16th conference this year brought welcome advances in the HIV prevention field. In particular, substantial progress is being made in approaches to preexposure prophylaxis in preclinical and clinical trials, and an efficacy trial of a vaginal microbicide appeared to provide women in Africa and the United States with modest protection against HIV acquisition. This review covers presentations on the epidemiology of HIV infection in specific global populations, strategies to improve the uptake of HIV testing, lessons from previous negative prevention trials, and progress in the development of new biomedical interventions.

HIV-Affected Populations

We are now nearly 3 decades into the HIV epidemic, and it is estimated that there were 2.7 million new HIV infections worldwide in 2008.[1] Several presentations at this year's conference highlighted the diverse nature of the epidemic, both in specific risk groups and in specific geographic regions.

Men Who Have Sex with Men

There was renewed recognition of the global nature of the HIV epidemic in men who have sex with men (MSM). Caceres pointed out that, despite limited data, approximately 7% of the populations of men in Latin America and Asia report having had sex with men in the prior year, and much higher rates globally report ever having had sex with men (Abstract 13). Conversely, more than half of MSM globally also reported having sex with women in the prior year, with rates especially high in Africa and Asia, and considerably lower (19%) in Latin America. Two posters at the conference (Abstract 1028 on data from Kenya, Abstract 1029 on data from Senegal) also found more than half of the MSM sampled in these regions reported having sex with both men and women, raising concerns about spread of infection from MSM into female populations. This speaks to the global need to move our thinking beyond risk-group categories and to ask all patients about sexual practices of all types.

Caceres also reviewed data from Baral and colleagues reporting on the high HIV prevalence in MSM compared with heterosexual populations in many regions of the world (odds ratio [OR], 33.3 in Latin America, 18.7 in Asia, and 3.8 in Africa).[2] Van Griensven and colleagues provided longitudinal data on an MSM cohort in Thailand with an HIV incidence rate of 5.7 per 100 person-years over 3 years of follow-up despite ongoing risk-reduction counseling, highlighting the severity of the epidemic in MSM populations (Abstract 1037b).

Caceres addressed some of the structural drivers of the MSM epidemic that limit access to prevention services. His group's survey of antisodomy laws worldwide found that highly prohibitive laws (with punishments of prolonged incarceration or death) still exist in 18 countries in Africa, 14 in East and Southeast Asia, 11 in the Caribbean, and 6 in the Middle East and North Africa. Caceres called for a 3-pronged approach to addressing the MSM epidemic, including collection of more data with better outreach to MSM populations globally, implementation of human rights protections, and an increase in access to prevention services.

There were several cross-sectional studies of MSM in resource-constrained settings. Solomon and colleagues estimated that there are 2.35 million MSM in India but that this population remains largely hidden, in part because of cultural "requirements" that young people marry, and because of Indian law forbidding same-sex relationships (Abstract 171LB). In their respondent-driven sample of 721 MSM, in which initial participants were primarily sex workers, HIV prevalence was 9%, and seropositivity was independently associated with marriage (adjusted OR [AOR], 1.91), herpes simplex virus 2 (HSV-2) seropositivity (AOR, 3.69), and having more than 50 sex partners in the past year (AOR, 3.81). One-third of the men were married, and two-thirds of married men reported having engaged in unprotected vaginal sex with at least 1 female partner in the prior year.

Beyrer and colleagues presented data on the MSM epidemic in Malawi, Namibia, and Botswana (Abstract 172). Overall prevalence was 17% in this sample of 537 men, with men older than 25 years having a 4-fold increased rate of HIV seropositivity (95% CI, 2–8), after adjusting for other demographic and risk variables. More than half of the men had had sex with both men and women in the previous 6 months, and 16% reported concurrent relationships with both men and women. Of note, being in concurrent bisexual relationships was statistically significantly associated with always using condoms with regular sex partners in this sample (AOR, 4.8; 95% CI, 2.8–8.2), which may reduce the risk of transmission to female partners. Stigma and discrimination were high in these populations, with 18% to 20% of men in the 3 coun-

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tries afraid to seek health services, and 18% to 26% reporting that they had been blackmailed because of their sexuality. Being blackmailed was statistically significantly associated with disclosing their same-sex behavior to family members or to a clinic or health care worker, and with not having had an HIV test in the previous 6 months. This report provides concrete evidence of how stigma, failure to protect confidentiality in clinical settings, and laws against homosexuality may directly affect the receipt of health care services.

HIV Infections in Diverse Geographic Regions

Other presentations focused on the diverse epidemics within specific geographic locations. For example, Session 16 focused on the global nature of the epidemic as told through the epidemiology and public health response in 4 cities in different regions of the world: Washington, DC (Abstract 57); Capetown, South Africa (Abstract 58); Rio de Janeiro, Brazil (Abstract 59); and Almaty, Kazakhstan (Abstract 60). Hader presented data on the diverse HIV epidemic in Washington, DC, where overall prevalence is 3%, rates are high in nearly all wards in the city, and new infections represent all high-risk-behavior groups (25% MSM, 15% injection drug users [IDU], > 35% heterosexual) (Abstract 57). Rates are particularly high among black men (prevalence, 6.5%) and persons aged 40 years to 49 years (prevalence, 7.2%) and 50 years to 59 years (prevalence, 5.2%). Numerous city agencies have begun implementing a broad array of prevention programs, with early indicators of success in an increased rate of HIV testing, higher CD4+ counts at initial presentation, increased rates of school-based testing for sexually transmitted diseases (STDs), and decreased STD prevalence in several schools.

Gray and McIntyre gave a broad overview of the evolution of the AIDS epidemic in South Africa in this year's N'Galy-Mann Lecture (Abstract 18). Well after HIV was recognized to cause AIDS, the epidemic continued unchecked in South Africa, growing from 160,000 infections in 1987 to 5.7 million in 2007. South Africa is home to 17% of HIV infections worldwide, while making up only 0.7% of the world's population. Gray and McIntyre reiterated Jonathan Mann's statement to the United Nations General Assembly in 1987 that the "social, cultural, economic and political reaction to AIDS [is] as central to the global AIDS challenge as the disease itself." Their informative and moving account of the South African AIDS story can be viewed on the conference Web site at www.retroconference.org.

Coetzee focused on the high rates of sexual concurrency fueling the HIV epidemic in Capetown, South Africa (Abstract 58). HIV prevalence is twice as high among persons living in "informal" (nonpermanent) housing as among persons living in standard housing. He also focused on efforts to roll out antiretroviral therapy and prevention of mother-to-child transmission (PMTCT), which was particularly challenging under the previous South African government that denied that HIV infection caused AIDS. Substantial progress is being made in these areas, and there is now government support for these programs.

El-Bassel discussed the rising epidemic in 2 cities in Khazakstan, the largest country in Central Asia (Abstract 60). Here, the epidemic largely affects IDUs, and the epidemic may be fueled by external forces (eg, drug-trafficking patterns in Asia) and internal policies in the treatment of IDUs (eg, lack of needle-exchange programs, criminalization of drug use, lack of harm-reduction programs). HIV prevalence has increased dramatically since the early 2000s, pointing to the need to act quickly to prevent a much more substantial epidemic in this region of the world.

Uptake and Impact of HIV Testing

HIV prevention and treatment both begin with knowledge of HIV serostatus. A number of presentations focused on the continuing problem of undiagnosed HIV infection in the United States and globally. Campsmith and colleagues at the US Centers for Disease Control and Prevention reported that as of the end of 2006, more than 1 million persons at least 13 years old were infected in the United States, and that 21% of these persons were unaware of their HIV infection (Abstract 1036). More than half of these undiagnosed infections occurred in MSM. The number of undiagnosed infections was highest among blacks (113,100), followed by whites (72,000), and Hispanics (41,900); by age, 35- to 44-year-olds (76,100) had the highest number. The proportion of all HIV-infected persons who remained undiagnosed was highest among MSM (23.5%) and heterosexual men engaging in high-risk behaviors (26.7%), although the absolute number of undiagnosed MSM was more than 4-fold higher than that of undiagnosed heterosexual men (125,900 vs 27,900, respectively). Of note, the proportion of undiagnosed HIV infections was lowest among men and women IDUs, possibly the result of the HIV testing and prevention services offered through drug-treatment programs, medical care, and syringe-exchange programs.

Chen and colleagues reported on data from administrative claims from 8 US health plans covering 7.8 million insured persons in the United States (Abstract 1044). After excluding persons with known HIV infection, organ-transplant recipients, hospice patients, and those receiving immunosuppressive medications, they found nearly 7500 continuously insured patients with new diagnoses of a potential AIDS-defining event. Overall, 4.3% had received an HIV antibody test, CD4+ count determination, or HIV viral load measure within 150 days before receiving their potential AIDS-defining diagnosis through 60 days after the diagnosis.

It has been estimated that worldwide, only 10% of persons at risk of HIV infection receive HIV testing (Abstract 12). Mohammed and colleagues reported that 63.5% of persons included in a nationally representative survey in Kenya had never received an HIV antibody test (Abstract 137LB). April and colleagues reported that testing rates among the population living near Capetown, South Africa, had increased

substantially from approximately 4% in 2001 to 20% in 2006, although median CD4+ count at the time of diagnosis did not change over that time period (Abstract 1048).

Two presentations documented progress in early HIV testing in some populations. Golden and colleagues reported on the proportion of persons newly diagnosed with HIV through a public health program in Seattle, Washington, from 1995 to 2008 (Abstract 1043). The proportion of newly diagnosed MSM reporting never previously receiving an HIV test declined substantially (from 25% in 1995–1996 to 5% in 2007–2008; $P < .0001$), although no statistically significant improvements were seen in other groups engaging in high-risk behavior (average, 40%). Median CD4+ count at diagnosis improved for both groups (to 487 for MSM, 407 for non-MSM). Bezemer and colleagues also reported reduced time from infection to diagnosis among MSM in the Netherlands (now 2.47 years) (Abstract 1019). Although they estimate that only 20% of HIV-infected men were unaware of their infection at the beginning of 2007, their models indicate that these men account for 89% of new infections, pointing to the importance of locating and frequently testing within this population.

Strategies to Improve HIV Testing Rates

Heffelfinger and colleagues reported on acceptance and completion of opt-out testing among nearly 50,000 emergency department visits in Alameda County (California) Medical Center from August 2007 to March 2008 (Abstract 1038). Only 36.3% of eligible patients accepted testing; younger patients, women, black patients, and patients not acutely ill were more likely to accept screening. Of those who accepted screening, only 62% actually had testing performed; predictors of receiving a test were older age and lack of acute illness. Walensky and colleagues reported results of a randomized controlled trial of counselor- versus emergency department provider–initiated HIV counseling and testing (Abstract 1039). Offer rates were higher in the counselor group (57% vs 27%; $P < .0001$), and provider rates declined statistically significantly over time. Christopoulos and colleagues reported on a program providing 1 dedicated rapid test counselor each to 2 emergency departments during business hours on Mondays through Fridays (Abstract 1040). Of nearly 70,000 emergency department visits, just over 2500 persons underwent rapid HIV testing, which yielded 24 new HIV diagnoses. In these studies, dedicated counselors increased testing rates, although only for a small fraction of the total population of patients seen in emergency departments.

Two presentations described home-based testing programs in Uganda. Lugada and colleagues made the case that family members of HIV-infected persons are among those with the highest HIV prevalence, with more than half of spouses and 5% of the children of HIV-infected persons also found to be HIV-seropositive (Abstract 138). They report on the first direct comparison of home- versus clinic-based testing for family members of HIV-infected persons in Jinja, Uganda. HIV testing rates were higher among home- than clinic-based testers (56% vs 11%, respectively; AOR, 10.4), and the authors estimate that they identified 56% of HIV-infected household members through the home-based group compared with 27% in the clinic-based group.

Gupta also reported on the impact of a door-to-door voluntary counseling and testing program in the Bushenyi district, Uganda, from 2005 to 2007, by comparing responses in a population-based, district-wide survey conducted before and after the intervention (Abstract 139). The proportion of persons who reported ever having been tested increased (from 20% to 63%; $P < .001$), as did the proportion disclosing serostatus to partners (72% to 81%, respectively; $P = .04$). Several measures of stigma also statistically significantly decreased. Self-reported condom use at last intercourse did not change overall (15.5% to 13.8%, respectively), although there was a statistically significant increase in condom use in the small number of HIV-infected men surveyed (1/9 to 21/46, respectively; $P = .02$) and no statistically significant change in women (18.6% to 27.6%, respectively; $P = .4$). These results point to the need to find successful behavior-change strategies that can be incorporated into home-based voluntary counseling and testing programs, including for HIV-uninfected persons.

There is interest in identifying persons with primary HIV infection, to interrupt transmission chains and refer newly infected persons into care. A number of posters at this year's conference reported on the sensitivity of fourth-generation assays that measure both p24 antigen and IgM and IgG antibodies in identifying newly infected individuals (Abstracts 988–992, Abstract 997). These assays identified 62% to 98% of persons with primary infection in these studies, substantially better than available third-generation assays, and nearly as sensitive as pooled nucleic acid testing. Most of the specimens that were nonreactive on these combination assays came from patients who had low levels of plasma HIV RNA. The new HIV antigen-antibody combination assay (Abbott ARCHITECT Ag/Ab Combo Assay; Abbott Park, IL) used in most of these reports is not currently sold in the United States and is not a point-of-care test. Although this strategy can detect early infection, it does not differentiate primary from chronic infection, so in situations for which it is important to differentiate primary from chronic infection, other strategies must be used.

Lessons from Negative Trials

The past several years brought disappointing results from efficacy trials of HIV vaccines, HSV-2 suppression, microbicides, and behavioral trials. Symposium 31 focused on lessons from these negative trials, differentiating failed trials (in which study design, selection of study population, or adherence to protocols fail to answer the research question) from trials that are successfully completed but yield negative results. The latter type are part of the scientific process of hypothesis testing and may provide important insights

that guide their respective fields. Buve quoted Popper, who said, "… science is one of the very few human activities—perhaps the only one—in which errors are systematically criticized and fairly often, in time, corrected. This is why we can say that, in science, we often learn from our mistakes, and why we can speak clearly and sensibly about making progress there."

Hunter presented a summary of results from the Step trial (HIV Vaccine Trials Network 502/Merck 023 study) of replication-incompetent adenovirus serotype 5 (Ad5) *gag/pol/nef* vaccine (Abstract 119). Initial results were presented at the 2008 (15th) conference and published last year.[3,4] Hunter made several points about lessons learned. First, he noted that despite robust immune responses among vaccinees, the vaccine failed to prevent HIV infection or control early plasma viral load. He speculated that this indicates that the magnitude, breadth, or quality of the immune response must be improved to provide protection with other T-cell-based vaccines. He noted the success of the test-of-concept trial design in achieving a definitive result relatively quickly (< 3 years). He also stated that the apparent increased acquisition of infection in subgroups of male participants is leading to new insights into the role of preexisting vector-based immunity in vaccine effects, and he called for additional effort in understanding this relationship. He noted that the trial provided insight into development of appropriate nonhuman primate models, stating that simian-human immunodeficiency virus (SHIV) is not an adequate challenge model for T-cell-based vaccines, but that $SIV_{mac239/251}$ challenge studies do indicate that T-cell-based vaccines can control viral replication in the absence of broadly neutralizing antibody, and that T-cell-based vaccines should continue to be pursued.

Hunter also showed data indicating sharp declines in risk behavior in both vaccine and placebo recipients, raising the issue of indirect benefit to participants in clinical trials. He closed with a discussion of unanswered questions in developing HIV vaccines, describing the need to develop and validate immunologic assays that correlate with immune protection, proposing a potential role of systems biology in differentiating protective and nonfunctional immune responses, and speculating about a potential role of nonneutralizing antibody in protection. Hunter also called for close coordination of clinical trials and nonhuman primate studies to ensure maximum relevance in developing an effective HIV vaccine.

Whitley summarized data from 2 trials of long-term acyclovir therapy to prevent HIV acquisition among HSV-2-infected women and men (Abstract 120).[5,6] After summarizing the major findings from the trials, Whitley pointed to several lessons from these trials. Given the substantial epidemiologic data linking HSV-2 infection with an increased risk of HIV acquisition, he speculated about several possible explanations for the lack of efficacy in these 2 well-conducted trials. He suggested that HSV-2 reactivates more frequently than previously appreciated and that more potent drugs may be required. He pointed to the potential need to use drugs that also control the local inflammatory response and reduce CD4 and CD8 activation, which may contribute to the increased susceptibility among HSV-2-infected persons. He also pointed to the importance of developing an effective HSV-2 vaccine to prevent initial acquisition of this STD. In the question-and-answer session, he reminded the audience that data will soon be available from a separate randomized controlled trial of acyclovir suppression among HIV-infected persons, a potential method to prevent HIV transmission to their HIV-uninfected partners.

Buve provided an overview of challenges in the topical microbicide field in the past several years and the insights gained from these trials (Abstract 121). Early trials overestimated HIV incidence in trial populations, particularly in populations receiving ongoing risk-reduction counseling. Use of nonoxynol-9 led to increased risk of HIV acquisition, and these results clarified that traditional safety measures of microbicide effects (eg, symptoms, colposcopy) may not correlate with in vitro studies on epithelial integrity and permeability. Buve also pointed out that nonhuman primate models of the efficacy of cellulose sulfate against SHIV challenge also failed to translate into actual protection in human efficacy trials, suggesting additional work is needed in developing animal models that predict clinical results. She noted the challenges in measuring product use (eg, self-report may not correlate well with objective measures of applicator use) and emphasized the importance of using accurate adherence measures in understanding microbicide trial results. She also pointed to the challenges in maximizing adherence and the need to study microbicide effects in pregnant women, to maximize their ultimate utility. Finally, she discussed the lessons being learned from the HIV Prevention Trials Network (HPTN) 035 microbicide trial, described further below.

Koblin described a recent meta-analysis that indicates that behavioral interventions reduce HIV-related risk behavior and sexually transmitted infections,[7] although their impact on HIV incidence has not been studied extensively (Abstract 122). She highlighted several challenges in this field, including the likely substantial behavioral intervention provided even to control participants, which may undermine measurement of effects in the intervention groups. Studies also suggest that maximal benefit from behavioral interventions may occur in the first year, so that trials of shorter duration may report beneficial effects, whereas trials of longer duration will fail to see sustained improvement.

Koblin differentiated between statistically significant reductions in self-reported risk and public health benefit. For example, data from the EXPLORE study (HPTN 015) in MSM in the United States found modest but statistically significant reductions in self-reported risk but no statistically significant reduction in HIV incidence. Initial evaluation of these data suggested that there was no correlation between sites with larger reductions in risk practices and those measuring more substantial declines in HIV incidence in the intervention group. However, additional analysis, in-

cluding use of multiple measures of risk to create a composite score and use of continuous rather than dichotomous variables, did uncover a high degree of correlation between those sites reporting statistically significant reductions in risk practices in the intervention group and statistically significant reductions in HIV incidence in intervention versus control participants. This points to the complexity not only of measuring HIV-related risk, but also of analyzing the data to understand intervention effects. Koblin also noted the wealth of ancillary studies supported by these clinical trials that address a range of important HIV prevention questions.

Progress in Biomedical Interventions

Microbicides

Karim and colleagues reported potentially promising results from an efficacy trial of 2 investigational microbicides (BufferGel, ReProtect, Baltimore, MD; and 0.5% PRO 2000/5 gel, Indevus Pharmaceuticals, Lexington, MA) when used vaginally by women at risk of sexually acquired HIV infection (Abstract 48LB). BufferGel was hypothesized to provide protection through its buffering effects on vaginal pH, and PRO 2000/5 (a polyanionic polymer) through its binding to the variable loop of HIV, thereby blocking attachment. In this 4-group test-of-concept trial, 3087 HIV-uninfected women in Malawi, South Africa, Zambia, Zimbabwe, and the United States were assigned randomly to receive either active product, a placebo gel, or no microbicide. Retention was greater than 90% in all groups in the trial; adherence to gel use was relatively high (81% overall); and adverse events were comparable between all study groups.

No efficacy was seen with the BufferGel product. There was a 30% reduction in infections in the PRO 2000/5 group compared with the placebo and no-gel groups, although neither comparison achieved statistical significance. However, subgroup analyses lent support to the possibility that PRO 2000/5 provided protection against HIV infection. Participants were divided into high-adherence and low-adherence gel users and high-adherence and low-adherence condom users, based on median use of these products. Among high-adherence gel-using women, those receiving PRO 2000/5 were 44% less likely to acquire HIV than were placebo recipients. Among the subgroup of high-adherence gel users and low-adherence condom users (the subgroup most likely to benefit from an efficacious microbicide), HIV incidence was reduced by 78% in PRO 2000/5 recipients compared with placebo recipients.

Karim was careful to point out that these exploratory analyses are not definitive and that potential for protection must be corroborated through additional clinical trials. A Microbicides Development Programme (MDP) trial of PRO 2000 (MDP 301) is currently under way that was designed to evaluate high-dose (2%) and low-dose (0.5%) PRO 2000 in women at high risk in South Africa, Tanzania, Uganda, and Zambia. Based on an interim analysis in February 2008, the high-dose group was stopped because of futility. However, the trial's independent Data and Safety Monitoring Board has recommended continuing follow-up of the low-dose group (identical to the product used in the HPTN 035 trial), and this follow-up is due to be complete in August 2009, with results released publicly by the end of 2009.

A themed poster discussion session focused on novel microbicide gels and rings (Session 41). Progress has been made in sustained delivery of antiretroviral drugs from vaginal rings, an approach that would not require coitally dependent administration (Abstracts 1065, 1069, 1070). Investigators are also beginning to explore methods for studying the safety (Abstract 1066) and potential efficacy (Abstract 1067) of topical microbicides for rectal use, which will be important both for heterosexual and MSM populations.

Preexposure Prophylaxis

Hillier provided an overview of the field of preexposure prophylaxis (PrEP), the use of antiretroviral medications in HIV-uninfected persons before and during periods of risk to prevent HIV acquisition (Abstract 73). She reviewed the 8 trials currently under way or soon to be launched that will include more than 20,000 participants worldwide. These trials each address somewhat different research questions, including PrEP efficacy in different populations (women engaging in high-risk behaviors, MSM, IDUs, serodiscordant couples), different regimens (tenofovir or combined tenofovir/emtricitabine), different routes of administration (oral or vaginal), and different dosing regimens (continuous or coitally dependent). The first results from the efficacy trials are expected in 2010, and results will be compared within and across trials. Additional work is being done to plan alternative strategies (eg, intermittent dosing, methods for sustained systemic or topical delivery). Further work is needed to enhance adherence in these trials and to consider how to scale up access to any particular strategy, should it prove efficacious.

Two nonhuman primate studies provided support for topical and intermittent dosing regimens. Dobard and colleagues reported on the success of a topical gel containing tenofovir or tenofovir/emtricitabine in protection against low-dose SHIV intravaginal challenge (Abstract 46). Gel was applied 30 minutes before challenge, twice weekly. Ten of 11 control animals were infected after a median of 4 challenges, but none of 6 animals receiving tenofovir gel and none of 6 animals receiving tenofovir/emtricabine gel became infected after 20 challenges. Systemic levels of the study drug were quite low, with absorption less than 0.03% of either drug.

Garcia-Lerma and colleagues reported on protection against rectal challenge with intermittent pre- and postexposure tenofovir/emtricitabine dosing (Abstract 47). In these experiments, animals were each given 2 oral doses of tenofovir/emtricitabine by gastric feeding tube at levels comparable to human dosing. Weekly rectal challenges used 10 50% tissue culture infectious doses of an R5-tropic SHIV strain to more closely mirror human exposures. Two groups of animals re-

ceived study drug 1 or 3 days before exposure followed by an additional dose 2 hours postexposure. These were the most successfully protected, with 5 of 6 animals protected in each of these 2 groups. Moderate protection was seen when the initial dose was earlier (7 days before) followed by the second dose 2 hours later (4/6 animals protected), or when dosing was given around the time of exposure (first dose 2 hours before or 2 hours after exposure) followed by a dose at 1 day postexposure (3/6 animals protected in each of these 2 groups). The authors stated the postexposure dose was needed to improve the protection seen in earlier experiments that used only a single preexposure dose. Protection did not seem to be associated with plasma drug levels or area under the curve, and no drug resistance was apparent in infected animals. The relevance of these animal models for predicting human efficacy is not yet known.

Treatment as Prevention

There has been substantial focus on the potential role that treating HIV-infected persons may play in reducing HIV transmission globally, including a recent publication suggesting that widespread roll-out of testing and treatment globally could substantially reduce new infections and provide cost savings within several decades.[8] Fraser focused on several questions related to the effect of HIV treatment on transmission (Abstract 14). The model used in the paper by Granich and colleagues[8] presumes a 99% reduction in transmission, although this effectiveness level has yet to be measured directly. In Fraser's models, lower levels of effectiveness would substantially diminish the effect of this approach, and levels of 80% would actually lead to a paradoxical increase in HIV transmission rates as HIV prevalence rises.

He also pointed out that HIV testing strategies may need to differ for different types of epidemics. For example, in generalized epidemics fueled by serial monogamy, almost all transmissions occur from persons with chronic HIV infection, so standard testing strategies would reach the appropriate populations. However, in subgroups of persons with numerous concurrent sexual partners, approximately one-third of new infections may come from persons with acute HIV infection, suggesting new strategies would be needed to reach and test these persons frequently using the appropriate diagnostic tests. Fraser called for more direct data to assess the impact of treatment on HIV transmission (such as data on serodiscordant couples, described below, and data from the HPTN 052 randomized controlled trial of the effect of treatment on transmission to uninfected partners). Fraser also encouraged more investigators to conduct mathematical models of the public health impact of various approaches to testing and treatment.

Two groups reported on HIV transmission rates in observational studies of serodiscordant heterosexual couples. Reynolds and colleagues (Abstract 52a) reported on data from 205 serodiscordant couples in Rakai, Uganda, observed from 2004 to 2007, 20 of whom initiated antiretroviral therapy. There were 34 transmissions in 396.4 couple-years of follow-up among couples not receiving antiretroviral therapy (incidence, 8.6/100 couple-years) versus no transmissions in the 24.6 couple-years of follow-up among treated couples. These are promising data, albeit on a relatively small group of serodiscordant couples.

Sullivan and colleagues reported on a larger group of serodiscordant couples from Lusaka, Zambia, and Kigali, Rwanda (Abstract 52bLB). In their study of 2993 serodiscordant couples, HIV incidence was 3.4 per 100 person-years among untreated couples and 0.7 per 100 person-years among treated couples, indicating a 79% reduction in transmission risk (95% CI, 41%–92%). Although they collected only limited behavioral risk data, there appeared to be a reduction in risk association with antiretroviral therapy, suggesting no behavioral disinhibition among treated couples. However, Smith and colleagues reported data on 1833 persons surveyed in a population-based, cross-sectional study in Kisumu, Kenya (Abstract 1017). Among this largely untreated sample, the belief that antiretroviral therapy cures HIV was associated with higher-risk sexual activity, particularly among younger participants, pointing to the need for broad education within communities, and not just directed at those receiving antiretroviral therapy.

Although these presentations point to the likely beneficial impact of treatment on risk of transmission to uninfected partners, 2 presentations focused on the potential for ongoing viral shedding in semen despite antiretroviral therapy. Sheth and colleagues used the branch DNA assay to measure virus levels in blood and semen (Abstract 50). Of 25 treatment-naive persons initiating antiretroviral therapy, suppression of virus in blood preceded suppression in semen. Overall, there was virus detectable in semen but not in blood at least once in 48% of study participants, with HIV RNA levels of 6600 copies/mL to 16,000 copies/mL in 3 of these 12 participants. All isolated virus was wild type. The investigators tested the individual with the highest semen viral load for infectivity in vitro and found this virus was infectious. They also found isolated semen shedding in 4 (31%) of 13 patients with long-term antiretroviral therapy suppression of plasma viremia (minimum, 4 years; median, 82 months). Marcelin and colleagues reported on 145 HIV-infected men seen in an assisted reproductive technology program (Abstract 51). In 264 paired semen and blood specimens tested using an in vitro nucleic acid amplification HIV-1 assay, 5% had low levels of seminal HIV RNA despite undetectable blood levels, most of whom were RNA positive at several time points.

A themed poster discussion session on genital tract HIV shedding in women confirmed the possibility of genital tract shedding in women receiving antiretroviral therapy, as well as factors associated with increased shedding (Session 11). Cu-Uvin and colleagues pointed out that in women switching antiretroviral therapy because of failed regimens, rebound may occur, but one-third of women with HIV RNA rebound had virus that was first detectable in the genital tract, rather than plasma (Abstract 973). Coleman and colleagues reported that cytomegalovirus and HSV-2 reactivation lead to increased HIV shedding among Kenyan women (Abstract 970). Graham and colleagues reported that genital tract shedding decreased by more than 2 $\log_{10}$ copies/swab

on average when 98 Kenyan women initiated antiretroviral therapy, although shedding continued to be detected in cervical samples from 33% of women and in vaginal fluid from 51% of women (Abstract 971). Poorer adherence and use of hormonal contraception with depot medroxyprogesterone acetate were associated with higher levels of genital tract shedding. Although there is no consensus on the quantitative or qualitative measures of genital tract HIV RNA levels that are likely to lead to HIV transmission events, these studies suggest that viral suppression in blood does not guarantee viral suppression in genital secretions.

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A list of all cited abstracts appears on pages 89-95.

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Cases on the Web

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HIV-Infection and International Travel: Pretravel Patient Assessment and Management

by Carlos Franco-Paredes, MD, MPH

Many HIV-infected persons live active lives that include business and leisure travel. Receiving a pretravel medical consultation is beneficial for all HIV-infected patients but crucial for those who are traveling to resource-limited regions of the world. This activity discusses how to determine HIV-related entry requirements at international travel destinations, surveys travel-related vaccinations and vaccine safety and efficacy issues specific to HIV-infected patients, and discusses prophylaxis for vector-borne diseases such as malaria and gastrointestinal infections.

Initial Evaluation of a Patient with a New HIV Diagnosis

by Michael Melia, MD, and Howard Libman, MD

More than 56,000 people receive an HIV diagnosis in the United States each year, and a substantial number present to primary care physicians for initial management. A systematic approach to the initial evaluation of patients with a recent HIV diagnosis should be adopted owing to the numerous and potentially complex issues that can affect care. This case will help learners identify relevant aspects of the medical history of those with a new HIV diagnosis, select diagnostic and screening tests that should be part of an initial evaluation, plan for antimicrobial prophylaxis for opportunistic infections, and determine necessary and contraindicated immunizations in this population.

Management of Cryptococcal Meningitis in the Antiretroviral Therapy Era: More than Just Antifungals

by Anuradha Ganesan, MD, and Henry Masur, MD

In many urban areas, one-third of patients presenting with an initial HIV diagnosis have CD4+ counts below 200 cells/µL, and many such patients present with opportunistic infections. This case reviews the epidemiology and major clinical manifestations of cryptococcal infections in HIV-infected patients and discusses an approach to the diagnosis of such infections. Learners will identify preferred treatment strategies for cryptococcal infections using amphotericin B, flucytosine, and azole antifungal drugs, review risk factors for immune reconstitution inflammatory syndrome (IRIS), and distinguish *Cryptococcus*-related IRIS from active cryptococcal infection.

Immune Reconstitution Inflammatory Syndrome in HIV-Infected Patients: Diagnostic and Management Challenges

by Jaime C. Robertson, MD, and Carl J. Fichtenbaum, MD

Despite the increase in the number of CD4+ lymphocytes and partial recovery of immune responses from starting antiretroviral therapy, some patients experience a clinical deterioration that is believed to be related to the restored ability of the immune system to mount an inflammatory response. This activity provides a comprehensive focus on the diagnosis and management of IRIS as a complication of antiretroviral therapy. Learners will identify the clinical criteria for the diagnosis of IRIS, examine considerations for starting antiretroviral therapy in HIV-infected patients with opportunistic infections, and identify approaches to managing patients with IRIS.

Issues in the Care of HIV and Hepatitis C Virus–Coinfected Patients: Antiretroviral Pharmacokinetics, Drug Interactions, and Liver Transplantation

by David L. Wyles, MD

An understanding of the sequelae of chronic hepatitis C virus (HCV) coinfection, such as antiretroviral drug intolerance and decompensated liver disease, is vital to the optimal management of coinfected patients. This presentation explains the impact of hepatic dysfunction on antiretroviral pharmacokinetics and the effect of antiretroviral therapy on the natural history of HCV infection. Learners will also identify unique issues in liver transplantation for end-stage liver disease resulting from HCV coinfection.

Managing Oral Health Problems in People with HIV Infection

by David A. Reznik, DDS

Late diagnosis of HIV is common, and a substantial portion of new patients with HIV infection receive an AIDS diagnosis. Such patients are more likely to present with oral diseases that are associated with HIV disease progression. This activity discusses common oral lesions that HIV practitioners can address in the absence of a dental health care professional. On completing this activity, learners will be able to explain the association between necrotizing ulcerative periodontitis and advanced HIV disease, discuss the role of biopsy for oral hairy leukoplakia, and differentiate and explain how to manage the 2 most common presentations of oral ulcers in HIV-infected patients.

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Neurologic Complications of HIV Disease and Their Treatment

Scott L. Letendre, MD, Ronald J. Ellis, MD, PhD, Ian Everall, MB, ChB, PhD, Beau Ances, MD, Ajay Bharti, MD, and J. Allen McCutchan, MD, MSc

Substantial work on the peripheral and central nervous system complications of HIV was presented at the 16th Conference on Retroviruses and Opportunistic Infections. Six studies of more than 4500 volunteers identified that distal sensory polyneuropathy remains common, ranging from 19% to 66%, with variation based on disease stage, type of antiretroviral therapy, age, and height. Eight studies of more than 2500 volunteers identified that neurocognitive disorders are also common, ranging from 25% to 69%, with variation based on stage of disease, antiretroviral use, diabetes mellitus, and coinfection with hepatitis viruses. Therapy-focused studies identified that resistance testing of cerebrospinal fluid (CSF)-derived HIV may improve management of people with HIV-associated neurologic complications, that poorly penetrating antiretroviral therapy is associated with persistent low-level HIV RNA in CSF, and that efavirenz concentrations in CSF are low but in the therapeutic range in most individuals. Neuroimaging reports identified that people living with HIV had abnormal findings on magnetic resonance imaging (gray matter atrophy, abnormal white matter), magnetic resonance spectroscopy (lower neuronal metabolites), and blood-oxygen-level dependent functional magnetic resonance imaging (lower cerebral blood flow). Other important findings on the basic neuroscience of HIV and diagnosis and management of neurologic opportunistic infections are discussed.

HIV-Associated Peripheral Neuropathy

Neuropathy Remains Common

Changes in the epidemic may affect the occurrence and severity of distal sensory polyneuropathy (DSPN) in people living with HIV or AIDS. Many of the potentially influential changes link to the use of combination antiretroviral therapy, including the substantial immune recovery that can occur, the advancing age of people whose survival has been extended by antiretroviral therapy, and declines in the use of neurotoxic nucleoside analogue reverse transcriptase inhibitors (nRTIs) (eg, the dideoxynucleoside analogues, stavudine and didanosine, sometimes referred to as "d-drugs"). Two complementary posters evaluated the changes in several putative risk factors for DSPN and their impact on its diagnosis and severity.

Ellis and colleagues reported on findings in the CHARTER (Central Nervous System [CNS] HIV Antiretroviral Therapy Effects Research) cohort, comprising 1539 HIV-infected individuals who enrolled in a prospective, observational study at 6 US sites (Abstract 461). DSPN was defined as having at least 1 clinical sign in a symmetric, bilateral pattern on neurologic examination; signs included diminished distal vibratory and pin sensation and reduced ankle reflexes. Correlates of DSPN and neuropathic pain evaluated in univariate and multivariate analyses were age, antiretroviral therapy and d-drug use, HIV disease markers (plasma viral load, the lowest CD4+ cell count [the lowest reported or measured "CD4+ nadir"], and extent of immune recovery [estimated by the difference between the current and nadir CD4+ cell counts]), hepatitis C virus (HCV) serostatus, substance use disorders (alcohol, opiates), and recent nonprescription opiate use. Pain and its effect on quality of life were assessed using the Medical Outcomes Survey for HIV (MOS-HIV). Fifty-seven percent of the patients had at least 1 abnormal clinical sign of DSPN, and 28% had 2 or more signs. Of those with at least 1 sign, 335 (38%) reported neuropathic pain, which was statistically significantly associated with reduced quality of life as measured by the MOS-HIV. Statistically significant risk factors for objective evidence of DSPN in multivariate analyses were older age, lower CD4+ nadir, current antiretroviral therapy use, past d-drug use, and a history of opiate abuse or dependence. Subjective neuropathic pain was predicted by prior d-drug use and lower CD4+ nadir.

The CHARTER study's findings on the burden of DSPN in a cohort of mostly antiretroviral-experienced individuals were complemented by an analysis from the ALLRT (AIDS Clinical Trials Group [ACTG] Longitudinal Linked Randomized Trials) cohort. Evans and colleagues studied 2135 antiretroviral-naive participants observed longitudinally for up to 7 years (Abstract 462). All volunteers initiated a new antiretroviral regimen, and approximately 90% of them had achieved undetectable viral loads after 48 weeks of therapy. Thirty percent of participants had at least 1 abnormal neuropathy sign on clinical examination at week 48. The frequency of abnormal signs increased to 41% among those who were observed for 8 years, even though d-drug use declined during

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the period of observation. Importantly, concurrent rates of symptomatic DSPN were 3% and 5%, indicating that most DSPN in this study was asymptomatic. Statistically significant risk factors for DSPN in multivariate models were older age, d-drug use during the period of observation, higher pretreatment viral loads in plasma, and lower pretreatment CD4+ cell counts in blood.

These 2 studies assessed 2 large and distinct cohorts, but their findings were consistent: DSPN remains common and is associated with older age and d-drug use. The consistent, strong association of DSPN with more advanced immunosuppression, even among those with successful virologic suppression from antiretroviral therapy, suggests that earlier introduction of antiretroviral therapy may protect patients from neuropathic disability and improve quality of life. As more effective and less toxic therapies are developed, this goal becomes increasingly achievable.

Other Risk Factors for Neuropathy

Recent Conferences on Retroviruses and Opportunistic Infections have included reports on genetic susceptibility factors for the neurologic complications of HIV disease. Prominent among these factors have been polymorphisms that increase the likelihood of developing painful neuropathy with the use of neurotoxic d-drugs. In light of the continuing use of stavudine and didanosine in resource-limited settings, such polymorphisms may be particularly important in sub-Saharan Africa, India, China, and elsewhere. Canter and colleagues approached this issue by performing a subanalysis of genetic risk factors for symptomatic neuropathy in non-Hispanic black participants exposed to zidovudine/lamivudine or stavudine/didanosine in clinical trial ACTG 384 (Abstract 160). These investigators sequenced the coding region of each participant's mitochondrial DNA and determined subhaplogroups based on published algorithms. Peripheral neuropathy was more likely to develop in individuals with African subhaplogroup L1c (9/16 patients, or 56%) than in those with other subhaplogroups (42/140 patients, or 30%; P = .048). In multivariate analyses, older age, randomization to the stavudine/didanosine group, and subhaplogroup L1c were each predictors for incident, symptomatic DSPN, even after adjustment for sex, pretreatment CD4+ cell count and HIV RNA level, and randomization to nelfinavir.

DSPN occurs more commonly in the legs than the arms, and one explanation for this is that longer nerves are more susceptible to injury. Because of this, DSPN may develop more frequently in taller patients than in shorter ones. Cherry and colleagues tested this hypothesis by examining the association between neuropathy risk and several simple clinical indicators, including height (Abstract 161). In a mixed cohort of 100 Australians, 98 Malaysians, and 96 Indonesians receiving antiretroviral therapy who did not have DSPN at baseline, the investigators screened for new-onset DSPN. In addition to stavudine exposure, taller height and older age were independently associated with the risk of incident DSPN. The DSPN risk increased from 20% in younger, shorter patients to 33% in younger, taller patients, 38% in older, shorter patients, and 66% in those older than 40 years and taller than 170 cm who received stavudine. These data suggest that older, taller patients may be prioritized to receive nonstavudine-containing antiretroviral regimens in resource-limited settings.

The metabolic syndrome includes hyperlipidemia, insulin resistance, hypertension, and inflammation and has been linked to the vascular disease that can occur with aging. HIV infection and antiretroviral therapy each appear to increase the risk of metabolic syndrome. Because components of the metabolic syndrome are known to also increase the risk of polyneuropathy, some investigators have speculated that the metabolic syndrome may be among the factors leading to persistent DSPN in individuals treated with antiretroviral therapy.

Ances and colleagues evaluated this possibility in a subgroup of 130 patients from the CHARTER cohort who had fasting measurements of blood levels of glucose and triglycerides (Abstract 463). For these analyses, the metabolic syndrome was defined as having 3 or more of the following 5 risk factors: (1) high body mass index (BMI > 30 kg/m^2), (2) hypertriglyceridemia (≥ 150 mg/dL), (3) low concentration of high-density lipoprotein (HDL) cholesterol (< 40 mg/dL for men and < 50 mg/dL for women), (4) hypertension (systolic ≥ 130 mm Hg, diastolic ≥ 85 mm Hg) or use of antihypertensive medication, (5) hyperglycemia (≥ 110 mg/dL) or use of antidiabetic medication. Although almost one-third of participants met criteria for the metabolic syndrome and more than half had DSPN, the 2 disorders were not associated. Among the metabolic syndrome components, only hypertriglyceridemia was associated with DSPN. In a separate analysis of the larger cohort, diabetes mellitus, although uncommon, was associated with an increased frequency of DSPN.

The role of HCV infection in neuropathy has been a matter of controversy for several years. Cherry and colleagues took advantage of unique cohorts comprising a total of 503 patients of diverse ethnic backgrounds in Melbourne, Australia; Jakarta, Indonesia; Kuala Lumpur, Malaysia; and Baltimore, Maryland, who had HCV seroprevalences ranging from 10% to 61% (Abstract 466). When results of all cohorts were combined, no association was found between HCV serostatus and symptomatic DSPN (P = .8). In fact, HCV infection was associated with a slightly reduced risk of DSPN at the Melbourne site. Adjusting for exposure to neurotoxic d-drugs did not alter these findings. Notably, in the CHARTER cohort, DSPN was more prevalent among HCV-seropositive individuals, but this relationship was not statistically significant in a multivariate model. Taken together, the findings of these studies suggest that HCV infection is not a major risk factor for DSPN in coinfected individuals. Table 1 summarizes the major findings of this group of abstracts.

Treatment of Neuropathy

Existing treatments for painful neuropathy are only symptomatic, and inves-

tigators have long sought treatments that would enhance peripheral nerve regeneration and restore function, in addition to relieving pain. The type of DSPN that is linked to the neurotoxicity of d-drugs—as opposed to the DSPN that occurs in people living with HIV who have never taken d-drugs—probably results from mitochondrial "poisoning." Although the use of d-drugs has declined in North America and Europe because of the availability of alternatives, they are still widely prescribed in resource-limited settings because low-cost generic versions are available.

Cherry and colleagues reported on a neuroprotective treatment for d-drug-associated DSPN, coenzyme Q10 (CoQ10; ubiquinone) (Abstract 447). CoQ10 is a component of the electron transport chain in mitochondria and participates in aerobic cellular respiration, which generates the vast majority of the body's energy in the form of adenosine triphosphate. These investigators studied an in vitro model of d-drug neurotoxicity using fetal rat dorsal root ganglia exposed to d-drugs with or without CoQ10 in a novel water-soluble formulation. Neurite growth was relatively preserved in the CoQ10-treated samples, despite the presence of d-drug. Furthermore, CoQ10 did not interfere with the antiviral activity of d-drugs. Although CoQ10 is currently too expensive for widespread use in resource-limited settings, these data support continued investigation of CoQ10 and related compounds as a potential management strategy for patients with possible nRTI-induced neuropathy.

One proposed mechanism of neurotoxicity causing DSPN in HIV infection is abnormal activation by the virus of CC chemokine receptor 5 (CCR5) receptors on sensory neurons, triggering apoptotic cellular pathways. Yeh and colleagues considered whether treatment with the investigational CCR5 antagonist vicriviroc might result in reduced frequency of DSPN or improvement in signs or symptoms in those with DSPN (Abstract 486). They studied 118 antiretroviral therapy–experienced patients with advanced HIV disease, 90 of whom underwent randomization to receive 1 of 3 dose levels of vicriviroc plus background antiretroviral therapy and 28 of whom underwent randomization to receive placebo plus background antiretroviral therapy. Approximately two-thirds of each group had abnormal signs of neuropathy; many were symptomatic. After 24 weeks of treatment, there was no difference in the prevalence of DSPN or symptomatic neuropathy in any of the treatment groups. The authors caution, though, that the relatively small numbers of enrolled subjects limited the study's power to demonstrate an effect on DSPN.

Basic Neuroscience of HIV

Basic neuroscience abstracts fell into 5 broad thematic categories that reflect growing trends in the field. The first and largest group encompassed the theme of neuroprotection. Ensuring adequate protection of the brain from the deleterious effects of HIV has become an important focus of investigational treatments, especially as modern cohort studies demonstrate that many individuals living with HIV have mild to moderate cognitive impairment despite good virologic responses to antiretroviral therapy.

Table **1.** Summary of Studies Evaluating HIV-Associated Distal Sensory Polyneuropathy (DSPN)

Abstract No. Authors	Location	Sample Size	Prevalence	Correlates
Abstract 461 Ellis et al	United States	1539	57% ≥ 1 sign 28% ≥ 2 signs 38% symptomatic	Older age, lower CD4+ nadir, history of d-drug use, current antiretroviral therapy use, history of opiate use
Abstract 462 Evans et al	United States	2135	30% ≥ 1 sign at 48 weeks 41% ≥ 1 sign at 8 years 5% symptomatic	Older age, history of d-drug use, higher pre–antiretroviral therapy plasma viral load, lower pre–antiretroviral therapy CD4+ count
Abstract 160 Canter et al	United States	230	Up to 56% DSPN	Mitochondrial haplogroup, older age, d-drug use
Abstract 161 Cherry et al	Australia, Indonesia, Malaysia	37	Up to 66% DSPN	Taller height, older age, d-drug use
Abstract 463 Ances et al	United States	130	55% DSPN	Fasting hypertriglyceridemia, diabetes mellitus
Abstract 466 Cherry et al	Australia, Indonesia, Malaysia, United States	503	Up to 62% DSPN	Varied by site (Kuala Lumpur, 19%; Baltimore, 62%), not hepatitis C virus infection

D-drug indicates the dideoxynucleoside analogue–containing drugs stavudine and didanosine.

A number of researchers are investigating protection of the brain in the presence of low-grade HIV replication and immune responses in the brain. For instance, Zhang and colleagues reported on a research collaboration between the University of Massachusetts and Bristol-Myers Squibb, identifying that HIV attachment inhibitors prevented neuronal viral Env-mediated toxicity in neuronally differentiated SH-SY5Y and B2-M17 cell lines, whereas CCR5 inhibitors did not display the same neuroprotection (Abstract 448). The investigators used a variety of virus particles (including Env from a patient with HIV-associated dementia [HAD], and particles deficient in *pol*, reverse transcriptase, *vif*, and *vpr*) and identified reduced apoptosis with the inhibitors, although only 1 marker, annexin V staining, was used. These promising findings should be confirmed with other apoptosis markers and performed in primary human neuronal tissue culture and an animal model.

The second theme was the role of the immune system in neurodegeneration. Zhu and colleagues have continued their work on the consequences of cleavage of stromal cell-derived factor 1α (SDF-1α, also called CXC chemokine ligand 12 [CXCL12]) into a neurotoxic peptide that binds CXC chemokine receptor R3 (CXCR3) (Abstract 449). They noted that CXCR3 was upregulated in neurons in HIV or feline immunodeficiency virus (FIV) disease, which was accompanied by suppression of autophagy, reduced neuronal viability, and neurobehavioral abnormalities. Interestingly, the investigators noted that didanosine may have neuroprotective properties independent of its effects on HIV replication because it seemed to prevent activation of CXCR3 and its consequent inhibition of autophagy.

Maingat and colleagues assessed the impact of the systemic immune response on neurodegeneration by exposing specific pathogen-free cats infected with a neurovirulent strain of FIV to repeated lipopolysaccharide (LPS) exposure (Abstract 457). LPS activates the innate immune system, and repeated LPS administration can induce tolerance or nonactivation of this immune response. The investigators found that repeated LPS administration reduced CD3+ cell infiltration into the brain and improved neurobehavioral performance. The importance of this observation is that selective modulation of the systemic innate immune system could affect cognition. In a similar vein, Yao and colleagues investigated the neuroprotective properties of CC chemokine ligand 2 (CCL2; also called monocyte chemotactic protein-1, [MCP-1]), which they demonstrated involved activation of the kinase Akt and nuclear factor κB (Akt/NF-κB) pathway (Abstract 451). This is in keeping with other work demonstrating that HIV neuroprotection is mediated via activation of Akt.

The third theme focused on HIV virology in the nervous system. Schnell and colleagues reported their cross-sectional and longitudinal analyses using single genome amplification of cerebrospinal fluid (CSF)- and blood-derived HIV, expanding their prior work that identified that the degree of compartmentalization was associated with neurocognitive impairment (Abstract 158).[1] In the reported analysis, 4 volunteers who had no neurocognitive symptoms had mixing of *env* sequences between CSF and blood, although some similar sequences tended to cluster in 1 compartment or the other. Eight volunteers with HAD, the severe form of HIV-associated neurocognitive disorder (HAND), had much more distinct partitioning between CSF and blood sequences, consistent with prior reports.[2-4] In volunteers with advanced immunosuppression, CSF-derived sequences appeared to be more closely related to each other than were blood-derived sequences, indicating amplification from a smaller number of clones in the nervous system.

The study's particularly provocative findings were based on changes in sequences over time preceding incident HAD, identifying that CSF-derived HIV sequences from up to 2 years before the diagnosis of HAD were present when HAD was diagnosed, consistent with restricted evolution of HIV in the CNS. When combined with their findings that some sequences in blood appeared to derive from CSF, these findings raise the possibility that "signature" sequences for HAD may be detectable in blood before the onset of HAD. If so, this could provide a valuable clinical tool for making a diagnosis in individuals who might be at risk of virus-driven HAND (as opposed to host-driven HAND).

Pasutti and colleagues provided additional evidence of limited expression of HIV in the brain by comparing genetic diversity of HIV DNA and RNA from the brains and spleens of 9 people who died with HIV or AIDS (Abstract 159). C2-V3 sequences were compartmentalized in all subjects and, within the brain, DNA and RNA sequences were phylogenetically distinct in most (8 of 9) cases. DNA diversity in brain was greater than RNA diversity in brain, and the genetic distances from the most recent common ancestor were shorter for brain-derived sequences than for spleen-derived sequences. Together, these data support the idea that only a subset of the viruses that infect the CNS are expressed, possibly reflecting CNS-specific constraints on viral fitness.[5-7]

The fourth theme was other mechanisms of HIV-associated neurotoxicity. Kandanearatchi and colleagues presented continuing work on the role of the kynurenine pathway, which involves the production of the excitotoxin quinolinic acid (Abstract 454). The current work identifies that quinolinic acid results in up-regulation of CCR5 expression, which can increase susceptibility to HIV infection, lead to damage of neuronal and glial cells, and is independent of the damage proposed to occur by quinolinic acid at *N*-methyl-D-aspartate (NMDA) receptors. Yang and colleagues presented work on NMDA receptor-mediated excitotoxicity, identifying that soluble factors produced by macrophages were associated with activation of extrasynaptic NMDA receptors with resultant neuronal injury (Abstract 453).

The fifth theme was new models for HIV-associated neurotoxicity. Pardo and colleagues reported work with adult human organotypic cerebral cortex cultures (Abstract 446). This

culture model is as close to the clinical in vivo situation as yet obtained. One important, potential drawback is that the tissue is obtained from surgical lobectomies, which are typically performed because of antiepileptic drug-resistant pathology in the temporal lobe. The nature of the underlying pathology raises concerns regarding its impact on the function of the tissue in culture. Gorantla and colleagues refined an existing mouse model using HIV-infected NOD/*scid*-IL-2Rg^{null} mice with human hematopoietic CD34+ stem cells (Abstract 456). This mouse model manifested hallmarks of human HIV-associated central nervous system disease, and the authors proposed that it would be useful to model virologic, immunologic, and pathologic manifestations of HIV disease.

HIV-Associated Neurocognitive Disorders

The widespread use of antiretroviral therapy has led to a decline in the more severe neurologic complications of HIV, such as HAD, but people living with HIV continue to experience mild and moderately severe forms of nervous system disease. The updated definition of HAND has helped standardize reports from different regions of the world. This diagnostic approach defines asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND) as impairment in cognitive functioning that involves at least 2 domains and is documented by performance that is at least 1.0 standard deviation below the mean for age-education-appropriate normative values on standardized neuropsychologic tests.[8] MND and ANI are distinguished by their impact on everyday functioning, with impairment occurring in MND but not in ANI. Implicit in the definition is the requirement to test or observe at least 5 cognitive domains through comprehensive testing using standardized neuropsychologic tests.

Heaton and colleagues reported many of the primary findings of the CHARTER cohort (Abstract 154). The 1555 volunteers in this observational study were mostly middle-aged (mean, 43 years), nonwhite (61%) men (77%) who had received a diagnosis of AIDS (63%) by CD4+ counts below 200 cells/µL. The mean CD4+ count at the time of assessment was 420 cells/µL, with 83% of values above 200 cells/µL. Consistent with this, a substantial majority (71%) was taking antiretroviral therapy, whereas about half of the remainder (14%) had discontinued antiretroviral therapy and the rest had never taken it (15%). Even though most subjects were taking effective antiretroviral therapy and had substantial immune recovery, a majority (53%) had impaired neuropsychologic performance compared with healthy controls. Among those who had impaired global performance, more than half performed poorly on tasks of learning, executive functioning, recall, and working memory.

Compared with the report on the University of California San Diego HIV Neurobehavioral Research Center cohort in 1995,[9] the proportion of impaired individuals among those who had US Centers for Disease Control and Prevention (CDC) stage C disease had declined, but the proportions of impaired individuals among those with CDC stages A or B disease had remained stable or increased. Following the updated nosology guidelines, the investigators carefully assessed comorbid conditions, such as history of severe head injury, severe or intractable epilepsy or psychiatric disease, and severe or ongoing substance use disorders, and they categorized volunteers into those who seemed to be affected or unaffected by these conditions. The majority (84%) did not seem to be severely affected by these comorbidities and, in this group, 47% still met criteria for neurocognitive impairment (compared with 84% of the remaining 238 whose performance was affected by these conditions). Neurocognitive impairment was associated with lower nadir CD4+ cell counts, detectable HIV RNA levels in blood, and the use of antiretroviral therapy. In particular, volunteers whose CD4+ counts had never dropped below 200 cells/µL and who currently had HIV RNA levels in blood below 50 copies/mL performed better than other volunteers, strongly arguing that earlier, effective antiretroviral therapy prevents or treats HAND.

Important and confirmatory findings of the impact of HIV on the brain were reported from other countries. In an analysis of data from 107 volunteers of the French Neuradapt cohort, Vassallo and colleagues reported that 25% of participants were diagnosed with HAND (ANI, 11%; MND, 10%; HAD, 4%), which requires impairment in at least 2 cognitive abilities, and an additional 44% had impairment in 1 cognitive domain, even though most volunteers in this study were antiretroviral therapy–treated (86%), middle-aged (mean, 44 years) men (77%) who did not have HCV coinfection (78%) (Abstract 464). Most were successfully treated, with viral loads in blood that were below 40 copies/mL and a mean CD4+ count of 527 cells/µL. Univariate analyses identified associations between any neurocognitive impairment and HCV seropositivity or antidepressants (used by 8% of the cohort). Multivariate analysis identified that HCV coinfection was the only independent risk factor for abnormal neuropsychologic performance.

Another analysis from France identified links between cognitive impairment and hepatitis B virus (HBV) coinfection instead of HCV coinfection (Abstract 474). Bonnet and colleagues assessed 230 volunteers who had similar demographic and disease characteristics to the other cohorts detailed above and were enrolled in the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) CO3 Aquitaine cohort. This analysis focused on the diagnosis of MND, identifying the condition in 24% of the cohort, which is substantially higher than the prevalence identified in the CHARTER cohort (10%). This difference is important because MND is, by definition, associated with impaired daily functioning. In a multivariate analysis, MND was associated with older age (10% increased odds for each year), AIDS (2.4-fold increased odds), and HBV surface antigenemia (4.0-fold increased odds) as well as lower levels of education and current unemployment.

The difference between the impact of HCV and HBV in these analyses from

Nice and Bordeaux raises important points. First, even though HCV can infect glial cells, the primary target cells of each virus are hepatocytes. Therefore, the consolidating explanation for the observed difference in the findings is that these viruses primarily injure the brain via their impact on the liver (eg, via subclinical hepatic encephalopathy) or perhaps via persistent immune activation. Second, even though many comorbid conditions can injure the brain, the ones that impact a particular population are strongly determined by the prevalence of those conditions in the local population. In the United States, where active HBV disease is uncommon relative to high-prevalence regions of the world, the impact of HBV coinfection on neuropsychologic performance in population analyses is negligible. In other regions where active HBV disease is more common, it may be a more influential determinant of clinically apparent brain injury.

The link identified between older age and worse neuropsychologic performance confirms prior observations.[10] Because antiretroviral therapy has improved survival, an expanding population has lived with the disease for many years. As this group reaches their 40s and 50s, their risk of cognitive impairment may be substantially higher than for people who do not have HIV. Candidate mechanisms that might affect the aging, HIV-infected brain include accelerated neurodegeneration of the type that can occur with normal aging, disorders of amyloid (similar to Alzheimer's disease), or vascular injury that can occur with metabolic disorders such as insulin resistance and dyslipidemias.

Dulioust and colleagues presented the results of a neurologic substudy of the Sigma cohort, which cross-sectionally assessed 37 antiretroviral therapy–treated individuals who were 60 years of age or older (Abstract 459). Most (36/37 patients) had suppressed HIV RNA levels in blood below 50 copies/mL with antiretroviral therapy, had a median nadir CD4+ count of 113 cells/μL, and had substantial immune recovery (median current CD4+ count, 522 cells/μL). Brief neuropsychologic testing identified that more than half (19/37 patients, 51%) of the older individuals in this study were impaired and that the pattern of impairment was subcortical and typical of HAND. A substantial proportion of participants also had cardiovascular risk factors (25/37 patients, 68%) such as hypertension and dyslipidemia, but they were not more likely to have impaired neuropsychologic performance.

The role of metabolic abnormalities, such as dyslipidemia or insulin resistance, was also examined in a substudy of CHARTER that was presented by McCutchan and colleagues (Abstract 458). Measurements of fasting glucose, insulin, and lipid levels were added to the comprehensive CHARTER assessments in 145 volunteers. Forty-five individuals (31%) in this subgroup had HAND, and these individuals also had higher body mass indices (27 vs 25, respectively; $P = .07$), lower HDL-cholesterol levels (43 vs 50 mg/dL, respectively; $P < .05$), higher triglyceride levels (184 vs 136 mg/dL, respectively; $P < .05$), and a greater prevalence of type II diabetes mellitus (17% vs 4%, respectively; $P < .05$), but not higher levels of fasting glucose, insulin, or a measure of insulin resistance (homeostasis model assessment for insulin resistance). Multivariate analysis identified that only diabetes mellitus was associated with worse neuropsychologic performance (odds ratio [OR] = 7.6; $P < .01$). One explanation for why this finding may differ from those of Dulioust and colleagues is that the Sigma group did not include individuals who had diabetes mellitus.

In addition to comorbid conditions, like infection with HCV or HBV, and host factors, like aging and metabolic disorders, the impact of HIV disease on the brain can be influenced by viral factors. Abstracts from prior Conferences on Retroviruses and Opportunistic Infections have identified specific mutations that are present in the brains of people dying with HAD and that these mutations can be associated with reduced dependence on CD4 for cell entry. Other investigators have found in vitro evidence that the subtypes of HIV may differ in their impact on the brain. This work has focused primarily on subtype C, but data presented at this year's conference focused on subtype F.

Romania has a unique population of young adults who were parenterally infected with subtype F HIV as infants and have been living for approximately 2 decades. Duiculescu and colleagues evaluated volunteers from this population who received care in Bucharest (Abstract 477). In a retrospective analysis of the 110 children (76 boys, 34 girls) with a mean age of 11.1 years at the beginning of the follow-up, HIV encephalopathy (HIVE) accounted for 20% of AIDS-defining illnesses before the availability of combination antiretroviral therapy and 18.8% afterward ($P > .10$).

HIV RNA levels measured in CSF from 19 children with HIVE were higher than those who did not have neurologic disorders ($P < .05$). In fact, HIV RNA levels in CSF were higher than those in blood in 12 of the 19 children with HIVE. Computerized tomography revealed that brain atrophy was the most frequent finding (84%), and magnetic resonance imaging (MRI) revealed white matter lesions in two-thirds. In a prospective evaluation of a subgroup of 43 young adults, 26 (60%) received a diagnosis of HAND: 16 (37%) had mild impairment, 4 (9%) had moderate impairment, and 6 (14%) were severely impaired. These data demonstrate the high prevalence of HAND in this unique Romanian cohort and do not support that the neurovirulence of subtype F HIV differs from that of subtype B.

Two studies reported on data from continents other than North America and Europe. Robertson and colleagues used a brief neuropsychologic testing battery and medical examination to determine the prevalence of HAND in volunteers in ACTG 5199 from countries within Africa (Malawi, Zimbabwe), Asia (India, Thailand), and South America (Brazil, Peru) (Abstract 485). They identified that 29% had at least 1 neurologic abnormality, including 6% with MND, 1% with HAD, 10% with "diffuse CNS disease," and 6% with "focal CNS disease."

Ruel and colleagues evaluated neurocognitive function in African children, a group that has been understudied in recent years (Abstract 920). The

investigators evaluated 96 HIV-infected and 122 HIV-uninfected children from Kampala, Uganda, who were aged 3 years to 12 years and enrolled in the CHAMP (Children with HIV and Malaria Project). All HIV-seropositive children had CD4+ counts that exceeded 250 cells/μL (median, 714 cells/μL) and 15% (median, 26%), with a median HIV RNA level of 52,500 copies/mL in blood.

Despite this relatively early disease, HIV-infected children who were between 3 years and 5 years old performed worse than HIV-uninfected children in 3 of 5 measures in the Mullen Early Learning Scales, an indication of developmental delay. Older HIV-seropositive children (6-12 years) also performed worse in 14 of 15 measures in the Kaufman Assessment Battery for Children-2 and in all 8 measures in the Bruininks and Oseretsky Test of Motor Proficiency-2. Worse performance was associated with higher HIV RNA levels in blood but not CD4+ counts. Although malaria is a focus of the research, this particular analysis did not address the impact of asymptomatic or minimally symptomatic malaria on performance.

The study has important implications because, as the investigators indicate, few clinics have the resources to assess children for developmental delay and, in the absence of testing, the children in this study would not be eligible to receive antiretroviral therapy based on current World Health Organization guidelines. Because HAND is not always completely reversible in adults, these findings argue for testing and early treatment of HIV-infected children with developmental delay or cognitive impairment.

From the US National NeuroAIDS Tissue Consortium, Everall and colleagues reported on the pathologic findings from brain tissue of 589 people who had died with HIV or AIDS (Abstract 155). One hundred nine (17%) cases exhibited evidence of typical HIV-related brain pathology (HBP; HIV encephalitis, HIV leukoencephalopathy, or microglial nodules). HBP was not more common when typical opportunistic conditions (eg, cryptococcal meningitis, toxoplasmic encephalitis) were present (19% of cases), with the exception of cerebral lymphoma, which occurred in 10% of cases that had HBP compared with 4% of cases without HBP ($P = .026$).

Even though most brains did not have typical HBP, most (78%) were not normal. One hundred fifteen (20%) had evidence of a noninfectious pathology, and another 69 (12%) had minimal abnormalities that were not typical for another diagnosis. Volunteers who died with evidence of HBP were less likely to be taking antiretroviral therapy before death and had lower nadir CD4+ counts and higher HIV RNA levels in blood before death. Substantial proportions of individuals had HAND (88%) or major depressive disorder (60%) during their lives, but neither condition was associated with typical HBP. Instead, HAND, particularly HAD, was associated with type II Alzheimer gliosis ($P = .027$). Overall, these findings indicate that the prevalence of HBP has remained stable or decreased since the widespread use of combination antiretroviral therapy but, despite this, other forms of brain pathology were common and few people died with normal-appearing brains. Table 2 summarizes the major findings of this group of abstracts.

Fatigue is a common symptom reported by HIV-infected individuals. Schifitto and colleagues found that 64% of participants of ACTG 5090 reported fatigue (Abstract 479). They found no statistically significant differences between fatigued and nonfatigued participants with regard to HIV RNA level in CSF or blood, CD4+ count, or performance on neuropsychologic tests. A subset of participants (n = 44) underwent magnetic resonance spectroscopy (MRS) imaging, identifying lower levels of the cellular energy marker creatine in the basal ganglia of fatigued participants. Based on these findings, alterations in energy metabolism in the brain may be responsible for the fatigue that afflicts a large proportion of people living with HIV.

Antiretroviral Therapy and the Nervous System

Penetration of antiretroviral drugs into the nervous system has been an important focus of research in recent years, identifying that drugs that better penetrate into the CNS result in greater reductions of HIV RNA levels in CSF and greater improvements in neuropsychologic performance. Such research is limited by the inability to directly measure antiretroviral concentrations in brain tissue in humans and by the absence of pharmacokinetic data in CSF for many antiretroviral drugs. Direct measurement of antiretroviral drug concentrations in brain tissue may best be accomplished in animal studies, but human studies reported at the conference extended work in the field by measuring drug concentrations in CSF and improving current assessment tools.

In a substudy of CHARTER, Best and colleagues measured efavirenz and emtricitabine concentrations in CSF (Abstract 702). Efavirenz concentrations have been measured previously in CSF,[11,12] but the results were inconsistent, with 1 study finding low levels of efavirenz in CSF and the other finding none. Best and colleagues initially found efavirenz to be undetectable in CSF also but used an extraction method (with methyl *tert*-butyl ether) to lower the sensitivity of the assay by an order of magnitude. Once they did so, they found that efavirenz concentrations were 0.5% of those in blood and exceeded the median inhibitory concentration in most of the 80 CSF specimens assayed. Emtricitabine was much easier to detect in CSF (43% of the concentration in blood) and exceeded the median inhibitory concentration in all 21 CSF specimens assayed. These results may explain the inconsistency in the published findings on efavirenz concentrations in CSF (ie, additional steps are necessary in the laboratory to measure the low concentrations of efavirenz present in CSF) and identify that emtricitabine may be an excellent choice for controlling HIV in the nervous system.

In another substudy of CHARTER, Letendre and colleagues used a modified version of a commercial nucleic acid sequence-based amplification assay to more sensitively measure HIV RNA levels in CSF from 300 individuals whose

Table 2. Summary of Studies Evaluating HIV-Associated Neurocognitive Disorders (HAND) and other Central Nervous System Disorders

Abstract No. Authors	Location	Sample Size	Prevalence	Correlates
Abstract 154 Heaton et al	United States	1555	53% global neuropsychologic impairment	Lower nadir CD4+ counts, detectable HIV RNA in blood, current antiretroviral therapy use
Abstract 464 Vassallo et al	France	107	69% HAND or neuropsychologic deficit	Hepatitis C virus coinfection
Abstract 474 Bonnet et al	France	230	25% mild neurocognitive disorder	Older age, AIDS, active hepatitis B virus disease
Abstract 458 McCutchan et al	United States	145	31% HAND	Diabetes mellitus, higher body mass index and triglycerides, lower high-density lipoprotein cholesterol
Abstract 459 Dulioust et al	France	37	51% HAND	Not cardiovascular risk factors
Abstract 477 Duiculescu et al	Romania	43	60% HAND	Higher HIV RNA in cerebrospinal fluid
Abstract 485 Robertson et al	Various	293	29% neurologic abnormalities	
Abstract 920 Ruel et al	Uganda	218	HIV-infected performed worse in most measures	
Abstract 155 Everall et al	United States	589	17% typical HIV brain pathology, 78% at least 1 central nervous system abnormality	Antiretroviral therapy nonuse, lower nadir CD4+ counts, higher HIV RNA levels in blood

HIV RNA levels were below 50 copies/mL when measured by a commercial reverse transcriptase-polymerase chain reaction assay (Abstract 484b). Forty-one percent (122) had HIV RNA levels between 2 copies/mL and 50 copies/mL in CSF, and these individuals used antiretroviral regimens that had worse estimates of penetration into the central nervous system (CNS penetration-effectiveness [CPE] scores < 1.5; 64% vs 51%, respectively; OR, 1.7; $P = .03$). The more sensitive assay was also performed in 100 matched blood plasma specimens from these 122 individuals, identifying that 26% had no detectable HIV RNA in blood, even though HIV was present in CSF. These individuals performed much worse on neuropsychologic testing (d = 0.71; $P = .006$) than did those who had detectable HIV RNA in both fluids. These findings indicate that a substantial proportion of effectively treated individuals have low-level HIV in CSF and that this is associated with worse antiretroviral drug penetration characteristics and worse neuropsychologic performance, suggesting that this measure may reflect ongoing viral-induced injury of the nervous system. These findings also support that a more sensitive viral load assay may have clinical value.

Canestri and colleagues also presented data supporting that antiretroviral therapy is not effective in the nervous system in all treated individuals and that this can lead to neurologic abnormalities (Abstract 484a). The group identified 10 individuals who were on stable antiretroviral therapy for a median of 14 months but had a new onset of acute or subacute neurologic abnormalities such as symptoms of neurocognitive impairment, psychosis, and nervous system inflammation. Even though HIV RNA levels were below 500 copies/mL in blood in all subjects and below the quantitation limit of the assay in 7, HIV RNA levels in CSF averaged 952 copies/mL and were more than 1 $\log_{10}$ copies/mL higher than in blood. Resistance testing was performed using HIV from CSF, and antiretroviral therapy was modified based on these results as well as estimates of antiretroviral drug penetration into the CNS (CPE scores). Treatment modification resulted in clinical improvement in all subjects and declines in HIV RNA levels in CSF below quantitation in 7. These data reinforce that antiretroviral therapy can fail primarily in the CNS and identify a clinical approach that improves the effectiveness of treatment when this occurs.

Cross-sectional analyses of data can be biased because they cannot accurately account for interindividual differenc-

es in time-dependent data such as duration of antiretroviral therapy, immune deterioration or recovery, and fluctuations in neuropsychologic performance. Longitudinal analyses can eliminate many of the biases inherent in cross-sectional analyses. Tate and colleagues used comprehensive, computerized neuropsychologic testing at 1 timepoint and the prior year's clinical records to calculate slopes of change in CD4+ cell counts and transitions between detectable and undetectable HIV RNA levels in blood (Abstract 476). Better performance in tasks assessing attention and executive functioning was predicted by increasing CD4+ cell counts over the prior year and transitions from detectable to undetectable HIV RNA levels in blood, consistent with use of effective antiretroviral therapy during that period. Although computerized testing can be flawed and the authors do not report global performance, this relatively small analysis (n = 81) reinforces the value of longitudinal data in understanding complex relationships between disease markers and brain health.

Few studies have reported on the cognitive benefits of antiretroviral therapy in regions outside Europe, North America, and Australia. After antiretroviral therapy was initiated in volunteers of ACTG 5199 (based in Africa, Asia, and South America), Robertson and colleagues identified statistically significant improvements in neuropsychologic functioning even after controlling for baseline performance, age, education, sex, CD4+ cell count, and HIV RNA levels in blood (Abstract 485). Of note, neuropsychologic response to antiretroviral therapy varied by country, suggesting important differences between treatment and regional differences such as HIV subtype, host characteristics, and comorbidities.

One challenge to understanding the impact of antiretroviral therapy on the brain is the rapidly expanding number of drugs available to patients and prescribers. A recent class of antiretroviral drugs, CCR5 antagonists, was designed to interfere with the use of this cell-entry receptor by HIV. Two drugs in this category are either currently available (maraviroc) or in development (vicriviroc), and physicochemical data indicate that both may penetrate into the CNS in therapeutic concentrations. The expression of CCR5 and of the other common coreceptor of HIV, CXC chemokine receptor R4 (CXCR4), varies by cell type. HIV strains that infect macrophages and microglia, the cells that are productively infected in the brain, are more likely to use CCR5 than CXCR4. The combination of preferential use of CCR5 in the brain and good penetration of CCR5 antagonists suggests that this class of drugs could play an important role in treatment of the HIV-infected nervous system.

This conclusion would be further supported if coreceptor usage assays indicated differences between HIV derived from the CSF and HIV from the blood. Spudich and colleagues compared coreceptor usage and replication capacity in 18 chronically HIV-infected individuals using a commercial tropism assay. They demonstrated that CCR5 usage was similar by HIV derived from CSF and from blood but, when CXCR4 was used by blood-derived HIV, the relative usage by CSF-derived virus was less (P = .022) (Abstract 469). They also demonstrated that HIV derived from blood had higher estimated replication capacity than HIV derived from CSF (P = .0017). The compartmentalization they observed in coreceptor usage, however, supports the idea that CCR5 antagonists may retain activity in the nervous system even when they fail in blood.

Neuroimaging of the Brain

An expanding role for neuroimaging in the neurocognitive complications of HIV was identified by findings from studies that used 3 techniques: structural MRI with morphometry, MRS, and functional MRI. Brain morphometry measures were assessed from a subset of the CHARTER cohort, identifying that lower volumes of cortical gray matter and larger volumes of abnormal white matter were associated with impaired neuropsychologic performance (Abstract 154). Data from the HIV Neuroimaging Consortium also identified that HIV-infected individuals had reduced brain volumes, whether evaluated as overall volumes or regional volumes, such as from the cortical (eg, parietal, temporal, and frontal cortex) or subcortical (eg, basal ganglia) regions (Abstract 480). Within certain brain regions, such as the corpus callosum, HIV-infected subjects who had the apolipoprotein E allele *ApoE4* had greater atrophy than HIV-infected subjects without this allele did (Abstract 460). These structural neuroimaging results confirm prior studies[13,14] and indicate that, in the current era, HIV is associated with loss of cortical and subcortical gray matter as well as white matter.

The HIV Neuroimaging Consortium also reported on the relationships between HIV and regional metabolite concentrations as analyzed by MRS (Abstract 156). HIV-infected individuals who were taking antiretroviral therapy had higher levels of inflammatory metabolites (myoinositol-to-creatine ratio) in the frontal gray matter, frontal white matter, and basal ganglia. Subjects who had HAND had lower levels of neuronal metabolites (*N*-acetyl aspartate-to-creatine ratio), especially in the basal ganglia. Interestingly, neuronal injury in the basal ganglia was also associated with a measure of fatigue, which afflicts many people living with HIV, as discussed above (Abstract 479). Navia and colleagues posited a multistage in vivo model of brain injury, in which early HIV disease is associated with inflammatory changes throughout the brain and leads to neuronal injury and subsequent clinically evident neurocognitive impairment.

The impact of aging in people living with HIV was demonstrated by functional MRI. A cohort of HIV-infected and -uninfected individuals ranging from 20 years to 63 years old identified that HIV and older age were each associated with lower cerebral blood flow. Overall, HIV-infected individuals had cerebral blood flow similar to HIV-uninfected individuals who were 15 years to 20 years older. These results have important implications for the clinical management of HIV-infected individuals because an increasing proportion is older than 50 years. Although these noninvasive neuroimaging results are

novel and enable better understanding of the basic pathophysiology of HIV in the brain, they have not yet assisted in clinical guidelines for diagnosing HAND (Abstract 181). Because of the relatively high costs and relatively limited availability of many of these techniques, these modalities may not be available in the clinical setting for many years.

Opportunistic Infections of the Nervous System

Progressive Multifocal Leukoencephalopathy

Interest in progressive multifocal leukoencephalopathy (PML) has increased in the wider scientific community as the disease has been identified in immunosuppressed individuals who are not infected with HIV but are treated with immune modulators such as natalizumab, an integrin inhibitor that reduces migration of activated immune cells into the CNS. Infection with JC virus (JCV), the causative agent of PML, is highly prevalent throughout the world, and reactivation of the virus during immunosuppression can lead to PML. Among people living with HIV, however, susceptibility to PML remains poorly understood.

Although antiretroviral therapy has generally improved the prognosis of PML in those with HIV, nearly all patients deteriorate neurologically and ultimately die despite immune recovery with antiretroviral therapy. To better understand interindividual differences in survival in people with PML, Khanna and colleagues studied 29 individuals with PML from the Swiss HIV Cohort Study, 18 of whom survived for longer than 1 year and 11 for less than 1 year (Abstract 794). They measured T-cell and humoral immunity against JCV using laboratory assays on cryopreserved cell and plasma samples at times before and after diagnosis. The principal finding was that longer durations of survival were associated with greater JCV-specific T-cell and antibody responses before the onset of PML compared with such responses either in patients who had shorter durations of survival or in CD4+-count-matched, HIV-infected individuals who did not have PML. These data indicate that better immune responses to JCV lead to better survival in people with PML, suggesting that enhancing immune responses, perhaps by vaccination, may improve survival.

Understanding the mechanisms by which reactivating JCV gains access to CNS tissues might lead to effective treatments to prevent PML or limit its progression. Chapagain and Nerurkar studied a potential mechanism of JCV migration involving initial infection of human brain microvascular endothelial cells, which form part of the blood-brain barrier (Abstract 793). This research showed that neuraminidase, which blocks specific sialic acids on endothelial cell surfaces, could prevent migration of JCV across an in vitro blood-brain barrier model. These findings suggest that addition of a sialic acid blocker to antiretroviral therapy might serve as a specific treatment for PML.

Cryptococcal Meningitis

Parkes-Ratanshi and colleagues compared prophylaxis for cryptococcal meningitis (CM) and candidal infections with fluconazole 200 mg thrice weekly in a large, community-based, randomized clinical trial enrolling antiretroviral therapy–naive Ugandans with CD4+ counts below 200 cells/μL (Abstract 32). Only 1 case of CM occurred in 760 fluconazole recipients compared with 18 CM cases in 759 placebo recipients (hazard ratio [HR], 0.05; $P < .001$); rates of candidal esophagitis (HR, 0.14; $P < .001$) and vaginitis (HR, 0.15; $P < .001$) were also reduced. Importantly, though, all-cause mortality did not differ between the groups (98 vs 100 deaths; $P > .10$).

Diagnosis of chronic meningitis in HIV patients in resource-limited settings requires differentiation of CM from tuberculous meningitis (TbM), but laboratory support for culture and even cryptococcal antigen detection is not widely available. When clinical profiles were compared in 112 CM and 46 TbM Malawian patients, high CSF pressure and low CSF glucose level supported a diagnosis of CM, and fever, neck stiffness, and lower Glasgow Coma Scale scores supported a diagnosis of TbM (Abstract 791). The investigators derived a potentially useful diagnostic index by multiple regression that distinguished CM and TbM with a sensitivity of 83% and specificity of 79% among HIV-infected individuals. CM was associated with higher opening pressure on lumbar puncture (OR, 0.99; $P = .015$) and lower leukocyte counts in CSF (OR, 1.0028; $P = .027$), and TbM was associated with fever (OR, 8.86; $P = .002$), neck stiffness (OR, 3.11; $P = .028$), and lower Glasgow Coma Scale scores (OR, 0.79; $P = .001$). Although the best sensitivity produced by a classification regression tree analysis of the algorithm was 57%, these findings still provide important guidance for distinguishing CM and TbM in resource-limited settings particularly when Gram and India ink stains may not be available.

To determine the optimal timing of antiretroviral therapy initiation in people with CM, Makadzange and colleagues compared early (within 72 hours) and late (after 10 weeks) treatment with stavudine, lamivudine, and nevirapine in a randomized clinical trial in Harare, Zimbabwe (Abstract 36cLB). Overall mortality rates were high (62%) and were substantially higher in the early (23/26 patients, or 82%) than in the late (8/28 patients, or 37%) treatment group; death occurred much earlier in the early treatment group (median, 5 weeks vs 39 weeks, respectively; HR, 2.4; $P < .03$). This striking difference in mortality appears to contradict conclusions of another, similar study in resource-limited settings in which a subgroup of CM patients survived longer when antiretroviral therapy was started early.[15]

In resource-limited settings, high-dose fluconazole (greater than 800 mg/day) could provide a simple, inexpensive alternative to amphotericin-based regimens for the first 2 weeks of therapy for CM. The potentially increased efficacy of doses greater than 800 mg per day in CM has been demonstrated by the recent finding of increased fungicidal activity against CSF cryptococci

of oral fluconazole at 1200 mg per day compared with 800 mg per day.[16]

Supporting this concept, serum and CSF levels of fluconazole were measured in 78 HIV-infected Thai patients receiving amphotericin in combination with 800 mg, 400 mg, or no fluconazole daily for induction therapy of CM (Abstract 792). CSF levels of fluconazole approached those in serum and nearly doubled in those receiving 800 mg per day compared with 400 mg per day. Higher levels in blood and CSF at day 14 were associated with improved clinical outcomes (alive, culture negative, and neurologically improved) at day 70. Thus, higher concentrations of fluconazole from larger doses seem to improve clinical outcomes.

Immune restoration inflammatory syndrome (IRIS) in CM was documented in 38 of 75 (51%) patients after a median of 6 weeks of treatment with antiretroviral therapy in a prospective study in Uganda (Abstract 774). Twenty-seven cytokines were measured serially in serum by multiplex bead-based immunoassays. Concentrations of many analytes differed between those who had been diagnosed with IRIS and those who had not (higher in IRIS: interleukin [IL]-6, IL-17, tumor necrosis factor-alpha, and granulocyte macrophage colony-stimulating factor; lower in IRIS: IL-8 and interferon-inducible protein-10). Higher levels of IL-6 were the most common correlate of IRIS. Nineteen subjects had high levels of C-reactive protein in blood (above 32 mg/L) and, among this subgroup, 14 (74%) had IRIS and 10 (53%) died, suggesting that this widely available inflammatory indicator may be a practical serum biomarker for high risk of IRIS in CM.

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Complications of HIV Disease and Antiretroviral Therapy

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Continued progress in the diagnosis, management, and prevention of complications of HIV disease and antiretroviral therapy were reported at the 16th Conference on Retroviruses and Opportunistic Infections. This year's conference brought new data on the optimal management of antiretroviral therapy in the presence of different opportunistic infections and included a number of important studies on pathogenesis and epidemiology of long-term complications. Major areas in which new information was presented are highlighted in this article.

Tuberculosis Coinfection

When to start antiretroviral therapy in patients with tuberculosis (TB) was addressed in the SAPIT (Starting Antiretroviral Therapy in Three Points in Tuberculosis Therapy) trial (Abstract 36a). In this 3-arm study, 645 South African adults with a CD4+ count lower than 500 cells/µL and a positive acid-fast bacillus (AFB) smear for TB underwent randomization to start antiretroviral therapy at TB treatment initiation or after the intensive phase of TB therapy but before TB treatment completion (the "integrated" groups), or after TB treatment completion (the "sequential" group). The antiretroviral regimen was daily didanosine, lamivudine, and efavirenz. The Data and Safety Monitoring Board (DSMB) halted the trial when the mortality of patients in the 2 integrated antiretroviral therapy and TB treatment groups was 56% lower than those in the sequential group.

These data support current World Health Organization (WHO) guidelines that patients with TB who meet criteria for antiretroviral therapy should not wait until completion of TB therapy to start antiretroviral therapy. Although mortality in patients with CD4+ counts between 200 cells/µL and 500 cells/µL was lower in patients in the integrated treatment groups, the study was not powered to determine the benefit of antiretroviral therapy in persons with a CD4+ count between 350 cells/µL and 500 cells/µL, for whom guidelines currently recommend completion of TB therapy before starting antiretroviral therapy. An important remaining question is the optimal timing of antiretroviral therapy during TB therapy, for which the ongoing 2 integrated treatment groups of the SAPIT trial, the CAMELIA (Cambodian Early Versus Late Introduction of Antiretrovirals) study and the AIDS Clinical Trials Group (ACTG) A5221 study, will inform the field.

Which antiretroviral therapy to start in patients with TB was addressed in Swaminathan and colleagues' Chennai, India–based TB treatment study (Abstract 35). In this study, 127 HIV-seropositive adults with TB underwent randomization to 1 of 2 once-daily antiretroviral regimens after completing a 2-month TB treatment induction phase: nevirapine, didanosine, and lamivudine or efavirenz, didanosine, and lamivudine. The DSMB also recommended stopping this study early when virologic suppression rates were 28% higher in the efavirenz- than in the nevirapine-containing regimen. The once-daily dosing of nevirapine and its interaction with rifampin likely resulted in lower levels of nevirapine and worse virologic outcome. Thus, when using a once-daily antiretroviral regimen in patients with TB, an efavirenz-based regimen is preferred to a nevirapine-based one to optimize virologic outcome.

In general, HIV-seropositive patients with TB are prescribed the same TB regimens as are HIV-seronegative patients. However, some TB regimens using intermittent therapy during TB treatment may not be optimal for HIV-infected patients. Swaminathan and colleagues evaluated TB treatment outcomes in HIV-seropositive (n = 212) and HIV-seronegative (n = 250) persons with TB treated with the Indian national TB-treatment regimen, which includes intermittent therapy for the intensive and continuation phase of TB treatment (Abstract 783). Among TB treatment failures, only 0.4% of HIV-seronegative persons had acquired rifampin resistance, whereas 8.9% of HIV-seropositive persons had acquired rifampin resistance. Several subjects had preexisting isoniazid resistance leading to multidrug-resistant (MDR) TB failures. Rifampin resistance was associated with a lower CD4+ cell count. None of the HIV-seropositive patients had access to antiretroviral therapy at the time of this study, which may have amplified the differences between the study groups. However, in view of the crucial role of rifampin in TB treatment and the dire outcomes in HIV-infected patients with MDR TB, the conclusion of this study is that intermittent TB treatment should be avoided.

Meintjes and colleagues presented the results of a randomized, placebo-controlled trial of a 4-week course of prednisone in mild to moderate TB-associated immune reconstitution syndrome (IRIS) (Abstract 34). The prednisone dose was 1.5 mg/kg daily for 2 weeks, then 0.75 mg/kg daily for 2 weeks. The major findings in this study were (1) a reduction in hospitalizations and procedures in the prednisone recipients compared with the placebo recipients, and (2) greater improvement in symptoms in the prednisone than in the placebo recipients at 2 weeks. Corticosteroid side effects were more frequent in prednisone (9 events) than in placebo (3 events) recipients, but serious infections were uncommon and did not differ between the groups. Thus, physicians can utilize steroids

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in such patients, knowing that at least in the first 4 weeks, benefits appear to outweigh risks. Of note, and as the authors acknowledged, extended steroid courses may be required to avoid recurrence of symptoms, which could increase toxicity over the long-term.

The enormous burden of TB among patients starting antiretroviral therapy and the difficulty in diagnosing these cases without access to TB culture was highlighted in several studies conducted in South Africa. Of 236 patients presenting to care in Capetown screened with TB smear, culture, and the urine-based test for lipoarabinomannan (LAM), 26.3% had culture-positive TB (Abstract 780). Sputum TB smear sensitivity was only 13%, and 22% of all cases were asymptomatic. LAM testing had a sensitivity of 51% in those with fewer than 100 CD4+ cells/μL. Symptom screens had a sensitivity of 78% but a poor specificity of 35%. Sputum induction did not improve diagnostic yield of cultures.

In another study in Durban, South Africa, 824 patients with a median CD4+ count of 100 cells/μL (range, 48–154 cells/μL) were screened for TB (Abstract 779). Nineteen percent of patients had a positive result from TB culture. The TB smear had a sensitivity of 9%, and 22% reported no TB symptoms. In a cost analysis, screening with cultures doubled the number of cases identified compared with cases identified using current WHO guidelines, with only a modest increase of cost per case identified. TB was detected in 18.1% of participants who provided sputum samples.

Another study conducted in Zimbabwe, where TB culture is not routinely available, tracked the outcomes of 240 smear-negative, TB-suspect cases (Abstract 778). Of these, HIV prevalence was 78%, and TB was ultimately confirmed by culture in 85 cases. Not surprisingly, undiagnosed and untreated TB was associated with a high mortality rate. Martinson and colleagues reported on 729 patients suspected of having TB (91% HIV-seropositive) admitted to 1 of 3 public hospitals in South Africa (Abstract 789). Among HIV-seropositive, TB-culture-positive patients, mortality was 15.2% at 90 days, compared with 2.3% for HIV-seronegative patients. Few patients were receiving antiretroviral therapy despite low CD4+ counts. This study underscores the high mortality rates in hospitalized patients coinfected with HIV and TB as well as the potential for nosocomial TB transmission.

Early data are emerging on the use of polymerase chain reaction (PCR) testing to obtain a more rapid assessment of TB and to facilitate early identification of MDR TB and extensively drug-resistant (XDR) TB. Hassim and colleagues presented preliminary data evaluating the use of TB smear, culture, and PCR testing results for diagnosis of TB in a cohort of 489 patients suspected of having TB (Abstract 781). TB was detected in 18% of patients. AFB smear testing was 37% sensitive. PCR testing revealed the diagnosis weeks before culture results did and was 97% sensitive for smear-positive TB and 37% sensitive for smear-negative TB. MDR TB accounted for approximately 20% of the TB cases in the cohort, with prior TB treatment the greatest risk factor. PCR testing rapidly identified MDR TB in 7 of the cases in this ongoing study.

Reported survival among HIV-infected patients living in South Africa with XDR TB or MDR TB has been abysmally low. Two reports from South Africa provided updated information on this group of patients. In a retrospective review of 272 MDR (41%) and XDR (59%) TB cases diagnosed from 2005 to 2007 in Tugela Ferry, 82% of patients with XDR TB and 69% of those with MDR TB were dead at 1 year (Abstract 784). Early mortality at 30 days was 54% for XDR TB patients and 40% for MDR TB patients. For MDR TB patients but not XDR TB patients, there was a trend for improved survival over time. In 2005, 87% of patients with MDR TB died, compared with 45% of such patients in 2007.

Better survival rates were reported in a review of 60 patients with XDR TB referred to a public TB hospital in KwaZulu-Natal, South Africa (Abstract 785). Of these patients, 43 were HIV-infected and had a median CD4+ count of 200 cells/μL, and 49% were receiving antiretroviral therapy. Forty-two percent of patients in this cohort died. Twenty percent had documented conversion of sputum cultures. The primary reason for the better outcomes in the KwaZulu-Natal study likely stems from the fact that only patients who survived from the time of diagnosis of MDR or XDR TB to entry into the TB referral center were included in the analysis.

Identifying optimal prevention strategies for TB remains a high research priority. Martinson and colleagues presented the results of a 4-year, 1150-patient study of 4 TB-preventive regimens conducted in South Africa (Abstract 36bLB). HIV-infected adults who were positive for purified protein derivative (PPD) of tuberculin underwent randomization to receive rifapentine plus isoniazid for 12 weeks, rifampin plus isoniazid for 12 weeks, or isoniazid continuously for the study duration; the control group received isoniazid for 6 months. The main finding of this study was that neither the short-course, 2-drug regimen nor the continuous isoniazid treatment was superior to the control group. In addition, rifampin resistance was detected in some of the breakthrough TB isolates in the combination-therapy groups. Toxicity and adherence issues led to an approximately 50% drop-off in the continuous isoniazid group at 2 years. However, in an on-treatment analysis, continuous isoniazid treatment resulted in a 70% reduction in TB compared with the other regimens. Thus, in highly TB-endemic areas, continuous isoniazid treatment for those who can adhere to it and tolerate it is highly effective in reducing TB, compared with the currently recommended 6-month course of isoniazid. How these data will be applied in the public health setting is currently under debate.

Mitchell and colleagues presented the results of an isoniazid prophylaxis study conducted in 3-month-old HIV-seronegative, perinatally HIV-exposed South African children (Abstract 907). In this study, 804 HIV-uninfected children underwent randomization to isoniazid treatment or placebo for 96 weeks, with an additional 96-week planned follow-up. The primary end-

points were defined as acquisition of latent TB, pulmonary TB disease, and death. The DSMB stopped the study at 96 weeks, at which point no difference was apparent between the 2 groups. Investigators reported similar findings for children in the HIV-infected groups of this study in 2008.[1] Thus, primary TB prophylaxis in infants does not appear to be an effective strategy for such patients, and new studies must address the most effective regimen and optimal time to prevent TB acquisition in TB-endemic areas.

A big challenge in the management of TB in resource-limited settings is determining the optimal antiretroviral therapy and TB regimen when HIV protease inhibitors (PIs) are required for efficacy. This situation is increasingly common in HIV-infected children for whom PIs are prescribed after previous use of nevirapine for prevention of mother-to-child transmission of HIV. The management is particularly complicated because of limited availability of pharmacokinetic information and drug preparations for the pediatric population. McIlleron and colleagues presented the results of a pharmacokinetic study comparing lopinavir exposure in 15 children treated for TB and HIV coinfection using double-dose lopinavir/ritonavir (lopinavir/r) and in 24 control patients monoinfected with HIV treated with standard-dose lopinavir/r (Abstract 98). This study was prematurely stopped by the DSMB because double-dose lopinavir/r could not overcome the effects of rifampin in this population and resulted in 60% of children with subtherapeutic levels of lopinavir.

Underdosing of lopinavir/r would be expected to lead to lower rates of viral suppression and to drug resistance, which is exactly what happened in 2 other studies conducted in South African children with TB. Reitz and colleagues compared virologic suppression rates in 254 children with and without TB (Abstract 910). As per country guidelines at the time, children were treated with lopinavir only (those younger than 6 months) or lopinavir/r (those older than 6 months). Virologic suppression rates were 94.8% in children never treated for TB compared with 74% in those treated for TB at antiretroviral therapy initiation and 51.6% in those treated for TB after suppression with antiretroviral therapy. In a complementary report of drug resistance mutations among pediatric patients for whom PI therapy failed, major PI mutations were more frequent in children receiving full-dose ritonavir in the presence of rifampin than in children receiving standard lopinavir/r regimens not concurrent with TB therapy (Abstract 888). These studies call for research optimizing antiretroviral therapy and TB therapy among infants and children, including studies exploring safety and efficacy of rifabutin-containing TB regimens.

Cryptococcal Disease

Cryptococcal disease is an important cause of morbidity and mortality in Africa, yet there are limited data on optimal prevention and management strategies. Parkes-Ratanshi and colleagues presented the results of a double-blind, randomized trial comparing fluconazole 200 mg thrice weekly with placebo (Abstract 32). The study enrolled 1519 HIV-infected adults residing in rural Uganda who had a CD4+ count lower than 200 cells/μL and a negative result for cryptococcal antigen. Of these patients, 1335 started antiretroviral therapy a median of 74 days after enrollment. Cryptococcal meningitis developed in 18 patients receiving placebo versus 1 patient receiving fluconazole. Of these, 12 cases occurred before antiretroviral therapy and 7 after. Candidal esophagitis was 86% lower in the fluconazole-treated recipients than in placebo recipients. Adverse events attributed to fluconazole were minimal. Thus, fluconazole was extremely effective in reducing the burden of both cryptococcal meningitis and candidal esophagitis. These results should stimulate discussion of the prophylactic use of fluconazole for high-risk persons starting antiretroviral therapy in Africa.

A second study of cryptococcal disease focused on determining the optimal point to start antiretroviral therapy in patients with acute cryptococcal meningitis. In this study, 54 antiretroviral therapy–naive, HIV-seropositive patients with cryptococcal meningitis living in Harare, Zimbabwe, underwent randomization to receive antiretroviral therapy at the initiation of cryptococcal meningitis treatment or 10 weeks later (Abstract 36cLB). The treatment regimen for cryptococcal meningitis was 800 mg of fluconazole daily. There was a 2-fold increased risk of death for patients treated immediately with antiretroviral therapy compared with those treated at 10 weeks. Overall mortality rates were extremely high, with 87% and 37% of patients in the immediate and delayed antiretroviral therapy groups dead at 2 years, respectively. Mortality rates were highest in the first 2 months of fluconazole treatment, suggesting a detrimental effect of early antiretroviral therapy.

These data stand in contrast to the results of a largely US-based trial presented at the 2008 conference by Zolopa and colleagues, which enrolled patients with a variety of opportunistic infections including cryptococcal meningitis and showed a benefit to early antiretroviral therapy.[2] More aggressive management of elevated intracranial pressures, use of amphotericin, and less-ill patients in the United States compared with those in Zimbabwe could explain some of these differences. However, these data underscore the need for caution in very early antiretroviral therapy initiation in patients with inflammatory central nervous system infections such as cryptococcal meningitis.

Trimethoprim-Sulfamethoxazole Prophylaxis Strategies in Africa

Stopping trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis treatment in patients who have restored immunity with antiretroviral therapy is safe and is the standard of care in most developed and middle-income countries. However, data are limited on the safety of TMP-SMX discontinuation in resource-limited settings, where malaria and bacterial diarrhea diseases are more common. Campbell and colleagues' data suggest that TMP-SMX discontinuation in areas such as rural Uganda is not particularly safe (Abstract

33). The US Centers for Disease Control and Prevention (CDC) conducted a randomized study of TMP-SMX discontinuation (n = 384) versus TMP-SMX continuation (n = 452) among HIV-infected patients in the home-based AIDS care (HBAC) program in eastern Uganda who had 2 consecutive CD4+ counts above 200 cells/μL. In these patients, median duration of antiretroviral therapy was 3.7 years, median CD4+ count was 489 cells/μL, and 94% had plasma HIV RNA levels below 400 copies/mL. The DSMB stopped this study after patients had been observed for only 116 days because of the 28-fold increase in the rate of smear-confirmed malaria among those who stopped taking TMP-SMX over those who continued. Diarrhea episodes were also 1.8-fold higher in the TMP-SMX-discontinuation group. This study highlights the need to test developed-world prophylactic and treatment strategies in resource-limited settings.

Hepatitis C Virus Coinfection

The first systematic evaluation of the influence of hepatitis C virus (HCV) RNA level and HCV genotype on liver-related death was presented by Rockstroh and colleagues (Abstract 101). The study included 1952 HIV and HCV-coinfected patients, of whom 21% had an HCV RNA level lower than 650 U/mL, 37% had an HCV RNA level between 650 U/mL and 500,000 U/mL, and 42% had a level higher than 500,000 U/mL. Among 1537 subjects with HCV genotype, 52%, 14%, 30%, and 3% had gentoypes 1, 4, 3, and 2, respectively. In the multivariate analysis, persons with the highest HCV RNA levels had a 1.8-fold higher risk of liver-related death than did people with the lowest HCV RNA levels. Patients with genotypes 2 and 3 had lower risks of death than did those with genotype 1. HCV RNA level did not predict response to HIV therapy, but having genotype 4 was associated with a worse response to antiretroviral therapy, as measured by HIV RNA levels lower than 500 U/mL or a 50% gain in CD4+ count.

Predictors of death, hepatocelllular carcinoma, or liver transplant among 248 patients coinfected with HIV and HCV with compensated cirrhosis in the GESIDA (Grupo de Estudio de SIDA, AIDS Study Group) Spanish cohort study were presented by Montes and colleagues (Abstract 106). Characteristics of this cohort included 27% with HCV genotype 2 or 3, 72% who had received antiretroviral therapy, and 63% with prior or current treatment for HCV. In the multivariate analysis, only liver disease classified as Child-Pugh class C and interrupted antiretroviral therapy were associated with decreased survival. Of interest, in this cohort, first hepatic decompensation was not delayed in patients who received treatment for HCV. HCV-specific T-cell responses augmented by antiretroviral therapy in coinfected patients may be an explanation, as demonstrated in a study presented by Rohrbach and colleagues (Abstract 105). Before starting antiretroviral therapy, 13% to 14% of patients had detectable HCV-specific T-cell responses as shown by ELISPOT assay. After antiretroviral therapy, up to 54% had detectable T-cell responses. Median plasma HCV RNA levels were inversely correlated with T-cell responses in the absence of specific therapy for HCV.

The efficacy of extended therapy with 72 weeks of treatment with peginterferon alfa and weight-based ribavirin in 169 patients who had achieved HCV early virologic response (EVR) in the ACTG SLAM-C (ACTG A5178) study was presented by Chung and colleagues (Abstract 103LB). Fifty-one percent of patients achieved SVR at week 96, 24 weeks after HCV treatment discontinuation. Virologic response at 12 weeks was predictive of this long-term outcome. Seventy-four percent of patients who had HCV RNA levels lower than 600 IU/mL at week 12 (complete EVR, cEVR) had sustained virologic response (SVR) versus 13% without cEVR. SVR was achieved by 60% in the on-treatment analysis of the 62 patients who completed the HCV treatment. This study reports some of the highest SVR levels seen among HCV- and HIV-coinfected patients with use of weight-based ribavirin; characteristics of patients most likely to achieve SVR included achieving cEVR and completion of HCV therapy.

Fierer and colleagues evaluated risk factors and outcomes of 31 HIV-infected patients identified with acute HCV infection in New York City (Abstract 802). In a case-control study, unprotected receptive anal intercourse, unprotected oral sex, and use of drugs were risk factors for acquiring HCV infection. HCV spontaneously cleared in 13% of patients. Among the 20 patients who agreed to undergo liver biopsy at 4 months, 17 had stage 2 fibrosis, 2 had stage 1, and 1 had stage 0.

Ghosn and colleagues identified 32 cases of acute HCV infection in the French National Institute for Public Surveillance system (Abstract 800). The median age of subjects was 40 years, and median time between the diagnosis of HIV infection and that of HCV was 10 years. Acute HCV infection was detected because of elevated levels of hepatic transaminases in 27 patients and jaundice in 3 patients. Eleven patients had concomitant sexually transmitted diseases (STDs), and high-risk sexual behavior was frequent. In a genotypic analysis of the isolates, 10 genotype 1a viruses segregated into 3 clusters, and 15 isolates segregated into 1 cluster. These 15 viruses were genotype 4d and were related to HCV viruses genotyped in Paris between 2001 and 2003, suggesting ongoing sexual transmission.

In a third study from Amsterdam, 46 cases of acute HCV infection were identified (Abstract 804). All patients denied injection drug use (IDU) or transfusion as a risk factor. Forty-four of 46 patients had elevated levels of hepatic transaminases. In contrast to the Paris outbreak, 76% had genotype 1 and 19%, genotype 4. Collectively, these data point to ongoing HCV epidemics among men who have sex with men (MSM) with high-risk sexual behaviors, the rapid progression of liver disease in some patients, the need for HCV prevention messages, and a call for increased HCV screening among populations at high risk for HCV infection. Hoover and colleagues reported that even the rate of one-time screening for HCV in the United States is low. Only 48% of HIV-infected MSM in a study of 1607 men in 6 US cities were screened (Abstract 803).

Hepatitis B Virus Coinfection

Hepatitis B virus (HBV) suppression rates in patients receiving tenofovir-containing regimens were reported by Lacombe and colleagues (Abstract 100). The median follow-up period was 32 months. In this French cohort of 168 patients, median time to achieve an HBV DNA level lower than 2000 IU/mL was 9.1 months, and 89.3% of patients had undetectable HBV DNA levels at the end of the follow-up period. Among the patients experiencing virologic failure, only one-third had detectable tenofovir levels, suggesting poor adherence as the major factor in failure. The L217R polymorphism but no other Pol mutations were identified in those with virologic failure. Thus, in this cohort, high rates of HBV suppression were achieved among patients adherent to tenofovir-containing therapy, and tenofovir drug resistance was not identified in those whose virus was not suppressed.

Treatment of HBV infection in patients not yet willing or prepared to take HIV therapy relies on drugs with anti-HBV but not anti-HIV activity, to avoid the selection for HIV drug resistance. In a case report of a 45-year-old man with HBV infection treated with adefovir and telbivudine at doses thought not to have anti-HIV activity, plasma HIV RNA levels decreased from 14,462 copies/mL to lower than 50 copies/mL (Abstract 813a). When telbivudine was stopped temporarily, his HIV RNA level increased to 3903 copies/mL. When rechallenged with telbivudine, his HIV RNA level resuppressed. An in vitro study presented next to this poster came to the opposite conclusion (Abstract 813b). In this study, numerous HBV strains were tested using a standard culture and a phenotypic assay. Telbivudine showed no activity against HIV isolates, in contrast to other drugs such as entecavir and efavirenz (as a control). Although the in vitro data are reassuring, even a single patient in whom HIV activity is exhibited with telbivudine treatment raises concern that the in vitro assays may not entirely reflect the in vivo environment.

Coinfection with HBV and HIV is prevalent in many resource-limited settings, but HBV screening is rarely performed, and tenofovir is not part of initial antiretroviral therapy in most countries. Burnett and colleagues reported that in a South African cohort, 23% of HIV-infected patients tested positive for hepatitis B surface antigen (HBsAg) and for HBV, and an additional 23% tested positive for HBV but not HBsAg (Abstract 799). In another report from South Africa, persistent HBV DNA was detected in 15.5% of patients receiving an antiretroviral therapy regimen containing lamivudine but not tenofovir (Abstract 813c). Cost but not toxicity appears to be a major barrier in the treatment of patients with a tenofovir-containing regimen in resource-constrained settings.

Serious Non–AIDS-Related Events

The past several years have seen a sharper focus on the relationship between HIV infection and a range of serious non–AIDS-related clinical events such as cardiovascular, renal, and hepatic complications. At this year's conference, several groups reported on the epidemiology and outcomes related to this collective group of serious non–AIDS-related events (Abstracts 706, 707, 708, 145).

Investigators from the Antiretroviral Therapy Cohort Collaboration (ATCC) examined causes of death in nearly 40,000 patients who initiated triple-drug therapy between 1996 and 2006 (Abstract 708). During the first year of antiretroviral therapy, AIDS events predominated as a cause of death (63% of all deaths); thereafter, they fell and were replaced by other types of events. Baseline levels of CD4+ were associated with AIDS events, non-AIDS malignancy, and renal failure. Of note, the rates of non-AIDS-infection, liver-related, non-AIDS-malignancy, violence-related, heart or vascular, and respiratory deaths were markedly elevated in patients infected via IDU. Strategies to reduce the rates of these non–AIDS-related events and to effectively manage IDU are needed to further reduce rates of mortality in patients receiving antiretroviral therapy.

Mocroft, Lundgren, and their EuroSIDA colleagues reported on the incidence and risk factors for serious non–AIDS-defining events in Europe (Abstract 707). The incidences of non–AIDS-defining events (malignancies, end-stage renal disease, liver failure [grade III/IV hepatic encephalopathy, death from liver-related disease], pancreatitis, cardiovascular disease [CVD; acute myocardial infarction or stroke]) and of AIDS-defining illnesses were evaluated. The incidence of non–AIDS-defining events was slightly higher than that of AIDS events (16.5 and 15.5 per 1000 patient-years, respectively). Malignancy, CVD, and liver failure were the most common events, and rates of all of these events were lower in patients with higher CD4+ counts, suggesting again that immunodeficiency contributes to the pathogenesis of non–AIDS-defining events. Collectively, these studies highlight the importance of non–AIDS-defining events as a focus in HIV research, including the need for standard reporting of clinical trials and cohort studies and as a target for future interventions.

The finding that smoking, hypertension, and diabetes were all risk factors for the development of non–AIDS-defining events is an important reminder about the role of management of these issues in HIV primary care. The crucial role of these modifiable risk factors, especially smoking and diabetes, was also highlighted by analyses from the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) cohort and the FRAM (Fat Redistribution and Metabolism) study examining causes of death (Abstracts 145, 706).

Smoking cessation has become an important topic in HIV management; however, data are limited on the efficacy of different interventions in HIV populations. Tashima and colleagues reported results of a large randomized trial to evaluate a smoking cessation intervention conducted in an HIV treatment setting (Abstract 148). Four hundred and forty-four patients underwent randomization to receive either a brief 2-session or more intensive 4-session motivational counseling intervention based on Public Health Service guidelines. Participants were provided

an 8-week supply of nicotine patches if they set a quit date. Unfortunately, overall quit rates in the intent-to-treat analysis were only 9%, with higher rates noted among Hispanic participants (19%). Use of the nicotine patch appeared to be an important factor for success in this study. Future intervention studies, possibly including medications that target nicotine receptors, are needed in HIV-infected individuals.

Cardiovascular Disease

As noted above, CVD remains an important contributor to overall mortality in the aging population of HIV-infected adults, much as it does in the general population. Rates of myocardial infarction (MI) in HIV-infected patients continue to be monitored in several cohort studies. Data from the California Kaiser Permanente cohort, a setting in which primary prevention and HIV care are integrated, demonstrated that rates of hospitalization for MI have declined since 2002 in the HIV-infected population (Abstract 710). In fact, the difference in relative rate of CVD in HIV-infected patients versus that in HIV-uninfected patients was no longer statistically significant in the period from 2006 to 2008 (relative rate [RR], 1.3; 95% confidence interval [CI], 1.0 – 1.7; P = .062). Of note, the rate of a combined endpoint of MI, peripheral vascular disease, and cerebrovascular disease remains higher in HIV-infected participants than in an HIV-uninfected control group. These data suggest that efforts to reduce CVD risk in HIV-infected patients are being implemented successfully, at least in this setting.

Cross-sectional and longitudinal studies using carotid intima medial thickness (IMT) as a measure of subclinical atherosclerosis have yielded conflicting results with respect to the contributions of HIV disease, antiretroviral therapy, and traditional risk factors as important risk factors for atherosclerosis in HIV-infected patients. Previous studies have varied widely by sample size, choice of control group, and protocol employed for carotid IMT measurement. Grunfeld and colleagues reported the results of a large cross-sectional study (FRAM) that compared a random sample of HIV-infected adults in care (n = 433) with a population-based control group from the CARDIA (Coronary Artery Risk Development in Young Adults) study (n = 5749) (Abstract 146). In this study, the IMT procedure included measurements from the common carotid artery and the internal bulb region. As has been previously noted, HIV infection was an independent risk factor for carotid thickening at both the common carotid artery and the bulb.[3]

Of note, the magnitude of the association between HIV infection and IMT was comparable to the associations with several traditional risk factors (10 years of aging, being male, smoking, or having diabetes), and the effect of HIV infection, although statistically significant at both sites, was greater at the bulb region than in the common carotid artery. Finally, another important finding from this study was the fact that the magnitude of the association between HIV infection and IMT appeared to be greater in women than men, after adjustment for other factors. Some of the discrepancy in results from previous cross-sectional studies may be explained by the smaller sample size of earlier studies and the absence of measurements of the bulb area.

Low levels of total high-density lipoprotein (HDL) cholesterol, as a consequence of chronic HIV infection, has been appreciated for decades. The mechanism mediating the HIV effect on HDL cholesterol metabolism has been less clear. Using the simian immunodeficiency virus macaques model of HIV (SIV_{mac239}), Bukrinsky and colleagues evaluated the impact of the HIV accessory protein Nef on cholesterol transport (Abstract 147). Earlier in vitro work suggested that Nef could inhibit reverse cholesterol transport by blocking adenosine triphosphate-binding cassette transporter A1 (ABCA1). At the conference, the authors reported that histochemical staining for ABCA1 in liver samples from SIV-infected macaques demonstrated a decrease in ABCA1 of 25% to 50%. Interestingly, Nef was detected in the hepatic tissue, despite the fact that SIV-infected cells were not detected. In addition, sera from SIV-infected macaques inhibited cholesterol efflux in vitro, an effect that was diminished when Nef was removed from the sera. Collectively, these studies suggest a potential role for Nef in the development of dyslipidemia in HIV infection.

The importance of HDL cholesterol particle size and risk of CVD events was further explored by investigators from the SMART (Strategies for Management of Antiretroviral Therapy) study (Abstract 149). Earlier reports from this group identified that in the setting of treatment interruption, declines in HDL cholesterol concentration were an important risk factor for serious cardiovascular events. Using nuclear magnetic resonance analysis, the investigators evaluated the relationship between lipoprotein particle size and risk of CVD. When comparing a subset of patients from the viral suppression and discontinuation groups of the study, the authors noted that the change in lipoprotein particle concentration was greatest for total HDL particles and for the small- and medium-size HDL particles. In addition, lower concentration values of total HDL particles and small HDL particles were associated with a statistically significant increased risk of CVD, whereas very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) particle concentrations were not associated with CVD risk. The relative contributions of HDL fractions to CVD risk during continuous treatment is an important topic for future study.

Lipid-lowering therapy is routinely recommended for HIV-infected patients based on guidelines developed for the general population, although limited information about the success of such interventions in HIV-infected patients is available from controlled studies. Statins are often the initial therapy, especially in patients with elevated levels of non-HDL cholesterol. Statins are thought to have immunomodulating properties, and in vitro studies suggest they might lower plasma HIV-1 RNA level.

Ganesan and colleagues performed a randomized, placebo-controlled study with a cross-over design to evaluate the role of high-dose atorvastatin (80 mg) versus placebo on immune activation and HIV-1 RNA level in chronically infected patients not receiving antiretroviral therapy (Abstract 577). Atorvastatin reduced the proportion of CD3+, CD4+, and CD8+ cells expressing the activation marker HLA-DR without changing absolute lymphocyte count or HIV-1 RNA level. As expected, LDL cholesterol levels fell statistically significantly during atorvastatin therapy. These findings suggest that the immune-modulating effects of statins occur without any change in HIV-1 RNA level. The longer-term sequellae of dampening-down immune activation in chronic HIV infection during statin therapy requires further investigation.

Ezetimibe, a drug that inhibits intestinal absorption of dietary and biliary cholesterol, is sometimes used as an adjunct to statin therapy. Chow and ACTG colleagues observed 44 statin-recipient patients with LDL cholesterol levels higher than 130 mg/dL who underwent randomization to ezetimibe (10 mg) or placebo for 12 weeks followed by a 4-week washout period, then 12 weeks with the alternative treatment (Abstract 712). Adverse events were very common (63%); however, no grade-4 events occurred. Statistically significant reductions in levels of LDL cholesterol, total cholesterol, non-HDL cholesterol, and apolipoprotein B occurred during ezetimibe treatment, leading the authors to conclude that addition of this drug to statin therapy is an option for HIV-infected patients whose LDL cholesterol levels are elevated while receiving statins.

Antiretroviral Therapy and Risk of Cardiovascular Disease

There is strong interest in determining how different drugs used in the treatment of chronic HIV infection might contribute to CVD risk. Data from cohort studies and randomized trials are now focused on the role of specific drugs (rather than broader drug classes) in CVD risk.

The D:A:D cohort was designed to examine the associations between various antiretroviral drugs and CVD risk. The D:A:D group has set a threshold of 30,000 patient-years of exposure needed before an individual drug can be analyzed. At the 2008 (15th) Conference on Retroviruses and Opportunistic Infections, the unexpected finding of an association between abacavir and MI was reported[4]; however, the cohort did not meet the exposure threshold for tenofovir that would allow comparison of these 2 drugs. This year, an updated analysis of individual nucleoside analogue reverse transcriptase inhibitors (nRTIs) and PIs was reported (Abstract 44LB). Of note, atazanavir is not included in this analysis because the level of exposure to atazanavir in the D:A:D cohort remains below the required threshold level to examine any association with MI risk.

The D:A:D cohort now includes 580 MIs during 178,835 person-years of follow-up. The new findings include the absence of any statistically significant association between recent or cumulative use of tenofovir and MI risk. As before, recent exposure to abacavir (RR, 1.68) or didanosine (RR, 1.41) remained associated with an increased risk of MI. Cumulative (but not recent) exposure to indinavir (with or without ritonavir) or lopinavir/r was also associated with an increased risk of MI (RR, 1.12 and 1.13/year, respectively). These increased risks were slightly reduced but not eliminated after adjustment for lipids, and they are similar to the overall risk of cumulative PI exposure and MI risk previously reported from this cohort. None of the other drugs with sufficient exposure examined in these analyses (zidovudine, zalcitabine, stavudine, lamivudine, nevirapine, efavirenz, nelfinavir, and saquinavir, with or without ritonavir) had associations with MI risk.

Investigators from the French Hospital Database conducted a nested, case-control study to evaluate the impact of specific antiretroviral therapy drugs on MI risk (Abstract 43LB). This design allowed for the collection of data on CVD risk factors directly from medical records. Cases included patients with a first MI validated by a standard definition. Logistic regression models were used to assess the association of cumulative and/or recent (current or within the previous 6 months) and past (> 6 months ago) use of each nRTI and cumulative use of each PI (including indinavir, saquinavir, nelfinavir, lopinavir, and amprenavir or fos-amprenavir), after adjustment for known cardiovascular risk factors and HIV-related factors.

An increased risk of MI was identified for those with less than 1 year of abacavir exposure (odds ratio [OR], 2.19; 95% CI, 1.19–4.02) but not for cumulative use. In contrast to the D:A:D study findings, the association between abacavir and MI risk was not statistically significant for those with use within the previous 6 months. The abacavir-MI association was not explained by the prevalence of CVD risk factors in patients exposed to abacavir. No other nRTI was associated with the risk of MI. Cumulative exposure to PI was associated with an increased risk of MI for all study drugs (indinavir: OR, 1.11/year; 95% CI, 0.98–1.25; nelfinavir: OR, 1.13/year; 95% CI, 0.99–1.30) except saquinavir (OR, 0.96/year; 95% CI, 0.80–1.15), reaching statistical significance for lopinavir (OR, 1.38/year; 95% CI, 1.10–1.74) and amprenavir/fos-amprenavir (OR, 1.55/year; 95% CI, 1.20–1.99).

Consistent findings between these 2 studies are the association between abacavir and MI, albeit with a different timeframe, and the statistically significant association of lopinavir/r with MI risk. These signals warrant further investigation in studies designed to investigate the mechanisms that could mediate the association.

Benson and colleagues examined the relationship between abacavir and MI risk in prospectively followed patients whose treatment assignments were randomized in the ongoing ALLRT (ACTG Longitudinal Linked Randomized Trials) study (Abstract 721). The analysis included 3205 patients who underwent randomization to their first antiretroviral therapy regimen, and endpoints included 63 severe CVD events, including 27 MIs. No statistically significant associations were identified

between either MI or severe CVD and recent abacavir use (RR, 1.02; 95% CI, 0.4–2.5; $P = .96$; and RR, 0.8; 95% CI, 0.5–1.6; $P = .58$, respectively). These findings are consistent with a previous report of randomized clinical trials in the past year.[5]

Several groups of investigators reported results of studies evaluating potential mechanisms to explain the association between abacavir exposure and MI risk. These included studies of inflammatory markers, endothelial function, and platelet function.

McComsey and colleagues measured markers of inflammation and endothelial activation from the HEAT (Head-to-Head Epzicom and Truvada) study, a randomized comparison of abacavir/lamivudine or tenofovir/emtricitabine combined with lopinavir/r in treatment-naive patients (Abstract 732). Samples from more than 400 patients were assayed for endothelial marker vascular cell adhesion molecule-1 (sVCAM-1), interleukin–6 (IL-6), and high-sensitivity C-reactive protein (hs-CRP) at baseline, week 48, and week 96. Levels of all markers fell with treatment; however, there was no statistically significant difference between the abacavir- and the tenofovir-treated patients.

Similarly, data from the ACTG 5095 study were used to examine changes in hs-CRP levels in patients who underwent randomization to a combination of zidovudine, lamivudine, and efavirenz with or without abacavir (Abstract 736). Again, no difference in changes in hs-CRP level were seen in those receiving or not receiving abacavir. (An interesting observation from this study was the finding that hs-CRP levels did not fall during treatment in either group of efavirenz-treated patients, an effect that appeared to be more exaggerated in women than in men.) Collectively, these studies, along with analyses from the WIHS (Women's Interagency HIV Study) and the MACS (Multicenter AIDS Cohort Study), failed to confirm the relationship between abacavir exposure and markers of inflammation that had been suggested from earlier, nonrandomized data.[6]

Alteration in platelet function is under investigation as another possible mechanism to explain HIV- and antiretroviral therapy–associated CVD risk (Abstract 151LB). Satchell and her colleagues from Dublin assessed platelet function in a cross-sectional study comparing 30 patients receiving abacavir-containing antiretroviral therapy with 28 patients receiving nonabacavir regimens. Platelet reactivity in response to different standard stimuli (collagen, epinephrine, and thrombin-receptor-activating peptide, TRAP) was higher in the abacavir-treated patients than in the nonabacavir recipients, an effect that remained statistically significant for all but the TRAP stimuli after adjustment for other covariates. These preliminary data, if confirmed by prospective, preferably randomized studies, suggest a potential mechanism for the abacavir-MI association. Future research to determine the time course and reversibility of these changes is awaited.

Finally, alteration in endothelial function is another potential mechanism for antiretroviral therapy–associated influence on CVD. Previous studies suggest that untreated HIV infection is associated with impaired flow-mediated dilation of the brachial artery and that this effect generally improves when treatment is initiated. Hsue and colleagues reported the results of a cross-sectional study measuring endothelial function in 61 patients with undetectable plasma HIV RNA levels, half of whom were receiving abacavir (Abstract 723). Flow-mediated vasodilation of the brachial artery was more impaired in abacavir-treated patients than in control patients, an effect that remained statistically significant after control for duration of antiretroviral therapy and CD4+ count. Although limited by the nonrandom assignment of abacavir, these findings suggest that further study of changes in endothelial function during treatment with abacavir are warranted.

How do we reconcile these seemingly conflicting clinical results and the mechanistic studies examining abacavir and CVD? This issue was reviewed in a comprehensive summary delivered by Reiss (Abstract 152), in which he contrasted the clinical studies demonstrating an abacavir signal (D:A:D, Abstract 44LB; French Hospital Case-Control Study, Abstract 43LB; and STEAL [Switching to Tenofovir-Emtricitabine or Abacavir-Lamivudine], Abstract 576) to those studies that did not see the association (ALLRT; Abstract 721).[5] One difference between the studies is the fact that a greater proportion of patients in the cohort studies and STEAL trial were virologically suppressed when abacavir was added, whereas in the clinical trials all patients were treatment-naive when exposed to abacavir.

Reiss presented a preliminary supplementary analysis from the French Hospital Database that provided further support to his hypothesis that an undetectable viral load may be an important factor for the association. Alternatively, it is still possible that unmeasured confounders are operating in the observational studies, although it is hard to reconcile this idea with the fact that the abacavir signal is no longer apparent in patients who discontinue the drug. As more data are compiled to address this important question, clinicians are reminded of the importance of addressing proven modifiable risk factors for CVD in HIV-infected patients.

Should Antiretroviral Therapy be Switched to Reduce Cardiovascular Disease Risk?

Clinicians are often faced with the dilemma of deciding whether to switch 1 or more of the antiretroviral drugs in a regimen as an option for reducing CVD risk. Prospective studies suggest more favorable lipid profiles with several newer drugs, but the short- and long-term consequences of these changes have not been well studied. Three switch studies addressing lipids and other measures of cardiovascular risk (all with catchy monickers) were presented this year.

SABAR study. Atazanavir is a well-tolerated PI that has been shown to have a favorable lipid profile in randomized clinical trials. Murphy and colleagues conducted a prospective randomized trial, the SABAR (Switch to Atazanavir

and Brachial Artery Reactivity) study, of 50 virologicaly suppressed, hyperlipidemic, PI-treated patients who underwent randomization (1:1) to switch to ritonavir-boosted atazanavir or remain on their current PI (80% were receiving lopinavir/r) for 24 weeks (Abstract 722). Measures of lipids, markers of inflammation, and endothelial function were obtained at baseline and after 24 weeks of follow-up. Declines in total cholesterol and triglyceride levels were greater in those who switched to atazanavir; however, no changes in endothelial function or cardiovascular inflammatory markers were observed. These findings suggest that although safe and associated with improvement in lipid profiles, the switch to atazanavir did not improve endothelial function over the short-term.

SWITCHMRK-1 and -2 trials. In studies of treatment-naive patients, raltegravir has demonstrated no impact on lipids, and hence there is great interest in the role of this drug in the treatment of dyslipidemic patients well suppressed with other drugs. The SWITCHMRK-1 and -2 studies were parallel, multicenter, double-blind, randomized, active-controlled studies conducted in patients who had virologic suppression with a lopinavir/r-containing regimen (Abstract 70aLB). Participants underwent randomization (1:1) to substitute raltegravir or remain on lopinavir/r. After 12 weeks, raltegravir was superior to lopinavir/r with respect to improvement in levels of total cholesterol (−12% vs 1%, respectively), trigycerides (−43% vs 8%), and non-HDL cholesterol (−15% vs 3%). After 24 weeks, however, the proportion of patients who remained virologically suppressed (as indicated by plasma HIV RNA level < 50 copies/mL) did not meet the noninferiority bound (−12%) for the raltegravir group (88% vs 93%; treatment difference, −5.8%; 95% CI, −12.2–0.22). Patients with prior virologic failure were allowed to enroll in this study, and based on the preliminary findings among those who did not remain suppressed after the switch, preexisting drug resistance to components in the background regimen may have contributed to the higher-than-expected rate of failure after substitution of lopinavir/r with raltegravir, similar to observations in earlier switch studies with abacavir. Identifying those patients most likely to benefit from treatment switches with respect to dyslipidemia remains a high priority.

Simplification with fixed-dose tenofovir-emtricitabine or abacavir-lamivudine study. The fixed-dose nRTI combinations of tenofovir/emtricitabine and abacavir/lamivudine reduce pill burden and offer the possibility of improved lipid levels compared with thymidine-containing nRTI regimens. The STEAL study randomly assigned 360 virologically suppressed patients receiving either nRTI or PI-based antiretroviral therapy to substitute tenofovir/emtricitabine or abacavir/lamivudine for their current nRTI(s) (Abstract 576). Of note, approximately 20% of patients in each group were previously receiving the nRTI to which they were assigned as a single agent. Although virologic response rates did not differ by group, patients who underwent randomization to abacavir/lamivudine experienced a higher rate of the predefined secondary endpoint of lipid changes (new cholesterol level > 6.5 mmol/L, or increase in level > 2 mmol/L; new HDL level < 0.9 mmol/L or decrease in level > 0.5 mmol/L, or new lipid-lowering therapy). The rate of serious non–AIDS-defining events was also higher in the group receiving the abacavir/lamivudine, and the rate of cardiovascular events was also higher in the abacavir/lamivudine recipients than the tenofovir/emtricitabine recipients (7 vs 1, respectively). Bone mineral density fell in the hip and spine in the tenofovir/emtricitabine group, whereas it increased in the abacavir/lamivudine group. Although this study did not target patients with dyslipidemia, it does suggest a potential lipid and possible cardiovascular benefit associated with the change to tenofovir/emtricitabine.

Does tenofovir have a direct effect on lipids? This question was addressed in a pilot study in patients receiving stable antiretroviral therapy to which tenofovir was added during a double-blind, placebo-controlled, randomized, crossover-design ACTG trial (Abstract 714). Dyslipidemic patients had tenofovir or placebo added for 2 12-week periods separated by a 4-week washout period. Despite the small size of the study (only 13 patients with complete data); levels of non-HDL cholesterol, total cholesterol, and LDL cholesterol all showed statistically significant improvement during tenofovir exposure compared with placebo. An unexpected finding in this study was the observed rebound in triglyceride levels during the tenofovir washout period. The mechanism by which tenofovir improves lipid levels requires further study.

Renal Complications

The impact of antiretroviral therapy, host factors, and direct or indirect effects of HIV replication on changes in renal function remain active areas of investigation, as evidenced by presentations at the conference.

The important association between HIV replication and loss of renal function was demonstrated in at least 3 studies. Choi and colleagues examined factors associated with continued loss of renal function among participants in the University of California San Francisco SCOPE (Study of the Consequences of the Protease Inhibitor Era) cohort and identified that in treated patients, transient increases in viral load (blips) were a risk factor for loss of renal function (Abstract 38). Similarly, in a randomized study evaluating intermittent use of antiretroviral therapy, the strategy of 7 days on followed by 7 days off antiretroviral therapy was associated with a greater rate of decline in glomerular filtration rate (GFR) than continuous antiretroviral therapy or the strategy of 5 days on followed by 2 days off therapy (Abstract 742). No statistically significant difference was found in the rate of GFR decline between the latter 2 groups. Finally, among a large group of Kenyans not yet meeting local criteria for antiretroviral treatment, renal function, as measured by estimated GFR, was an independent risk factor for HIV progression (Abstract 741).

The relationship between tenofovir exposure and renal function remains

an active area of investigation. Small but statistically significant changes in GFR have been observed with tenofovir in cohort studies and randomized trials.[7] The HEAT study team reported on changes in renal function over 96 weeks in the randomized comparison between tenofovir/emtricitabine and abacavir/lamivudine combined with lopinavir/r (Abstract 744). Consistent with earlier studies showing an improvement in renal function after initiation of antiretroviral therapy, small increases in the estimated GFR and creatinine clearance were observed in both treatment groups, although the improvement was slightly greater in the abacavir/lamivudine group. Progression to an estimated GFR of less than 60 mL/min occurred more commonly in the tenofovir/emtricitabine recipients (n = 11) than in the abacavir/lamivudine group (n = 4). Proximal renal tubule dysfunction occurred rarely but only in tenofovir/emtricitabine-exposed patients (n = 5).

Risk factors for proximal renal tubular (PRT) dysfunction were examined in 2 cohort studies (Abstracts 743,745). PRT dysfunction was identified in 18 of 92 consecutively studied patients who received tenofovir for longer than 6 months (Abstract 745). A higher mid-dose plasma level of tenofovir (> 160 ng/mL) was identified as an important predictor of PRT and had a sensitivity of 61% and specificity of 80%. A larger cross-sectional study from the Swiss HIV cohort (n = 1202) identified the highest prevalence of PRT in patients treated with tenofovir with (49%) or without (16%) concurrent PI therapy (Abstract 743). In a multivariate model adjusting for several factors associated with renal disease, both tenofovir and PI exposure remained statistically significant predictors. Currently, only limited data are available to examine the longer term outcomes of patients identified with subclinical tubular dysfunction; however, there is concern that increased excretion of phosphate could lead to bone loss over the longer term. Longitudinal studies addressing this issue are needed in patients treated with a range of therapies for HIV infection.

Is there a genetic predisposition for tenofovir-associated PRT dysfunction? Novoa and colleagues hypothesized that polymorphisms in genes encoding for drug transporters in the renal tubules could explain why some patients may be predisposed to this complication (Abstract 37). The study was limited to patients receiving tenofovir at a single center. In examining 12 single nucleotide polymorphisms in 5 genes, they identified an association between patients harboring the genotype GG in the *ABCC2-24* gene and the development of renal tubulopathy. The authors noted that the mechanism through which this polymorphism may operate is unclear because tenofovir is apparently not a substrate for this particular transporter. Nonetheless, this emerging area of investigation could lead to testing to identify patients at highest risk of this complication.

Bone Disease

Contributions of HIV disease, immune activation and inflammation, antiretroviral therapy, and host factors to loss of bone density in HIV infection continue to be explored. Data from cross-sectional studies confirm high rates of osteopenia and osteoporosis in men (higher rates in men than in postmenopausal women, in fact), without an excess rate in hypogonadal men (Abstract 754) compared with eugonadal men, and a higher rate of low bone density in women with HIV and HCV coinfection (Abstract 820). In one of the few longitudinal studies, investigators from the Menopause Study (MS) noted a higher prevalence of low bone density in HIV-infected women than in HIV-uninfected women but no difference in the rate of bone loss in the 2 groups over 18 months of follow-up (Abstract 757). Opioid use and the presence of depressive symptoms were associated with bone loss in the women in this study.

Potential mechanisms of bone loss in HIV were explored in clinical and in vitro studies. Gazzola and colleagues reported an association between lower frequency of central memory CD8+ CD127+ cells and low bone density as measured by dual x-ray absorptiometry scan, suggesting that immune activation (a possible contributor to the loss of CD127+ cells) might be an important contributor to bone loss (Abstract 752). Levels of several cytokines involved in bone loss (tumor necrosis factor-alpha, IL-6, and receptor activator for nuclear factor κB ligand), although higher in postmenopausal HIV-infected women than in HIV-uninfected women, did not correlate with levels of bone mineral density (Abstract 758). Among HIV-infected women, markers of bone resorption (N-telopeptide and C-telopeptide) were higher in those receiving antiretroviral therapy, but the duration of antiretroviral therapy did not appear to be associated with lower bone mineral density. A small study of changes in markers of bone turnover in patients starting antiretroviral therapy with different regimens demonstrated increases in bone resorption and formation markers. Initiation of treatment with tenofovir or a PI was associated with greater increases in osteocalcin (a bone formation marker); these effects did not appear to be mediated through osteoprotegerin receptor agonist and the receptor activator for nuclear factor κB ligand (Abstract 760).

Collectively, the studies presented at this year's conference extend our understanding of the prevalence, pathogenesis, risk factors, and in some cases treatment for the expanding array of complications of HIV disease and antiretroviral therapy. A consistent theme across many of these areas of research is the attempt to more accurately define and quantify the contributions of the virus, the host, and antiretroviral therapy to the development of these important clinical problems.

A list of all cited abstracts appears on pages 89-95.

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Advances in Antiretroviral Therapy

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

The 16th Conference on Retroviruses and Opportunistic Infections maintained its tradition of being recognized as the preeminent forum for detailing the state-of-the-art of antiretroviral therapy. Abundant new and updated information was presented on investigational drugs, approaches to the management of treatment-naive and -experienced patients, the use of drugs for prevention of mother-to-child HIV-1 transmission, and antiretroviral drug resistance. Of particular note were the continued advances in antiretroviral treatment and research emanating from resource-limited settings and the presentation of the results of 2 much-anticipated, phase III trials of interleukin-2, ESPRIT (Evaluation of Subcutaneous Proleukin in a Randomized International Trial) and SILCAAT (Subcutaneous, Recombinant Human Interleukin-2 in HIV-Infected Patients With Low CD4+ Counts Receiving Active Antiretroviral Therapy).

Investigational Drugs

Cytochrome P450 3A Inhibitors

GS-9350. Data were presented on 2 compounds that inhibit cytochrome P450 3A (CYP3A) without having antiretroviral activity. These are being developed as alternatives to ritonavir. Mathias and colleagues presented data on GS-9350 (Abstract 40). This compound provides potent irreversible inhibition of CYP3A without demonstrable anti-HIV-1 activity. GS-9350 exhibited more specificity for CYP3A inhibition than ritonavir (ie, other CYP450 enzymes were less likely to be inhibited by GS-9350). GS-9350 did not inhibit normal lipid accumulation or glucose uptake in adipocytes, suggesting less potential for metabolic abnormalities. Numerous single-dose and multiple-dose studies of GS-9350 were performed in HIV-uninfected participants. These studies evaluated change in clearance of midazolam, which is metabolized by CYP3A. GS-9350 100 mg once daily or 200 mg once daily provided similar reductions in midazolam clearance to that provided by ritonavir 100 mg daily. A coformulated 4-drug tablet of elvitegravir (an investigational integrase inhibitor)/tenofovir/emtricitabine/GS-9350 is currently under development. Elvitegravir concentrations with GS-9350 150 mg once daily resemble those with ritonavir 100 mg once daily. The exposure to emtricitabine was increased 20% in the presence of elvitegravir/GS-9350, and the tenofovir exposure was bioequivalent. There were no substantial safety concerns; a drug-related, transient grade 3 elevation of alanine aminotransferase developed in 1 participant. Phase II studies of the 4-drug tablet are under way.

SPI-452. Gulnik and colleagues from Sequoia Pharmaceuticals presented data on SPI-452, a potent inhibitor of CYP3A4 with no discernible inhibition of HIV-1 protease or HIV-1 replication (Abstract 41). SPI-452 was generally well tolerated, with no serious adverse events. No changes in serum lipid levels were observed compared with placebo. The half-life was 15 hours to 20 hours at higher doses. SPI-452 enhanced the pharmacokinetic profile of darunavir and atazanavir in a manner similar to that of ritonavir in historical cohorts. However, the investigators did not evaluate a concurrent ritonavir control group.

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Entry Inhibitors

VCH-286. Roldan and colleagues presented preclinical data on VCH-286, an investigational, potent, and selective CC chemokine receptor 5 (CCR5) antagonist (Abstract 550). VCH-286 showed potent inhibition of 62 primary HIV-1 isolates to CCR5.

CD4-BFFI. Jekle and colleagues presented data on a novel entry inhibitor, CD4-BFFI (Abstract 551). This compound combined an anti-CD4 monoclonal antibody (anti-CD4 mAb 6314) with a fusion inhibitor (T-651). The antiviral activity of the bifunctional compound was much greater than that of the individual components.

Reverse Transcriptase Inhibitors

CMX157. CMX157 is a lipid conjugate of tenofovir that leads to 30-fold higher intracellular levels of tenofovir-diphosphate. Lanier and colleagues tested the hypothesis that CMX157 also enters peripheral blood mononuclear cells by associating with HIV-1 virions (Abstract 556). They found that approximately 30,000 molecules of CMX157 were associated with each virion compared with approximately 100 molecules of tenofovir. HIV-1 virions inoculated with CMX157 were less infectious, whereas inoculation with tenofovir did not affect infectivity.

Ribonuclease H inhibitors. Current reverse transcriptase inhibitors (ie, nucleoside analogue reverse transcriptase inhibitors [nRTIs] and nonnucleoside analogue reverse transcriptase inhibitors [NNRTIs]) work by inhibiting the polymerase function of reverse transcriptase. Williams and colleagues presented data on inhibitors of ribonuclease (RNase) H, a portion of reverse transcriptase responsible for cleaving the RNA template following synthesis of the first DNA strand during reverse transcription (Abstract 559). They

found a series of inhibitors of RNase H that also showed antiviral effects in the cell culture; however, these compounds had a modest therapeutic index with relatively low levels of 50% cellular cytotoxicity.

Integrase Inhibitors

QNL111. Two abstracts presented preclinical data on integrase inhibitors with novel mechanisms of action. Raltegravir and the investigational integrase inhibitor elvitegravir work by inhibiting the strand-transfer reaction. Thibaut and colleagues presented data on a new quinoline family of compounds (Abstract 553). These compounds are integrase binding inhibitors that inhibit the 3' processing step. The lead compound, QNL111, has a 50% inhibitory concentration for HIV replication of 800 nM and retained activity against isolates resistant to raltegravir and elvitegravir.

Integrase-LEDGF/p75 inhibitors. Lens epithelium-derived growth factor p75 (LEDGF/p75) acts as a tethering factor for integrase to chromatin. Benarous and colleagues screened 70,000 compounds for their ability to inhibit the LEDGF/p75-integrase interaction (Abstract 555). Compounds were identified that inhibited HIV-1 integration without inhibiting the catalytic activity required for the strand-transfer reaction, and these compounds retained activity against HIV-1 resistant to raltegravir.

Maturation Inhibitors

MPC-9055. Baichwal and colleagues presented data on a new maturation inhibitor, MPC-9055 (Abstract 561). This compound blocks the processing of the CA-SP1 Gag intermediate to the mature protein CA. Serial passage experiments identified a single amino acid substitution in Gag, A364V, which induced resistance. Beelen and colleagues presented the safety, tolerability, and pharmacokinetics of MPC-9055 in HIV-uninfected volunteers (Abstract 570). Fifty-five participants received a single dose of MPC-9055, and 20 received placebo. There were more treatment-emergent events in those receiving MPC-9055. All events were mild except for 1 instance of moderate diarrhea. The half-life was 23 hours to 42 hours, and absorption was increased in the presence of meals. Further multiple-dose studies are planned.

Dolabella diterpene. Abreu and colleagues presented data on dolabella diterpene (DT), a natural extract from the Brazilian brown algae *Dictyota pfaffi* (Abstract 562). This compound had a median effective concentration versus HIV-1 of 30 nM. The researchers found unprocessed p55 Gag and partially processed p41 and p25 precursors accumulating in HIV virions in the presence of DT. This compound retained activity against viral strains with high-level resistance to bevirimat, another HIV maturation inhibitor. The authors concluded that DT binds to a different site than bevirimat, possibly the p55 Gag precursor.

RNA Interference

***tat* and *vif* short-interfering RNA**. Choi and colleagues evaluated RNA interference in a humanized mouse model of HIV (Abstract 564). They noted that HIV is highly mutable, and it is likely that escape mutants would develop if only a single RNA sequence were targeted. They targeted 2 highly conserved regions in *tat* and *vif* genes by administering synthetic short-interfering RNA specific to those sequences that was delivered using a T-cell-targeting, single-chain antibody as a carrier. This was highly effective at suppressing viral replication, with all mice having plasma HIV-1 RNA levels below the limit of detection throughout the treatment period.

Immune-Based Therapies

Interleukin-2

Results were presented of 2 large, long-awaited, randomized, controlled, open-label trials evaluating the efficacy of subcutaneous administration of interleukin-2 (IL-2) in combination with antiretroviral therapy versus antiretroviral therapy alone (Abstracts 90aLB, 90bLB). Both studies used occurrence of an opportunistic disease or death as the primary endpoint.

ESPRIT. The ESPRIT (Evaluation of Subcutaneous Proleukin in a Randomized International Trial) enrolled 4111 participants from 25 countries. Eligible enrollees had a CD4+ count above 300 cells/μL. Participants either continued or initiated combination antiretroviral therapy at study entry. Patients who underwent randomization to receive IL-2 were given 3 5-day cycles of 7.5 mIU subcutaneously, twice daily at 8-week intervals. Additional cycles were recommended as needed to keep the CD4+ cell count greater than twice the baseline, or at least 1000 cells/μL.

At study entry, the median CD4+ count was 457 cells/μL; the median nadir CD4+ count was 197 cells/μL; 80% had a plasma HIV-1 RNA level at or below 500 copies/mL; 26% had a prior AIDS-defining illness; 19% were female; 24% were nonwhite; and mean age was 41 years. The median length of follow-up was 6.9 years.

Patients in the IL-2 group maintained, on average, a CD4+ count 160 cells/μL higher than that of the control group. However, the rate of primary endpoints (opportunistic disease or death) did not differ between the IL-2 and control groups (1.13 vs 1.21 events/100 person-years, respectively; hazard ratio [HR], 0.93; 95% confidence interval [CI], 0.75–1.16). Similarly, the rate of death and serious non-AIDS events was similar between the 2 groups. There were more grade 4 (ie, life-threatening) events in the IL-2 group (HR, 1.23; P = .003). The difference in grade 4 events was driven by administration and injection site reactions, psychiatric events, and vascular events such as deep venous thrombosis.

SILCAAT. The SILCAAT (Subcutaneous, Recombinant Human Interleukin-2 in HIV-Infected Patients With Low CD4+ Counts Receiving Active Antiretroviral Therapy) study randomized 1695 participants from 14 countries. Eligible participants had a CD4+ count between 50 cells/μL and 299 cells/μL. Patients either continued or initiated combination

antiretroviral therapy. Participants who underwent randomization to IL-2 were given 6 5-day cycles of 4.5 mIU subcutaneously, twice daily at 8-week intervals. Additional cycles were recommended as needed to keep the CD4+ count 150 cells/μL greater than baseline.

At study entry, the median CD4+ count was 202 cells/μL; the median nadir CD4+ count was 60 cells/μL; 81% had a plasma HIV-1 RNA level at or below 500 copies/mL; 32% had a prior AIDS-defining illness; 17% were female; 20% were nonwhite; and mean age was 40 years. The median length of follow-up was 7.6 years.

Participants in the IL-2 group maintained, on average, a CD4+ count 57 cells/μL higher than that of the control group. However, the rate of primary endpoints (opportunistic disease or death) did not differ between the IL-2 and control groups (HR, 0.91; 95% CI, 0.70 – 1.18). The rate of grade 4 adverse events was similar between the IL-2 and control groups (HR, 1.11; $P = .30$). However, the rate of grade 4 events in the first year after randomization was statistically significantly higher in the IL-2 group (HR, 2.02; $P = .01$). Taken together, data from these studies show that the CD4+ count gain associated with IL-2 administration does not translate into reduced clinical events. In addition, there appears to be an increased risk of serious adverse events attributed to IL-2 therapy.

Interleukin-2 and inflammatory markers. Porter and colleagues evaluated the effect of subcutaneous IL-2 treatment on levels of high-sensitivity C-reactive protein (hsCRP) and D-dimer (Abstract 533). They found that the levels of these molecules were increased statistically significantly in patients with (n = 34) and without (n = 19) virologic suppression. The median level of hsCRP increased from 1.15 mg/L to 63.8 mg/L and 1.01 mg/L to 62.6 mg/L, respectively, in these groups. The D-dimer level increased from below 0.20 μg/mL to 0.79 μg/mL and from 0.27 μg/mL to 2.91 μg/mL, respectively ($P < .001$ for all 4 comparisons). The increases were transient and returned to baseline within 1 month after IL-2 administration.

Genetically modified CD4+ cells. There has been a recent appreciation that HIV-1 infection causes a profound depletion of gut lymphoid tissue early in the infection. Collman and colleagues presented data on 12 patients receiving suppressive antiretroviral therapy in an ongoing phase I/II open-label trial of genetically modified autologous CD4+ cells (Abstract 83). The CD4+ cells are collected and transduced ex vivo with lentiviral vector encoding a 937-nucleotide antisense construct to the *env* gene. Six infusions of 10^{10} cells each were given to each participant, followed by interruption of antiretroviral therapy in 7 patients. The genetically modified CD4+ cells persisted in the plasma after treatment interruption. The researchers also found that these cells migrated to the rectal epithelium and persisted after treatment interruption. Future analyses will evaluate whether this therapy can partially control HIV-1 replication.

Histone deacetylase inhibitors. Histone deacetylase (HDAC) is a key enzyme for maintaining latency of HIV-1 infection in resting CD4 + cells. HDAC inhibitors are being pursued in an effort to clear this latent reservoir of HIV-1 infection as a key step toward HIV-1 eradication. Hong and colleagues presented data on 2 synthetic HDAC inhibitors, CGMC0005 and CGMC0006 (Abstract 418). They found that both compounds induced HIV-1 replication, as measured by p24 antigen production in latently infected cell lines with 50% effective doses of 0.11 μM and 0.04 μM, respectively.

Clinical Trials of Antiretroviral Therapy in Treatment-Naive Patients

Antiretroviral Therapy in Patients with Tuberculosis

Swaminathan and colleagues presented data on 127 HIV-1-infected patients with active tuberculosis (Abstract 35). Participants received standard short-course tuberculosis therapy, and underwent randomization after the 2-month induction phase to receive either open-label efavirenz (600 mg once daily) or nevirapine (400 mg once daily after 2 weeks of 200 mg once daily); both were given with didanosine and lamivudine. The median age was 35.5 years, and 99 (78%) were men. The median CD4+ count was 84 cells/μL, and the median plasma HIV-1 RNA level was 310,000 copies/mL. After 24 weeks of antiretroviral therapy, more patients in the efavirenz group achieved a plasma HIV-1 RNA level below 400 copies/mL (50/59 patients, 85%) compared with 38 of 57 patients (67%) in the nevirapine group ($P = .038$). Moreover, there were 5 deaths in the nevirapine group and none in the efavirenz group. These results along with the virologic data prompted the Data and Safety Monitoring Board to stop the study early.

Efavirenz Versus Lopinavir/Ritonavir; Didanosine Plus Zidovudine Versus Stavudine Plus Lamivudine

Ratsela and colleagues presented data from Phidisa II, a randomized, factorial-design study of lopinavir/ritonavir (lopinavir/r) versus efavirenz and didanosine plus zidovudine versus stavudine plus lamivudine (Abstract 594). Eligible participants had a CD4+ count below 200 cells/μL or a prior clinical AIDS diagnosis. The primary endpoint was AIDS or death. The study included 1771 patients with a median CD4+ count of 106 cells/μL and plasma HIV-1 RNA level of 144,000 copies/mL. There was no statistically significant difference in the primary endpoint between the groups. There did not appear to be any statistically significant difference in the rates of virologic suppression between the efavirenz and lopinavir/r groups 48 weeks after randomization (66% vs 65%, respectively). Consistent with prior studies, the CD4+ count responses were greater in the lopinavir/r group than in the efavirenz group: an increase of 317 cells/μL at 3 years versus 272 cells/μL, respectively ($P = .004$). Although the rates of the primary endpoint did not differ between the didanosine plus zidovudine recipients and the stavudine plus lamivudine recipients, the CD4+ cell count and virologic data favored stavudine plus lamivudine.

Clinical Trials of Antiretroviral Therapy in Treatment-Experienced Patients

PRO 140

PRO 140 is a humanized monoclonal antibody that blocks binding of HIV to CCR5. Thompson and colleagues presented data from a phase IIa study that evaluated the subcutaneous administration of PRO 140 in HIV-1-infected subjects (Abstract 571a). Eligible participants had plasma HIV-1 RNA levels above 5000 copies/mL, CCR5-using HIV, and no antiretroviral therapy within the past 12 weeks. The 44 patients underwent randomization to receive placebo, PRO 140 162 mg once weekly, PRO 140 324 mg once every 2 weeks, or PRO 140 324 mg once weekly. The mean change in plasma HIV-1 RNA level was +0.15, −0.75, −1.2, and −1.51 $\log_{10}$ copies/mL in the 4 groups, respectively. Administration site reactions were mild or absent in all subjects. The authors concluded that this study supported further investigation of infrequent subcutaneous administration of PRO 140.

Antiretroviral Treatment Strategies

Intensification

New antiretroviral assays can measure plasma HIV-1 RNA level with a lower limit of detection of 1 copy/mL; many patients taking combination antiretroviral therapy with virologic suppression using standard ultrasensitive assays have detectable residual viremia using this 1 copy/mL assay. The source of the residual viremia is not known. If it represents complete cycles of virus replication, then suppressing this residual viremia could hasten the clearance of the latent reservoir. Several studies examined whether this residual viremia could be suppressed by intensifying combination antiretroviral regimens with a new drug.

Raltegravir. Jones and colleagues enrolled 5 participants with a mean level of residual viremia of 1.9 copies/mL (Abstract 423b). Participants added raltegravir to their existing antiretroviral drug regimen for 30 days. The mean level of viremia at the end of the intensification period was 3.2 copies/mL, which was not statistically significantly different from the level prior to intensification.

Buzon and colleagues randomly assigned 65 participants with plasma HIV-1 RNA levels below 50 copies/mL to either intensify their existing regimen by adding raltegravir for 48 weeks (n = 44) or continue their regimen without intensification (n = 21) (Abstract 423a). Intensification did not alter the level of proviral DNA. There was a statistically significant increase in episomal HIV-1 DNA at week 2, but the difference was not seen after week 2. The authors concluded that this increase provided evidence for continued de novo viral infection with suppressive antiretroviral therapy (ie, raltegravir prevented integration of viral DNA from ongoing replication that was instead converted to episomal DNA).

Enfuvirtide. Gandhi and colleagues evaluated the latent reservoir directly in participants initiating an intensive first antiretroviral regimen of enfuvirtide, saquinavir/ritonavir, and tenofovir/emtricitabine (Abstract 424). They enrolled 19 patients with a median CD4+ count of 262 cells/μL and plasma HIV-1 RNA level of 4.8 $\log_{10}$ copies/mL. Seventeen participants achieved a plasma HIV-1 RNA level below 50 copies/mL within 48 weeks, 9 of whom remained on enfuvirtide for at least 48 weeks and were included in the primary analysis. The primary endpoint was the proportion of latently infected, resting memory CD4+ cells, which was measured every 24 weeks. This endpoint did not change over the 96 weeks of study follow-up. The primary endpoint was similar to that observed in previous studies using less intensive regimens. The authors concluded that other strategies were needed to decrease the size of the latent reservoir.

Switching from Lopinavir/Ritonavir to Raltegravir

Eron and colleagues presented data on 2 large, randomized, placebo-controlled trials of switching lopinavir/r to raltegravir in patients with successful virologic suppression on a lopinavir/r-containing regimen (SWITCHMRK-1 and SWITCHMRK-2) (Abstract 70aLB). Eligible participants had a plasma HIV-1 RNA level below 50 copies/mL (or < 75 copies/mL by branch DNA assay) for at least 3 months and had not received lipid-lowering therapy for at least 12 weeks. Patients with prior virologic failure were not excluded, and enrollees were not required to be intolerant of lopinavir/r. The primary objectives of these studies were to show a decrease in lipid levels 12 weeks after randomization and noninferiority of continued virologic suppression 24 weeks after randomization for those switching to raltegravir compared with those continuing treatment with lopinavir/r.

In SWITCHMRK-1 and -2, 348 and 354 patients, respectively, underwent randomization. The mean age was 44 years and 42 years; 79% and 78% were men; and 28% and 53% were nonwhite, respectively. The mean CD4+ count at baseline was approximately 480 cells/μL in both studies. The median number of prior antiretroviral drugs taken was 5 and 6, respectively.

Levels of triglycerides, total fasting cholesterol, and non-high-density-lipoprotein (HDL) cholesterol decreased statistically significantly with the switch to raltegravir ($P < .001$ for each comparison in both studies). However, switching to raltegravir did not achieve noninferiority for maintaining virologic suppression compared with continuing lopinavir/r treatment. The proportion of patients with a plasma HIV-1 RNA level below 50 copies/mL at week 24 was 81% for the raltegravir group versus 87% for the lopinavir/r group (treatment difference, −6.6%; 95% CI, −14.4 to +1.2) in SWITCHMRK-1 and 88% versus 94% (treatment difference, −5.8%; 95% CI, −12.2 to +0.2) in SWITCHMRK-2. When combining both studies, the proportion with plasma HIV-1 RNA level below 50 copies/mL at week 24 was statistically significantly lower for the raltegravir group. Of the 32 patients with virologic failure, 27 (84%) reported that this was not their first antiretroviral regimen, and 18 (66%) reported having experienced virologic failure with a prior regimen.

Antiretroviral Treatment in Resource-Limited Settings

The conference kicked off this year with an impressive keynote address, the N'Galy-Mann Lecture by Gray and McIntyre, who detailed their experiences in HIV clinical research and care in Soweto, South Africa (Abstract 18).

Treatment Scale-Up in Resource-Limited Settings

Gray, McIntyre, and colleagues founded the Perinatal HIV Research Unit (PHRU) in Soweto in 1996 and have expanded the program over the past 2 decades to include 50 active research programs in HIV prevention, care, treatment, and the sociobehavioral and economic impacts of the HIV epidemic. Relevant to this article on antiretroviral therapy advances, the PHRU launched its first antiretroviral treatment trial in 1996, as a means of providing access to antiretroviral therapy in a setting where it was otherwise unavailable. The PHRU began offering antiretroviral therapy outside of clinical trials in 2001 with funds from the French government, and the program expanded with PEPFAR (President's Emergency Plan for AIDS Relief) support to include 45,000 people started on antiretroviral therapy in a collaboration of 10 partners and 45 sites over 4 provinces.

Gray and McIntyre also have been leaders in clinical research, including an ongoing treatment trial comparing nurse-monitored with physician-monitored treatment; the CHER (Children with HIV Early Antiretroviral Therapy) study, which showed that early treatment of infants with antiretroviral therapy led to substantial improvements in mortality; and the OCTANE (Optimal Combination Therapy After Nevirapine Exposure) study (Abstract 94LB), which demonstrated improved outcomes with lopinavir/r-based antiretroviral therapy compared with nevirapine-based antiretroviral therapy in women exposed to single-dose nevirapine for prevention of mother-to-child transmission (PMTCT) of HIV.

Throughout this time, the South African President, Thabo Mbeki, and his Health Minister, Manto Tshabalala-Msimang, waged both active and underground campaigns to question the role of HIV as the cause of AIDS and the efficacy of antiretroviral treatment. Their interventions ranged from restructuring the South African Medicines Control Council when it refused to approve treatment trials of a toxic industrial solvent as antiretroviral therapy to casting personal aspersions against the PHRU and its researchers. Despite this opposition, the support of outside funding institutions and a strong treatment advocacy program led by activists allowed the PHRU to continue functioning and the South African national antiretroviral treatment program to grow.

Gray and McIntyre concluded by discussing current challenges in confronting the South African epidemic, including the 1.8 million people estimated to be in need of antiretroviral therapy by 2011, looming funding shortfalls, and the need for increased outreach and care for older women and men who have sex with men (MSM). They also emphasized the continuing need for activist scientists, in the mold of N'Galy and Mann, who recognize the importance of human rights in the response to the HIV epidemic.

Coutinho spoke on the "Limits and Realities of Antiretroviral Therapy Scale-up" (Abstract 12). He noted that, currently, 30% of individuals needing antiretroviral therapy receive it, and antiretroviral therapy scale-up does not keep pace with the rate of new infections. The success in global expansion of access to antiretroviral therapy, as indicated by the increase from the 200,000 people living with HIV or AIDS receiving treatment in resource-limited settings (RLS) in 2002 to the over 3 million receiving treatment in 2007, is largely the result of increased access by the "low-hanging fruit," Coutinho's term for individuals who were waiting for initial antiretroviral therapy in situations where capacity was in place to deliver care. The challenge of the future is to scale up antiretroviral therapy access in locations without current capacity and for people living with HIV who are less likely to seek care.

As signs of progress in antiretroviral therapy scale-up, Coutinho cited the increases in life expectancy in Botswana, reductions in mortality among HIV-infected people after antiretroviral therapy became available in Uganda, and the fact that task-shifting, which places more responsibilities for patient care onto nurses and midwives, does not appear to have affected treatment outcomes. However, he drew attention to the global underperformance of PMTCT, with only 18% of women giving birth in low- and middle-income countries being tested for HIV, and in diagnosis of HIV and tuberculosis coinfection, with only 12% of people with tuberculosis being tested for HIV. Rates of mortality (20%) and loss to follow-up (15%–17%) in the first 5 years of treatment are also unacceptably high. Coutinho concluded by anticipating future challenges to the second, more difficult stage of antiretroviral therapy scale-up, including the dramatic lack of human resources and laboratory capacity, the geographic distribution of people in need of care, the transition to more complicated cases and second-line therapy, and the gap between current funding and that needed for universal access to antiretroviral therapy.

Coetzee and Boulle presented data on the response to the HIV epidemic in Cape Town, South Africa, including information relevant to antiretroviral treatment scale-up (Abstract 58). Currently, antiretroviral therapy coverage in Cape Town is estimated at 60% using antiretroviral therapy eligibility criteria of those with World Health Organization (WHO) stage 4 disease. However, between 2006 and 2007, as clinics reached saturation, the rate of increase in people requiring antiretroviral therapy outstripped the increase in those receiving antiretroviral therapy. Five-year outcomes for those receiving antiretroviral therapy in the city remain good, with 73% remaining in care, 12% taking second-line therapy, and 87% of those in care with suppressed plasma HIV-1 RNA levels. The burden of HIV disease on hospitals in Cape Town is high, with 60% of admissions and 52% of deaths in 1 hospital HIV-related and a 70% rate of HIV and tuberculosis coinfection. Coetzee also noted a decrease in HIV prevalence among 15- to 19-year-olds over the past 5 years and a decrease

in the incidence of sexually transmitted infections in Khayelitsha, from 0.27 per 100,000 people in 2003 to 0.13 per 100,000 people in 2007.

Schechter described the Brazilian response to scale-up as a reflection of its political climate (Abstract 59). The military dictatorship that led the country from 1964 to 1985 gave way to a democratic regime and a national universal health care system. When the first AIDS cases were recognized in the 1980s and private insurance companies refused to provide care, activists joined ranks to fight for HIV care. In 1988, nongovernmental organizations and governmental bodies began to work together to provide universal HIV care, and the government began to provide zidovudine therapy. Currently, the Brazilian program offers numerous options for initial therapy, including both protease inhibitor (PI)- and NNRTI-based regimens, most of which are provided by the government regardless of patient insurance status.

The responsibilities for laboratory testing and other services in Brazil are divided between state and federal government, which leads to disparities between states in access to services. Antiretroviral therapy outcomes are comparable to those in many resource-rich settings: baseline CD4+ count at antiretroviral therapy initiation is 200 cells/μL, and 72% of individuals starting antiretroviral therapy achieve plasma HIV-1 RNA levels of less than 500 copies/mL after 6 months. Non-HIV-related causes of death are on the rise; the cardiovascular disease death rate is growing at 8% per year for those with HIV and 0.8% per year for those without. The majority of people in Brazil are unaware of their HIV serostatus, and the complexity of injection drug use and MSM subepidemics that vary by region requires targeted outreach campaigns.

Schechter concluded by summarizing future improvements necessary for the continued success of the Brazilian program, including an expanded definition of universal access from antiretroviral therapy alone to treatment as 1 component in a sustainable access-to-treatment effort, an increase in targeted and operational research efforts, and improvement in the speed and quality of actions by institutional review boards.

Mohammed and colleagues presented data on the unmet need for HIV testing, care, and treatment in Kenya derived from the 2007 Kenya AIDS Indicator Survey (KAIS) (Abstract 137LB). This survey included individuals 15 years to 64 years of age in a stratified, 2-stage, cluster-sample design covering 8 provinces and urban and rural areas. Household- and individual-level data were collected between August 2007 and December 2007 in the form of interviews and venous blood samples. Overall response rates were 97% for households, 91% for individuals, and 80% for blood samples. HIV prevalence results showed that 8.4% of women and 5.4% of men were HIV seropositive, with peak prevalences in age 30 years to 34 years for women and 40 years to 44 years for men. These results were similar to the country's 2003 estimates of HIV prevalence. Uncircumcised men were 3.4 times more likely to have HIV infection than were circumcised men. Of HIV-seropositive adults in the sample, 84% were unaware they were infected, and 44% of married or cohabitating HIV-infected persons had an uninfected partner. An estimated 120,000 HIV-infected adults with CD4+ counts below 250 cells/μL are in need of antiretroviral therapy, but among those who knew their HIV serostatus and were eligible for antiretroviral therapy, 92% were receiving therapy. The authors concluded that low awareness of HIV serostatus was the major barrier to universal antiretroviral therapy access in Kenya, and that this type of nationally representative survey is essential for monitoring the epidemic and improving the national response.

Primary Treatment Outcomes in Resource-Limited Settings

Lockman and colleagues presented the results of the OCTANE A5208 Trial, a randomized trial examining whether prior single-dose nevirapine treatment for PMTCT limits future virologic response to nevirapine-containing antiretroviral regimens (Abstract 94LB). Two concurrent trials were conducted within the study design. The first compared lopinavir/r plus tenofovir/emtricitabine with nevirapine plus tenofovir/emtricitabine in 240 women with prior receipt of single-dose nevirapine and was designed to show superiority of the lopinavir/r regimen. The second trial compared the same 2 regimens in 500 women without single-dose nevirapine exposure and was designed to show equivalence; it is still under way.

Inclusion criteria for the first trial were as follows: CD4+ count less than 200 cells/μL, no prior antiretroviral therapy except single-dose nevirapine at least 6 months previously, up to 10 weeks of prior zidovudine treatment, and an estimated creatinine clearance rate of over 60 mL/min. Ten sites in 7 countries in sub-Saharan Africa enrolled study participants, and the primary endpoint was death or time to virologic failure. The authors defined virologic failure as a confirmed plasma HIV-1 RNA level less than 1 $\log_{10}$ copies/mL below the baseline level after 12 weeks of treatment or more than 400 copies/mL after 24 weeks of antiretroviral therapy and conducted a primary intent-to-treat analysis.

In October 2008, the Data and Safety Monitoring Board recommended cessation of the first trial after enrollment of 243 women into the trial, when the median duration of follow-up was 73 weeks. There were no statistically significant differences in the baseline characteristics of participants by treatment group. Overall, 41 women reached the primary endpoint described above: 31 in the nevirapine group and 10 in the lopinavir/r group. The estimated HR of reaching the endpoint in the nevirapine group was 3.55 (95% CI, 1.71–7.34 compared with the lopinavir/r group), and the difference in risk between the 2 groups was established by 24 weeks on treatment. The rate of treatment discontinuation was statistically significantly higher in the nevirapine group: 38 women (31%) compared with 6 (5%) in the lopinavir/r group (HR, 7.43; 95% CI, 3.14–17.59), and common reasons for discontinuation were adverse events and virologic failure.

Drug resistance testing showed that 14% of women had nevirapine resis-

tance mutations at baseline, and the median time since last single-dose nevirapine exposure was 11 months in women with nevirapine resistance compared with 17 months in women without resistance (P = .024). Although the proportion of women with virologic failure or death was higher among those with nevirapine resistance, there was a trend toward virologic failure or death in the nevirapine group, even among women without nevirapine resistance (P = .057). The data, when broken down by time since last single-dose nevirapine exposure, also suggested that the difference between treatment groups was lower among women starting antiretroviral therapy more than 24 months after receiving single-dose nevirapine. The authors noted that these findings may not be applicable to women who received PMTCT regimens other than single-dose nevirapine, and that treatment success in the lopinavir/r trial was higher than anticipated.

Lawn and colleagues presented data, now published, on the changes in mortality risk associated with CD4+ count response to antiretroviral therapy in South Africa (Abstract 140).[1] They sought to determine mortality estimates for those receiving antiretroviral therapy for longer than 1 year and examined the relationships between risk of mortality, pretreatment CD4+ counts, and CD4+ count response to antiretroviral therapy, using an observational cohort in the Gugulethu township of Cape Town, South Africa. National antiretroviral therapy guidelines allow for initiation of a first-line NNRTI-based regimen when the CD4+ count falls below 200 cells/μL or a patient has WHO clinical stage IV HIV disease.

Between 2002 and 2007, 2434 patients in the cohort initiated antiretroviral therapy; 67% were women, median age was 33 years, median CD4+ count at antiretroviral therapy initiation was 101 cells/μL, and 23% of patients had WHO stage IV disease. The median follow-up period was 1.3 years, or 3155 person-years, and 192 deaths occurred during this time. Cumulative mortality was 8.4% at 12 months and 13.2% at 48 months. Mortality at 48 months for patients with a pretreatment CD4+ count less than 100 cells/μL was 16.7%, almost twice that of those with CD4+ counts above 100 cells/μL (9.5%). Comparing these data with data from the ATHENA (AIDS Therapy Evaluation in the Netherlands) cohort, mortality for similarly stratified patients is approximately 3 times higher across all strata for the Gugulethu cohort.

To determine the effect of CD4+ count response to antiretroviral therapy on mortality, the investigators calculated the amount of person-time accrued in each 100 cells/μL stratum of CD4+ counts during the follow-up period. The mortality rate in deaths per 100 person-years falls as CD4+ count rises, with a threshold effect at 200 cells/μL. Mortality ranged from 5.4 to 38.6 deaths per 100 person-years for CD4+ counts below 200 cells/μL to 1.2 to 2.7 deaths per 100 person-years for CD4+ counts above 200 cells/μL. In the multivariate analysis, age, WHO stage IV disease, and plasma HIV-1 RNA level above 400 copies/mL all correlated with mortality, but the largest correlation was for CD4+ count response strata. For those whose CD4+ count remained between 0 cells/μL and 49 cells/μL, the risk ratio for mortality was 11.63 (95% CI, 3.95–34.29) compared with those whose CD4+ counts rose to over 500 cells/μL during antiretroviral therapy.

The authors also note that most of the person-time accrued in the lower CD4+ count strata occurred in the first 12 months after antiretroviral therapy initiation, and that those with a pretreatment CD4+ count below 100 cells/μL made up 53% of the time accrued with CD4+ counts less than 200 cells/μL compared with those with a pretreatment CD4+ count above 100 cells/μL (28% of the time with CD4+ count < 200 cells/μL). Thus, the patients with the lowest baseline CD4+ counts spent more time with levels below 200 cells/μL and had higher risks of death. The investigators concluded that these data argue for an increase in the CD4+ cell count threshold at which to initiate antiretroviral therapy.

Brinkhof and colleagues from the ART-LINC (Antiretroviral Therapy in Lower Income Countries Collaboration) compared the mortality of HIV-infected patients initiating antiretroviral therapy with that of the general population in sub-Saharan Africa (Abstract 141). They pooled data from 13,249 HIV-infected, treatment-naive patients age 16 years or older receiving treatment in 5 public antiretroviral therapy clinics in South Africa (2 sites), Zimbabwe, Cote d'Ivoire, and Malawi. The baseline characteristics of this cohort included the following: 67% women, median age of 34 years, median CD4+ count of 107 cells/μL (interquartile range [IQR], 46–175), and 85% with WHO stage III or IV disease. In the first 2 years of antiretroviral therapy, 1177 deaths occurred. The overall cumulative mortality at 2 years was 11.7% (95% CI, 11.1–12.3). The authors used data on expected mortality from the WHO Global Burden of Disease estimates and used multiple imputation to account for missing baseline CD4+ counts, clinical stage, and mortality outcome in those lost to follow-up.

The investigators found that the excess mortality rate in those who initiated antiretroviral therapy with CD4+ counts below 25 cells/μL was 17.5 per 100 person-years (95% CI, 14.5–21.1) compared with the general population in sub-Saharan Africa. Among patients who initiated antiretroviral therapy with CD4+ counts above 200 cells/μL and in WHO clinical stage I/II, excess mortality was only 1 per 100 person-years (95% CI, 0.55–1.81) and decreased to 0.29 per 100 person-years (95% CI, 0.17–0.49) if they survived the first year of antiretroviral therapy. When accounting for prognostic factors such as age, sex, baseline CD4+ count, and clinical stage of HIV disease, half of the patients in the cohort had excess rates of 5 to 20 deaths per 100 person-years, and half had fewer than 5 additional deaths per 100 person-years. The investigators concluded that, though excess mortality rates are high in these cohorts, those without severe disease who survive into the second year with therapy have mortality rates comparable to those of the general population.

Mwango and colleagues described preliminary outcomes of Zambia's decision to introduce tenofovir as a component of an initial antiretroviral regimen in their national antiretroviral therapy pro-

gram (Abstract 142). Tenofovir/emtricitabine plus efavirenz replaced the prior initial regimen of stavudine, lamivudine, and nevirapine in July 2007. Data were extracted from 14,295 treatment-naive patients observed for at least 90 days in 18 government antiretroviral therapy clinics in Lusaka who started antiretroviral therapy between July 2007 and December 2008. Patients were classified by the type of initial regimen: tenofovir, stavudine, or zidovudine. Baseline characteristics of patients starting with each of the initial regimens were similar, with the notable exception of more advanced disease in the patients receiving tenofovir. Of the tenofovir recipients, 63% met WHO stage III or IV disease criteria compared with 45% and 55% in the zidovudine and stavudine groups, respectively. Baseline CD4+ count was 141 cells/μL for patients starting tenofovir, 152 cells/μL for patients starting stavudine, and 176 cells/μL for patients starting zidovudine.

As a measure of regimen tolerability, the investigators looked at substitutions made after treatment start per 100 person-years: 29.3 (95% CI, 27.0–31.6) for the zidovudine group, 18.6 (95% CI, 16.9–20.4) for the stavudine group, and 11.7 (95% CI, 10.9–12.5) for the tenofovir group. Switches were highest in the zidovudine group in the first 90 days of therapy. Mortality after 90 days of treatment was 5.2 per 100 person-years for the stavudine group, 4.8 per 100 person-years for the tenofovir group, and 2.7 per 100 person-years for the zidovudine group. After adjustment for baseline demographics and disease stages, the HR values for mortality in each treatment group had overlapping 95% CI values. The only statistically significant subgroup difference was between patients who started with zidovudine and then switched and those who remained with initial tenofovir. The adjusted HR for 90-day mortality in the zidovudine-switch group was 2.41 (95% CI, 1.41–4.12). The proportion of patients with creatinine clearance rates below 50 mL/min at 6 months and 12 months increased in all 3 groups, but no statistically significant difference between treatment groups was found. Overall, the investigators noted that high levels of drug switching and relatively short follow-up periods in this observational study made the outcomes difficult to interpret, but they concluded that tenofovir-based regimens were more easily tolerated and did not lead to higher rates of renal insufficiency.

Treatment Outcomes in Children in Resource-Limited Settings

Moultrie and colleagues presented clinical, virologic, and immunologic outcome data from HIV-infected children receiving antiretroviral therapy at the Harriet Shezi Children's Clinic, a tertiary academic center that is the largest public pediatric HIV site in South Africa (Abstract 97). The study observed a prospective cohort of 2102 children under 15 years of age who initiated antiretroviral therapy between April 2004 and March 2008. Only children with at least 1 post-antiretroviral therapy initiation follow-up visit were included, but the authors noted that 18% of children who had accessed care at the clinic at least once were lost to follow-up before antiretroviral therapy initiation.

At the time of antiretroviral therapy initiation, median age was 4.3 years, 51% were boys, median CD4+ cell percentage was 11.5% IQR, 6.9–16.2), and 29% of patients were receiving treatment for tuberculosis. The median number of months of follow-up during antiretroviral therapy for members of the cohort was 17 (IQR, 5.7–29.2). Most of the 152 deaths in the cohort occurred in the first 3 months of antiretroviral therapy and in children under 18 months of age. Factors predicting mortality in a multivariate analysis included severe underweight for age, high plasma HIV-1 RNA level, concurrent tuberculosis treatment, and younger age. By 18 months of antiretroviral therapy, 90% of the children had plasma HIV-1 RNA levels below 400 copies/mL, and statistically significant improvements in immunologic status were seen in the first 12 months of antiretroviral therapy. The investigators concluded that the timing of antiretroviral therapy initiation in the clinic is not optimal, that mortality is highest in the first 3 months after initiation of antiretroviral therapy but excellent virologic and immunologic outcomes are seen, and that improved outcomes would be likely if infants received earlier diagnoses and initiated antiretroviral therapy earlier.

Prendergast and colleagues examined the impact of coinfection with cytomegalovirus (CMV) on HIV disease (Abstract 93LB). Compared with resource-rich settings, where 36% to 65% of children are infected with CMV by adolescence, 85% of infants in RLS are infected. The investigators collected data as a part of the PEHSS (Pediatric Early Highly Active Antiretroviral Therapy Sexually Transmitted Infections Study) in Durban, South Africa, which is examining the efficacies of 3 antiretroviral therapy management strategies in infants to determine the impact of CMV coinfection on HIV disease progression in these infants. They used CMV real-time polymerase chain reaction assays to test plasma samples from infants 3 months to 4 months of age enrolled in the PEHSS and compared the pre–antiretroviral therapy rate of CD4+ percentage decline from birth in CMV-seropositive and CMV-seronegative infants. Samples were available for 54 of the 63 infants in the cohort, and 59% were CMV seropositive by 3 months to 4 months of age.

CMV-seropositive infants were more likely to be breastfed (53%) than CMV-seronegative infants (18%; $P = .01$), but otherwise there were no statistically significant differences in baseline characteristics between the 2 groups. There was also no difference overall in morbidity and mortality and no difference in weight or head circumference at 12 months. There was a trend toward more failure to thrive in the CMV-seropositive infants (43% compared with 17% in CMV-seronegative infants; $P = .07$). For CD4+ percentage, the decline was twice as rapid in CMV-seropositive as in CMV-seronegative infants: 10.5% per month and 5.0% per month, respectively ($P = .007$). This led to progressive differences in CD4+ percentage in each group, which persisted up to 12 months post–antiretroviral therapy initiation ($P = .004$). No difference was seen in the absolute nadir CD4+ count, which the authors speculate may be related to observed CD8+ cell count increases seen

in CMV-seropositive infants. This raises the question of whether the CD4+ percentage decline in CMV-seropositive infants is a result of primary CMV infection rather than HIV infection, and the authors are pursuing this question in further studies.

Outcomes of Second-Line Antiretroviral Therapy in Resource-Limited Settings

The number of studies presenting data on treatment strategies and second-line antiretroviral treatment outcomes in RLS increased substantially this year. Keiser and colleagues presented data on transitions to second-line antiretroviral therapy and mortality from the ART-LINC Collaboration of the International Epidemiological Databases to Evaluate AIDS (IeDEA) (Abstract 608). The investigators examined data from 20,113 patients from 17 HIV and AIDS treatment programs in Africa, South America, and Asia who met the following criteria: 16 years of age or older, antiretroviral therapy–naive, NNRTI-based initial antiretroviral therapy, and at least 6 months of follow-up data available. Second-line regimens were defined as a change after 6 months of initial therapy with an NNRTI-based regimen to a PI-based regimen along with a change of at least 1 nRTI. WHO guidelines for immunologic or virologic failure of antiretroviral therapy were used.

The primary outcome was change to a second-line regimen, which occurred in 576 patients after a median of 20 months, with a rate of 2.4 per 100 person-years, determined by Kaplan-Meier analysis. A low CD4+ count at baseline was the most important predictor of switching to second-line therapy. The availability of plasma HIV-1 RNA level monitoring at the treatment site was a predictor of an earlier switch to second-line therapy, and CD4+ counts at treatment change were higher at sites with plasma HIV-1 RNA monitoring (161 cells/μL) than at those without it (102 cells/μL; $P < .001$). Mortality was higher in patients who continued their initial antiretroviral regimens after meeting WHO criteria for immunologic or virologic failure (10.7 deaths/100 person-years; 95% CI, 7.3–15.6) than in patients who switched (5.1 deaths/100 person-years; 95% CI, 3.2–8.1) and in those whose initial regimen did not fail (2.9 deaths/100 person-years; 95% CI, 2.4–3.7). The authors concluded that the rate of change to second-line therapy was relatively low and that patients continuing treatment with failing initial regimens are at risk for increased mortality.

Hosseinipour and colleagues determined outcomes of standard second-line antiretroviral therapy (zidovudine, lamivudine, tenofovir, and lopinavir/r) in a cohort of 109 patients receiving treatment in 2 clinics in Malawi (Abstract 605). Participants qualified for second-line therapy if they met clinical or immunologic criteria for antiretroviral therapy failure and had failure confirmed with a plasma HIV-1 RNA level above 400 copies/mL. Of 109 patients whose antiretroviral therapy failed by these criteria, 101 initiated second-line therapy, 5 (5%) died before initiating second-line therapy, and 10 (9%) died within 6 months of initiating second-line therapy. Factors associated with death by 6 months in a multivariate analysis included clinical failure (odds ratio [OR], 3.47; 95% CI, 1.14 – 10.59) and body mass index below 18.5 kg/m^2 (OR, 4.43; 95% CI, 1.15 – 17.12). Among the 101 patients initiating second-line antiretroviral therapy, approximately 70% had achieved plasma HIV-1 RNA levels below 400 copies/mL by 12 months despite extensive baseline nRTI-associated resistance mutations, and 19% experienced grade 3 or grade 4 antiretroviral therapy toxicities.

Fox and colleagues presented findings on the outcome of second-line antiretroviral therapy from a prospective cohort of 382 patients in South Africa (Abstract 606). They included all patients older than 18 years from a single treatment site in Johannesburg who initiated antiretroviral therapy with a standard initial treatment regimen followed by the public-sector second-line antiretroviral therapy regimen of zidovudine, didanosine, and lopinavir/r. The mean increase of CD4+ count 12 months after initiation of second-line therapy was 118 cells/μL, and 89% were alive and in care. Seventy-eight percent of the cohort achieved a plasma HIV-1 RNA level below 400 copies/mL. Predictors of plasma HIV-1 RNA level below 400 copies/mL at 1 year after adjusting for age, sex, adherence to initial treatment, and total duration of antiretroviral therapy included the following: at least 1 single antiretroviral drug substitution before initiation of second-line antiretroviral therapy (adjusted HR, 0.71; 95% CI, 0.56 – 0.89); and a duration of more than 3 weeks between a repeat plasma HIV-1 RNA level above 1000 copies/mL and the change to second-line antiretroviral therapy (adjusted HR, 0.60; 95% CI, 0.43 – 0.83).

Ive and colleagues presented data on time from virologic failure to antiretroviral therapy regimen change from the same clinic population in Johannesburg, South Africa (Abstract 607). Of 8649 patients receiving initial antiretroviral therapy with 2 nRTIs and 1 NNRTI, 428 had confirmed virologic failure, with 2 consecutive plasma HIV-1 RNA level measurements above 1000 copies/mL. Of these, 190 (44%) patients initiated second-line antiretroviral therapy within 3 months of meeting criteria for virologic failure, 141 (33%) patients initiated second-line antiretroviral therapy more than 3 months after failure, and 95 (22%) never switched antiretroviral therapy regimens. Survival analysis was used to estimate the median time to switching from first- to second-line therapy after confirmed virologic failure: 200 days (95% CI, 174 – 280). The authors are currently exploring reasons for the delay in transition from first- to second-line treatment after virologic failure.

Evaluation of World Health Organization Clinical and Immunologic Criteria for Treatment Failure of Initial Antiretroviral Therapy

In 2006, the WHO published guidelines for antiretroviral therapy in adults and adolescents that included clinical, CD4+ count, and virologic definitions of treatment failure for patients receiving an initial antiretroviral regimen.[2] Three groups evaluated the value of these criteria in clinical cohorts of HIV-seropositive individuals in RLS.

Reynolds and colleagues examined the WHO immunologic criteria for anti-

retroviral therapy failure among adults receiving treatment from the Rakai Health Sciences Program in Uganda (Abstract 144). Participants were included who initiated antiretroviral therapy between June 2004 and September 2007 and who had at least 6 months of follow-up care. Patients in the program had both virologic and immunologic monitoring every 6 months, and they switched to second-line therapy if their plasma HIV-1 RNA level surpassed 10,000 copies/mL after an adherence intervention. Of 1133 participants with a median 20 months of follow-up who were receiving an initial NNRTI-based regimen, 125 (11%) met immunologic criteria for antiretroviral therapy failure, 80 (7%) met virologic failure criteria of plasma HIV-1 RNA levels above 10,000 copies/mL, but only 18 (1.6%) met both criteria.

The sensitivity and specificity of the immunologic criteria for determining virologic failure were 23% and 90%, respectively. These did not change when the criteria for virologic failure were made more stringent: having 2 samples with plasma HIV-1 RNA levels above 400 copies/mL. Using the WHO criteria, only 107 of the 125 immunologic failures were considered virologic failures, and the authors determined that use of the immunologic criteria was both insensitive for identifying failures and would lead to cost increase because of unnecessary switches in those whose regimens were not failing.

Two other groups examined this same question in settings where plasma HIV-1 RNA level monitoring is not routinely available and is used only to confirm treatment failure in patients meeting WHO clinical or immunologic criteria for failure. Rewari and colleagues collected data from the Indian national antiretroviral therapy program; they found that referral of cases of suspected treatment failure to a panel of clinical experts was useful in helping determine the need for antiretroviral therapy regimen changes but that 24% of patients meeting clinical or immunologic criteria for antiretroviral therapy failure had plasma HIV-1 RNA levels below 400 copies/mL (Abstract 609).

Etiebet and colleagues conducted a retrospective analysis of data from the ACTION (AIDS Care and Treatment in Nigeria) project, and found that the immunologic criteria had a sensitivity and specificity of 81% and 49%, respectively, for predicting virologic treatment failure of an initial regimen (Abstract 610). Predictors of virologic failure in the cohort included previous antiretroviral therapy exposure, having more than 1 "first-line" regimen, CD4+ count below 200 cells/μL before plasma HIV-1 RNA level testing, and a decrease in weight by more than 10%.

Laboratory Monitoring in Resource-Limited Settings

Several poster sessions were dedicated to laboratory monitoring in RLS. Session 185, "Methods of Viral Load Monitoring," covered improved detection of diverse viral subtypes (Abstracts 998, 1004, 1005), comparisons of new and old plasma HIV-1 RNA level detection methods (Abstracts 999–1002), and the efficiency of pooled viral load testing (Abstract 1003). Session 186 included 4 presentations (Abstracts 1006–1009) evaluating the use of dried blood spots for plasma HIV-1 RNA level testing in RLS.

Breastfeeding and Mother-to-Child Transmission

Review of Transmission of HIV Through Breastfeeding

HIV transmission from mother to child continues to result in as many as 700,000 infections yearly worldwide. In a plenary presentation, Stringer elaborated on the contribution of breastfeeding to transmission of HIV to children, outlining the field's current understanding as well as emerging strategies to prevent MTCT through breast milk (Abstract 127).

Breastfeeding now contributes up to one-third of HIV transmissions to children, and the risk of transmission to infants is approximately 0.5% per month while breastfeeding, according to the BHITS (Breastfeeding and HIV International Transmission Study). Studies aimed at supporting formula feeding in lieu of breastfeeding (Mashi Study) or early weaning (Zambia Exclusive Breastfeeding Study, ZEBS) have proven disappointing, revealing that reductions in HIV transmission are offset by infectious complications and mortality.

Specific strategies under investigation include providing antiretroviral therapy for lactating women and antiretroviral prophylaxis for the breastfeeding infant. Promising data from Kenya (Kisumu Breastfreeding Study) and Tanzania (MITRA-Plus Study) have shown that antiretroviral therapy for mothers beginning in the third trimester and continuing through breastfeeding (6 months) greatly reduces the transmission of HIV attributable to breastfeeding compared with historical controls.

Postexposure prophylaxis of infants is a second promising option for prevention of mother-to-child transmission. The SWEN (Six Week Extended Nevirapine) and PEPI (Post-Exposure Prophylaxis for Infants) studies, presented at the 2008 (15th) conference last year, also offer a hopeful alternative to avoidance of breastfeeding by treating babies with antiretroviral therapy during the breastfeeding period.

Stringer emphasized that most of the transmissions occur among women with more advanced HIV disease, suggesting that maternal treatment is advisable for women who require treatment, whereas infant prophylaxis is a suitable alternative for women in whom antiretroviral therapy is not yet indicated for their own health. The ongoing study comparing maternal treatment to infant prophylaxis during breastfeeding, the BAN (Breastfeeding, Antiretrovirals, and Nutrition) study, should inform us as to the best practice when completed in summer 2009.

Impact of Breastfeeding on Infant Health in Resource-Limited Settings

ZEBS. Follow-up analysis on the ZEBS was presented by Kuhn and colleagues (Abstract 963). Previously published results of this randomized study of 958 HIV-infected postpartum women in Zambia concluded that there was no HIV-free survival benefit of abrupt weaning at 4 months of age compared with gradual weaning at 6 months. The

authors evaluated the contribution of ineffective abrupt weaning on the lack of difference in the 2 groups. HIV-free survival was the same among women who effectively weaned (83.9%) as it was for those who continued to breastfeed (84%); however, an interaction was detected between the results of weaning and the severity of maternal disease. Among babies of asymptomatic women with CD4+ counts above 350 cells/μL, those who weaned were at increased risk of HIV infection or death (HR, 3.01; 95% CI, 1.16 – 7.81) compared with those who did not. Among babies of symptomatic women or those with CD4+ counts below 350 cells/μL in the absence of antiretroviral therapy, early weaning improved rates of HIV-free survival. The authors concluded that for asymptomatic women with higher CD4+ counts, breastfeeding has better HIV-free survival than early abrupt weaning.

Also from the ZEBS trial, Arpadi and colleagues evaluated the impact of the timing of breastfeeding cessation on infant growth; they found that continued breastfeeding mitigated growth faltering among uninfected children born to HIV-infected mothers (Abstract 962). They analyzed the weight and height for age z-scores in 593 uninfected infants who were still alive and breastfeeding at 4 months of age and found statistically significantly more rapid declines in weight for age z-scores in children who were weaned.

Breastfeeding and malaria. Breastfeeding was associated with protection against malaria in a Ugandan prospective study of children born to HIV-infected women, as presented by Homsy and colleagues (Abstract 961). The authors observed 200 HIV-exposed children who were tested for HIV at 6 weeks of age, and again at 6 weeks after breastfeeding cessation. Exclusive breastfeeding for 6 months was recommended for HIV-seronegative infants, and breastfeeding for as long as possible was recommended in HIV-infected infants. Breastfeeding cessation occurred by 15 months of age in 185 children (median age of cessation, 7.2 months). The analysis was stratified by HIV serostatus and age (ages 6 to < 9 months, and 9–15 months). Children breastfed from ages 9 months to 15 months had a statistically significant reduction in malaria as diagnosed by fever and blood smear (HR, 0.51; $P = .003$). Results remained unchanged after stratification by HIV serostatus.

Maternal Health During Breastfeeding

Mashi study. To further explore previous reports of the negative impact of breastfeeding on maternal health, Lockman and colleagues presented results of a randomized trial from the Mashi study in Botswana on the effect of breastfeeding versus formula feeding on maternal HIV progression, mortality, and micronutrient levels (Abstract 176). From 2001 to 2003, 1200 women were randomly assigned to either breastfeeding with zidovudine for infant prophylaxis and weaning at 6 months or formula feeding; participants were followed up for a median of 54 months. Antiretroviral therapy was available for women who met WHO criteria. Baseline characteristics were similar between the 2 groups. The primary endpoint of time to CD4+ count below 200 cells/μL, AIDS, or death was reached in 34% of breastfeeding women and 28% of women randomly assigned to use of formula, but the difference was not statistically significant ($P = .08$).

Further exploration of this trend revealed that the largest contributor to this composite endpoint was CD4+ count below 200 cells/μL, which occurred in 25% of women randomly assigned to breastfeeding and only 21% in the formula-feeding group. Rates of death were the same in the 2 groups at 3%. Statistically significant predictors of the composite endpoint in multivariate analysis were CD4+ count at or below 350 cells/μL ($P < .01$) and plasma HIV-1 RNA level at or above the median ($P < .01$), and any education was protective ($P = .04$). No statistically significant differences in micronutrient levels were appreciated between the 2 groups. The authors did detect statistically significantly higher high-sensitivity C-reactive protein levels in the breastfeeding group ($P < .01$) and plan to explore reasons for this in future studies. The authors concluded that breastfeeding was not associated with an increase in maternal mortality.

Weight status during breastfeeding. ZEBS investigators Murnane and colleagues examined the role of breastfeeding on maternal weight loss (Abstract 982). The authors reported on a secondary analysis of weight and weight changes in 758 HIV-infected, breastfeeding women. HIV-infected, breastfeeding women were more likely to gain rather than lose weight from 4 months to 24 months postpartum and, in particular, women with low baseline body mass index values or lower CD4+ counts were spared substantial weight loss.

Prevention of Mother-to-Child Transmission

Third-trimester testing for HIV-seronegative women. Routine testing for HIV during early pregnancy has become the standard of care, allowing for early diagnosis in pregnancy and affording the greatest likelihood for prevention of transmission of HIV from mother to child. Increasingly, it has been recognized that repeat testing in the third trimester is advisable in high-risk populations. Lu and colleagues reviewed their data on HIV incidence among women in Botswana during pregnancy and during breastfeeding in the first year postpartum (Abstract 91). They found that 470 of 1090 (43%) infant infections were attributable to incident HIV in the mother during pregnancy or breastfeeding, emphasizing the importance of third-trimester and postpartum retesting.

Antiretroviral therapy to prevent transmission through breastfeeding. Taha and colleagues presented updated analyses of the PEPI-Malawi study on the effect of maternal antiretroviral therapy on postnatal HIV-1 transmission after cessation of extended infant antiretroviral prophylaxis (Abstract 92). The study involved breastfeeding, HIV-seronegative infants who underwent randomization at birth to receive single-dose nevirapine and 1 week of zidovudine (control regimen), control regimen plus extended daily nevirapine until 14 weeks, or

control regimen plus extended daily nevirapine and zidovudine for 14 weeks. Previous study results showed that extended nevirapine treatment resulted in a 67% reduction in transmission to infants during their time on treatment. This analysis examined the association of maternal antiretroviral therapy use on transmission to infants after cessation of the infant prophylaxis.

Of 2318 infants not infected at 14 weeks, 130 (5.6%) became infected at follow-up between 14 weeks and 24 months. Women with a CD4+ count below 250 cells/μL were eligible to receive antiretroviral therapy. After adjusting for infant prophylaxis, the HR for transmission to infants was lower in the antiretroviral therapy-eligible women who received antiretroviral therapy (adjusted HR, 0.18; 95% CI, 0.07 – 0.44) than in the antiretroviral therapy-eligible women who did not receive treatment.

The authors also noted that the transmission risk was lower in antiretroviral therapy–ineligible women (ie, CD4+ count at or above 250 cells/μL) who did not receive antiretroviral therapy (adjusted HR, 0.35; 95% CI, 0.25 – 0.50) than in antiretroviral therapy–eligible women who did not receive antiretroviral therapy. There was no statistically significant difference in HIV transmission comparing women who received antiretroviral therapy and those who were antiretroviral therapy–ineligible and did not receive treatment. The authors recommended treating antiretroviral therapy–eligible women with antiretroviral therapy to prevent MTCT through breastfeeding.

Preventing resistance after PMTCT. Given its prolonged half-life, nevirapine, when given as a single dose, is associated with subsequent NNRTI resistance in 24% to 76% of women. This limits subsequent antiretroviral therapy options. Numerous presentations reviewed strategies to reduce the rate of NNRTI resistance after single-dose nevirapine for PMTCT. Van Dyke and colleagues reviewed the IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials) P1032 phase II study of the incidence of resistance mutations in HIV-infected Thai women receiving a single intrapartum dose of nevirapine followed by either 7 days or 30 days of a PI-based regimen or 30 days of an nRTI-based regimen compared with a historical control group (Perinatal HIV Prevention Trial-2, PHPT-2) (Abstract 95aLB). They included data from 169 nonbreastfeeding women older than 18 years. Women were randomly assigned to receive 7 days of zidovudine, didanosine, and lopinavir/r (group A), 30 days of zidovudine and didanosine alone (group B), or 30 days of zidovudine, didanosine, and lopinavir/r (group C). At 2 weeks or 6 weeks of follow-up, all 3 groups had statistically significantly less nevirapine resistance (A, 3.6%; B, 7.1%; C, 5.3%) than historical control patients did (31%); however, the 3 groups were not statistically significantly different from each other. The authors concluded that 7 days of combination antiretroviral therapy prevents most nevirapine resistance from emerging after single-dose nevirapine administration and has little toxicity.

Lallemant and colleagues presented data on the use of an nRTI tail to prevent NNRTI resistance emergence after use of single-dose nevirapine (Abstract 95bLB). They enrolled 222 pregnant, antiretroviral therapy-naive women ("cases") with a CD4+ count above 250 cells/μL who were treated with zidovudine in the third trimester, followed by intrapartum single-dose nevirapine, followed by 1 month of zidovudine and didanosine. The authors compared the rate of nevirapine resistance-associated mutations in these cases with that of matched control patients treated with single-dose nevirapine alone in the earlier PHPT-2 trial. Both groups underwent consensus sequencing and oligonucleotide ligation assay for K103N, Y181C, and G190A mutations. Cases and matched control patients had similar baseline characteristics. Combining results of both assays, resistance mutations were found in 1.8% of cases and 20.7% of control patients. Such data offer a practical solution in RLS, where alternatives to single-dose nevirapine and its associated resistance are not yet readily available.

Response to nevirapine-containing regimens after single-dose nevirapine. Jourdain and colleagues reported on follow-up analysis of PHPT-2 and found a continued, statistically significant effect of single-dose nevirapine after 4 years of therapy (Abstract 954). Women from the initial cohort received zidovudine from 28-weeks' gestation followed by either single-dose nevirapine or placebo. Women with a CD4+ count at or below 250 cells/μL who subsequently received a nevirapine-based regimen were included in the analysis of resistance. There were 221 single-dose nevirapine–exposed women and 48 unexposed women. At 4 years, 41% of exposed women and 23% of unexposed women ($P = .02$) experienced treatment failure (plasma HIV-1 RNA level > 400 copies/mL after 4.5 months, CD4+ count < 50 cells/μL at 6 months, switch to PI, or death). The authors noted that the risk of failure in exposed women decreased with time from delivery to treatment initiation (adjusted OR, 0.93/month increment; $P = .001$).

Lockman and colleagues also provided long-term maternal and pediatric virologic outcomes of nevirapine-based antiretroviral therapy following receipt of single-dose nevirapine or placebo in the Mashi study in Botswana (Abstract 955). Three hundred sixty women were randomly assigned to receive either single-dose nevirapine or placebo and were observed for a median of 42 months. Virologic failure was more common when initiating antiretroviral therapy less than 6 months after single-dose nevirapine than when initiating it at or more than 6 months later ($P = .003$). Among HIV-infected children, 56 started antiretroviral therapy. The highest rates of virologic failure were identified in infants who received single-dose nevirapine born to mothers who also received single-dose nevirapine.

Table 1 summarizes some of these presentations on antiretroviral treatment in RLS.

Resistance

Transmitted Drug Resistance

Review of transmitted drug resistance. Pillay lead a symposium on "HIV Drug Resistance and Treatment Response"

Table **1.** Selected Studies on Antiretroviral Treatment Outcomes in Resource-Limited Settings

Abstract No. Study Title	**Research Question**	**Study Design (No. Participants) Participating Locations**	**Findings**
Abstract 94LB. Lopinavir/ritonavir + Tenofovir/emtricitabine Is Superior to Nevirapine + Tenofovir/emtricitabine for Women with Prior Exposure to Single-Dose Nevirapine: A5208 (OCTANE)	Does single-dose nevirapine use for PMTCT limit future virologic response to nevirapine-containing regimens?	Multisite randomized control trial: Lopinavir/ritonavir + tenofovir/emtricitabine vs nevirapine + tenofovir/emtricitabine (n = 243) Botswana, Kenya, Malawi, South Africa, Uganda, Zambia, Zimbabwe	Trial stopped early by DSMB with median duration of follow-up at 73 weeks. Hazard ratio for reaching primary endpoint of death or virologic failure (confirmed plasma HIV-1 RNA level less than 1 $\log_{10}$ copies/mL below baseline after 12 weeks of treatment or > 400 copies/mL after 24 weeks of treatment) in nevirapine arm compared with lopinavir/ritonavir arm: 3.55 (95% CI, 1.71–7.34)
Abstract 140. Changing Mortality Risk Associated with CD4 Cell Response to Long-Term ART: Sub-Saharan Africa	What is the relationship between mortality risk and CD4+ count response in those on antiretroviral therapy for more than 1 year?	Single-site observational cohort study (n = 2434) Cape Town, South Africa	Cumulative mortality: 8.4% at 12 months and 13.2% at 48 months 48-month mortality: baseline CD4+ < 100 cells/μL, 16.7% baseline CD4+ > 100 cells/μL, 9.5% Strongest predictor of mortality was on-treatment CD4+ count strata: CD4+ 0-199 cells/μL: mortality rate, 5.4-38.6 deaths/100 person-years; CD4+ 200-≥500 cells/μL: mortality rate, 1.2-2.7 deaths/100 person-years
Abstract 143. Randomized Trial of Trained Patient-Nominated Treatment Supporters Providing Partial Directly Observed ART in South African Adults Initiating HIV Therapy	Does partial DOT from trained treatment supporters improve immunologic and virologic outcomes in patients initiating antiretroviral therapy?	Single-site randomized controlled trial: 48-week partial DOT intervention vs standard of care (treatment supporter but no DOT) (n = 274) Cape Town, South Africa	Trial stopped 6 months early by DSMB because of futility No difference in proportion of patients with plasma HIV-1 RNA levels < 50 copies/mL (primary endpoint) at 24, 48, 72, and 96 weeks However, odds ratio for death at 48 weeks in intervention arm was 0.3 (P = .05) compared with control arm
Abstract 97. Mortality and Virological Outcomes of 2105 HIV-Infected Children Receiving ART in Soweto, South Africa	What are the clinical, immunologic, and virologic responses to antiretroviral therapy among children in South Africa?	Single-site observational cohort study (n = 2102) Soweto, South Africa	Plasma HIV-1 RNA at 18 months: 90% < 400 copies/mL CD4+ percentage: baseline median, 11.5% 12-month mean, 25% 42-month mean, 31.7% Mortality rates: first 90 days, 14.4/100 child-years after 90 days, 1.99/100 child-years Loss to follow-up: 18% of children accessing care at least once 6% of those initiating antiretroviral therapy
Abstract 608. Switching to Second-line ART, and Mortality in Resource-Limited Settings: Collaborative Analysis of Treatment Programs in Africa, Asia, and Latin America	What is the rate of switching from initial to second-line antiretroviral regimens in resource-limited settings and what factors predict this switch?	Multisite observational cohort study (n = 20,113) 17 programs in Africa, South America, and Asia ART-LINC	Change to a second-line regimen (primary outcome): 576 patients at median 22 months (IQR, 14-22); rate, 2.4/100 person-years Predictors of switch: low baseline CD4+ count; earlier switch associated with presence of plasma HIV-1 RNA monitoring at site Mortality (deaths/100 person-years): patients remaining on initial ART after immunologic or virologic failure, 10.7 patients switching to second-line ART, 5.1 patients on nonfailing initial regimens, 2.9

ART indicates antiretroviral therapy; ART-LINC, Antiretroviral Therapy in Lower Income Countries Collaboration; DOT, directly observed therapy; DSMB, Data and Safety Monitoring Board; IQR, interquartile range; OCTANE, Optimal Combination Therapy After Nevirapine Exposure; PMTCT, prevention of mother-to-child transmission.

with a thoughtful review of the epidemiology, clinical implications, and biology of transmitted drug resistance in resource-rich settings (Abstract 123). There is strong evidence that transmitted antiretroviral resistance compromises initial therapy and contributes to initial therapy failures. Recent cases illustrate the concerning clinical consequences of transmitted drug resistance. At present, however, large-cohort data from the CASCADE (Concerted Action on Seroconversion to AIDS and Death in Europe) study do not suggest that drug-resistant virus transmission results in an accelerated decline in CD4+ counts or clinical progression. In fact, drug resistance in general does not appear to be associated with progression, per an ALLRT (ACTG [AIDS Clinical Trials Group] Longitudinal Linked Randomized Trials) cohort case-control analysis (Abstract 659). Transmitted drug resistance is seen at various rates depending on the population and risk factors, which can make overall estimates of transmitted drug resistance difficult. Notably, there has been a rise in NNRTI resistance since 2000, reflecting treatment patterns. Most current guidelines recommend resistance testing at HIV diagnosis.

Transmitted drug resistance can be distinguished from resistance that emerges during drug treatment in that the infecting resistant virus undergoes rapid clonal expansion. Later, reversion to wild-type virus may occur because of fitness costs. Time to reversion of transmitted drug-resistant virus varies based on the mutations present. In an effort to detect small populations of mutant viruses, many investigators are using assays to detect low-frequency populations.

Transmitted drug resistance is likely underestimated. Metzner and colleagues analyzed baseline plasma samples from 93 acutely infected patients using the sensitive allele-specific real-time polymerase chain reaction (AS-PCR) to detect minority quasispecies (Abstract 649). None of the patients had resistance mutations detected by population sequencing, however, AS-PCR revealed the presence of the mutations M184V (12.1%) and K103N (6.5%). In this study, viruses were suppressed by a ritonavir-boosted PI regimen. Similarly, other investigators have found that in patients with detectable resistance mutations, using bulk sequencing, additional mutations can be revealed using assays for minority species. Numerous assays to detect minority populations are available that differ in their sensitivity and specificity.

Interpretation of the clinical and biologic meaning of results generated by these sensitive assays is crucial. Ideally, use of these assays would help guide initial treatment choices. Unfortunately, detecting most low-proportion minority subpopulations of transmitted drug resistance requires sampling within a short time of the primary infection (prior to reversion). The findings with regard to the minority species need to be understood within the context of the populations in which they are occurring as well as the length of time from the primary infection, which is rarely known.

The clinical implication of resistant minority populations was appreciated in ACTG 5095, which showed that the response to efavirenz-containing antiretroviral regimens was substantially reduced in patients with baseline resistance to NNRTI (ie, the mutation Y181C) detected by AS-PCR alone. Application of these findings in clinical management or epidemiology, however, remains unclear.

San Francisco cohort. Jain and colleagues delineated the increasing prevalence of NNRTI-associated drug resistance mutations in patients with acute or early HIV infection in San Francisco (Abstract 673). Two hundred twenty-four participants were enrolled in the observational cohort of patients with acute or early HIV infection who had yearly resistance test results from 2003 to 2007 available. Of those patients, 16% had evidence of transmitted drug resistance with the initial genotypic testing. The prevalence of NNRTI resistance–associated mutations was statistically significantly increased over time, whereas PI resistance remained stable in this population. The authors suggested that these findings may be attributable to the increasing use of NNRTI-based therapy.

Seattle cohort. Stekler and colleagues reported the prevalence of low-level mutations in primary HIV-1 infection and its effect on antiretroviral therapy in patients of the University of Washington Primary Infection Clinic (Abstract 674). One hundred patients had results from consensus sequencing and the oligonucleotide ligation assay to assess for low-frequency mutations at a median of 30 days from the estimated time of infection. Consensus sequencing detected mutations in 6 patients, and oligonucleotide ligation assay detected mutations in 28 additional patients. Among patients receiving antiretroviral therapy, no association was found between the presence of low-level mutations and time to virologic suppression. The authors posited that this surprising finding may be attributable to the small sample size as well as the increased potency of current antiretroviral therapies. However, it is also possible that the low-level mutations were false-positive results.

New York City. Castor and colleagues investigated the prevalence of transmitted drug resistance and phylogenetic clustering in a cohort of patients identified during acute and early HIV-1 infection in New York City (Abstract 500). Five hundred forty recently infected patients were enrolled from 1995 to 2008; data were grouped for the period from 1995 through 1999 and biennially for 2000 through 2008. Investigators found a prevalence of transmitted drug resistance of 19% in the cohort overall, which increased over time. In the 2007 to 2008 period, the prevalence was 23%. Specifically, the K103N mutation increased in prevalence from 1.9% to 6.7% from 2007 to 2008.

Young men of color. Hightow-Weidman and colleagues reported on transmitted drug resistance among young men of color who have sex with men (Abstract 905). Eightly-six men, aged 13 to 24 years, were enrolled in a prospective multicenter cohort who had baseline resistance testing before antiretroviral

therapy initiation. Most patients were new to care (84.9% in care < 3 months), African American (84.9%), and between 19 years and 22 years old (61.9%). Over 21% had a plasma HIV RNA level above 100,000 copies/mL at pretreatment. There was major resistance in 15 (17.4%) participants, of whom 9 had NNRTI resistance mutations, 4 had nRTI resistance mutations, 3 had the PI resistance mutation L90M, and 1 had cross-class resistance to nRTIs and NNRTIs. The authors urged early detection and secondary prevention efforts in young men of color.

Low-Frequency Mutant Viral Subpopulations

Review of pyrosequencing. New techniques provide lower cost, complex sequence information on the HIV viral genome that include sequences of low-frequency populations that are not usually detected via standard sequencing techniques. High-throughput sequencing technologies parallelize the sequencing process, allowing for the processing of millions of sequences at once at lower cost per sequence. Known as pyrosequencing, this method relies on the light emission of pyrophosphates and has been commercialized. The ability to identify and sequence low-frequency subpopulations of virus is known as deep or ultradeep sequencing.

Deep sequencing at time of virologic failure. Le and colleagues discussed low-frequency HIV-1 drug-resistant variants from antiretroviral-experienced patients at the time of virologic failure (Abstract 684). Plasma samples from 22 antiretroviral-experienced patients with virologic failure were evaluated using ultradeep pyrosequencing compared with standard bulk sequencing. Low-frequency drug mutations made up 37% of the total 247 drug resistance mutations detected by deep sequencing, the majority (95%) of which were not detected by standard sequencing methods. Roughly 4 additional mutations were detected, on average, by ultradeep sequencing compared with standard sequencing. Of the 22 patients, 17 (77%) had additional low-abundance drug resistance mutations that increased the person's level of resistance to 1 or more antiretroviral drug(s). Interestingly, thymidine analogue-associated mutations (TAMs) were detectable even in patients in whom a zidovudine- or stavudine-containing regimen was not failing. Nine of 10 patients had detectable TAMs despite having stopped treatment with thymidine analogues from 2 years to more than 7 years previously. These findings suggest that low-abundance HIV resistance mutations detected at the time of failure may partly reflect archived virus from virologic failure to prior regimens rather than to only the current failing regimen.

Deep sequencing at reinitiation of antiretroviral therapy. Swenson and colleagues presented a case series looking at the role of deep sequencing upon reinitiation of antiretroviral therapy in 7 antiretroviral-experienced patients with known resistance to prior regimens (Abstract 683). All 7 exhibited reversion to wild-type virus by standard genotypic testing up to the time of reinitiation of antiretroviral therapy. Deep sequencing was performed pretreatment and an average of 3 times during antiretroviral therapy until the virus became undetectable. Minority M184V, M184I, or both mutations were detected in 6 of the 7 baseline samples. These minority species neither reliably increased nor decreased in prevalence after the patients restarted lamivudine-containing regimens. In cases exhibiting changes in the predominance of M184V or M184I, the subpopulations remained rare at less than 1% of the virus population.

Deep sequencing of integrase. Ceccherini-Silberstein and colleagues compared standard sequencing with deep sequencing of integrase at baseline and at the time of treatment failure in patients receiving a raltegravir-containing regimen (Abstract 682). Standard sequencing did not reveal any major integrase mutations in 74 patients before initiation of a raltegravir-containing regimen. The investigators conducted deep sequencing on plasma samples from 6 patients, of whom 4 had experienced virologic failure and 2 had achieved virologic success. At baseline, quasispecies with substitutions at known integrase resistance positions were detected in the 4 participants experiencing virologic failure but not in the 2 with virologic success. The frequencies of these quasispecies were often close to the assay reliability limit. Quasispecies present at baseline were not necessarily associated with mutations at the same position from samples obtained during virologic failure. However, the authors suggested that baseline variability at known resistance positions may influence the antiviral efficacy of raltegravir, and they urge further investigation of such underrecognized complex pathways.

Liu and colleagues also reported on low-frequency mutations in integrase before initiation of a raltegravir-containing regimen and found that low-frequency mutations associated with raltegravir resistance were uncommon (Abstract 685). Of the 32 patients for whom raltegravir failed, 10 had evidence of integrase inhibitor resistance–associated mutations Q148K, Q148H, and G140S at low frequencies (< 0.5% of genomes) and of L74M (14.3% of genomes). Pretreatment mutations in the principal pathways for resistance were uncommon and, when identified, were present at low frequencies. No statistically significant differences in pretreatment drug resistance mutations were noted between the treatment-failure and treatment-success groups.

Viral tropism. The use of deep sequencing for identification of viral tropism was also presented during a symposium, a themed discussion, and in numerous posters. See the **CC Chemokine Receptor 5 Antagonists** section below.

Resistance to Nonnucleoside Reverse Transcriptase Inhibitors

Etravirine. Marcelin and colleagues described the analysis of 243 treatment-experienced patients receiving an etravirine-containing regimen. Patients were exposed to a median of 6 nRTIs, 1 NNRTI, and 5 PIs at baseline

(Abstract 645). Overall, 81.9% of patients achieved a virologic response, defined as a decrease of at least 1.5 $\log_{10}$ copies/mL or a plasma HIV RNA level below 50 copies/mL at 2 months. Factors associated with virologic response were the number of new drugs used with etravirine ($P < .0001$) and the use of raltegravir, darunavir, or enfuvirtide for the first time. A history of exposure to efavirenz or nevirapine was associated with a poorer response (77% versus 91%, respectively; $P < .03$). Consistent with prior studies, the presence of K103N had no effect on the virologic outcome.

Nevirapine and A376S. The A376S mutation in the reverse transcriptase connection domain was associated with an increased risk of virologic failure of nevirapine-based therapy in NNRTI-naive, HIV-infected subjects in the EuroSIDA study (Abstract 646). Paredes and colleagues evaluated the relationship of bulk genotypic sequencing before initiation of the NNRTI-containing regimen with virologic outcome in 287 NNRTI-naive patients who were treated with nevirapine-based (n = 115) or efavirenz-based (n = 172) 3-drug regimens. Virologic failure was identified in 142 (49%) patients (77 receiving nevirapine and 65, efavirenz). The A376S mutation was associated with a greater than 10-fold increased risk of virologic failure with the nevirapine-based antiretroviral therapy but did not have an impact on the response to the efavirenz-based regimens.

Resistance to Nucleoside Reverse Transcriptase Inhibitors

Zidovudine and tenofovir resistance. Das and colleagues elucidated the structural basis for HIV-1 reverse transcriptase drug resistance to zidovudine and tenofovir (Abstract 67). X-ray crystallography was used to study the structural basis for the mechanisms of resistance to zidovudine and tenofovir. Investigators created crystal structures of reverse transcriptase of zidovudine-resistant HIV-1 and reverse transcriptase with the K65R mutation in various complexes, enhancing the understanding of the effects of these mutations on reverse transcriptase polymerization and excision, and on zidovudine and tenofovir resistance. They also investigated the effects of the presence of K65R in combination with other mutations and the clinical benefit of administering tenofovir along with zidovudine, emtricitabine, or lamivudine.

Radzio and colleagues presented biochemical and cell-based analyses of the N348I mutation (Abstract 68). The success of regimens containing zidovudine and nevirapine partly stems from the antagonistic interactions between TAMs and Y181C. The investigators hypothesized that N348I emerges to counteract this antagonism. This mutation occurs in the connection domain of HIV-1 reverse transcriptase in patients treated with these antiretroviral regimens. They found that the addition of Y181C to molecular clones of HIV-1 that included K70R or M41L/T215Y mutations restored viral susceptibility to zidovudine. However, viruses containing Y181C, TAMs, and N348I displayed substantial levels of zidovudine resistance. This represents experimental evidence that N348I restores the zidovudine resistance phenotype in the presence of an antagonistic mutation, Y181C. The authors suggested that N348I may represent a novel pathway to dual zidovudine-NNRTI resistance.

Two presentations suggested that emtricitabine with tenofovir conferred more favorable resistance patterns than lamivudine with tenofovir does (Abstracts 642, 644).

Joyce and colleagues showed data on the risk of K65R mutations in viral populations after repeated interruptions of a regimen of zidovudine/lamivudine plus tenofovir in the DART (Development of Antiretroviral Therapy in Africa) trial (Abstract 681). The authors examined the presence of resistance using standard sequencing and pyrosequencing techniques for K65R and M184V in 18 patients treated with this antiretroviral regimen who underwent 4 successive structured treatment interruptions consisting of 12 weeks on and 12 weeks off therapy. All drugs were stopped together, and plasma HIV RNA level was measured 8 weeks into the cycles. There were 82 samples, of which 69 were taken when patients were off treatment. A single M184V mutation was detected in 1 patient, but no K65R mutations were detected in any sample by either method of viral sequencing. The authors concluded that, despite tenofovir's longer half-life, the clinical risk of the emergence of tenofovir-associated mutations after treatment interruptions is low, and they note that this information may be useful in areas where intermittent drug shortages are common or in the context of PMTCT.

Resistance to Protease Inhibitors

Substrate envelope hypothesis. Nalam and colleagues described a process, based on the "substrate envelope hypothesis," for designing PIs that avoid emergence of drug-resistant virus (Abstract 65LB). Current PIs bind the HIV-1 substrate envelope in a similar way, interfering with the protease function. Only a limited portion of the protease envelope is conserved, leaving a substantial portion at risk for the emergence of mutations leading to PI resistance in patients undergoing drug therapy. The team used computational designs to predict inhibitors that would fit within the confines of the substrate envelope, followed by synthetic chemistry to create the inhibitors and test the inhibitory function in wild-type and resistant HIV-1 variants. Crystal structures were determined, and the inhibitors were tested using a commercial phenotypic resistance assay (PhenoSense, Monogram Biosciences, South San Francisco, CA). The scaffolds for design were amprenavir and darunavir, which have high affinity for the substrate envelope.

From that point, thousands of inhibitors were designed after small adjustments were made in the scaffolds. Of those, 36 inhibitors were found to have very tight binding in the substrate envelope even in highly resistant viruses. Investigators tested 40 inhibitors against 3 viral subtypes by phenotypic testing. They found a series of 10 inhibitors that had higher affinity for HIV-1 protease than darunavir and many more that had higher affinity than lopi-

navir. Ten inhibitors had excellent affinity and success against wild-type and resistant viruses by phenotypic testing. The authors speculated that such techniques can be used for other HIV drug targets and other diseases in which resistance emerges.

Darunavir versus lopinavir. Dierynck and colleagues characterized virus from patients experiencing virologic failures through 96 weeks of follow-up in the randomized, controlled, phase III ARTEMIS (Antiretroviral Therapy with TMC114 Examined in Naive Subjects) trial in treatment-naive patients randomly assigned to receive tenofovir/emtricitabine and either once-daily ritonavir-boosted darunavir (darunavir/r) (n = 343) or lopinavir/r (n = 346) (Abstract 655). Virologic failure, defined as loss of or failure to reach a plasma HIV RNA level below 50 copies/mL after 12 weeks, occurred in 11.7% (40 patients) in the darunavir/r group and 17.1% (59 patients) in the lopinavir/r group. No major PI resistance mutations were identified in either group. Minor PI resistance mutations were also uncommon (4 in the darunavir/r group; 7 in the lopinavir/r group), as was development of nRTI-associated resistance mutations (2 in the darunavir/r group; 5 in the lopinavir/r group). In both groups, a statistically significant proportion of patients meeting criteria for virologic failure had undetectable HIV RNA at follow-up visits without any change in regimen (30% in the darunavir/r group; 27.1% in the lopinavir/r group).

Integrase Inhibitors

Review of raltegravir resistance. Patterns of resistance in the integrase inhibitor class were a major focus at the conference. Raltegravir was approved in 2007 by the US Food and Drug Administration for use in treatment-experienced patients. Miller and colleagues shared analysis of resistance data from phase II and III clinical trials of raltegravir, emphasizing mutations and resistance pathways and implications for treatment-experienced and -naive patients (Abstract 125). Three major pathways to resistance have been identified: major mutations at sites Y143C/H/R, Q148H/K/R (preferred), or N155H. Minor mutations are also seen that lead to higher resistance. If none of these mutations is present at the time of virologic failure, they will likely emerge over time.

The impact of polymorphisms and minority variants on clinical response was explored. Integrase, like all HIV-1 proteins, is polymorphic. Baseline polymorphisms have little effect on susceptibility in vitro. Analysis of polymorphisms and clinical outcomes suggests that some polymorphisms may be associated with treatment outcome. In the BENCHMRK (Blocking Integrase in Treatment-Experienced Patients with a Novel Compound Against HIV, Merck)-1 trial, at week 48, 51 patients experienced virologic failure, of whom 35 had raltegravir resistance; 138 patients were treatment responders. In an effort to identify polymorphisms associated with virologic failure, the investigators compared baseline polymorphisms in the 2 groups. No major mutations were identified at baseline. The analysis revealed 1 polymorphism, T97A, which is a known minor mutation but was not associated with increased rates of treatment failure. Polymorphisms at S17N, M50I, and D256I may have had some association with failure but will require additional investigation.

Deep sequencing of integrase. Again, the question of the utility of minority subpopulations was addressed for raltegravir. Liu and colleagues used parallel allele-specific sequencing technology to quantify minority raltegravir resistance–associated variants in patients participating in BENCHMRK-2, comparing the presence of baseline minority variants with virologic outcome and patterns of resistance (Abstract 685, also discussed above under **Low-Frequency Mutant Viral Subpopulations**). Major raltegravir resistance mutations were identified. However, these were found infrequently, and the presence of these minority variants was not associated with treatment failure in this small data set. Ceccherini–Silberstein and colleagues raised the question of whether the variability at known resistance-associated positions might influence antiviral efficacy of raltegravir through more complex pathways and suggested that minor integrase pathways should be investigated further (Abstract 682, discussed as well in **Low-Frequency Mutant Viral Subpopulations**).

Raltegravir monotherapy. Raltegravir in treatment-naive patients has been studied in a 2-phase treatment trial (Abstract 125). The first phase was raltegravir monotherapy compared with placebo for 10 days. Treatment-naive patients from this study were invited to participate in a noninferiority study comparing raltegravir at 3 different doses with efavirenz (all with tenofovir and lamivudine). Ninety-six-week follow-up of this study showed that raltegravir was noninferior to efavirenz (83% of patients receiving raltegravir and 84% of patients receiving efavirenz achieved plasma HIV RNA levels below 50 copies/mL).

Ultradeep sequencing was used to analyze the emergence of mutations associated with low-level raltegravir resistance in patients treated with raltegravir monotherapy followed by combination therapy (Abstract 125). Deep sequencing was performed at baseline, while receiving monotherapy, and just before the initiation of combination therapy. Resistance by ultradeep sequencing was identified infrequently and at very low levels and was not associated with virologic failure. At the end of 96 weeks of combination therapy, participants who received raltegravir monotherapy were not more likely to experience virologic failure than participants who initiated raltegravir as part of combination therapy. The sole monotherapy patient who experienced virologic failure through 96 weeks did not show any raltegravir resistance.

Integrase resistance and fitness. Fransen and colleagues reported that HIV-1 mutations at positions 143, 148, and 155 in integrase define different genetic barriers to raltegravir resistance in vivo (Abstract 69). Ninety-three subjects for whom raltegravir therapy was failing were included in the analysis. Clonal analysis, susceptibility, and replication capacity were assessed. Though viruses

with mutations at positions 148 and 143 show high-level resistance to raltegravir, mutations at these sites appear to have less effect on replication capacity than do mutants at the 155 position. The authors suggested that this could explain reported shifts from the N155H pathway to mutations at either 143 or 148 position with ongoing drug pressure.

Gupta and colleagues presented a poster on combinations of primary NNRTI and integrase inhibitor resistance mutations by constructing in vitro single-site-directed mutants of NNRTI mutations alone or together with integrase inhibitor mutations (Abstract 652). They found that site-directed mutants containing both mutations for NNRTI and for integrase displayed reduced replication capacity, which is especially evident with viruses containing the K103N and E92Q mutations.

CC Chemokine Receptor 5 Antagonists

Coreceptor tropism assays. Most clinical studies have relied on coreceptor tropism phenotype results from a common commercial assay (Trofile, Monogram Biosciences, Inc, South San Francisco, CA). Other methods to measure tropism were presented for comparison. Another assay (Virotect Tropism assay, Invirion Diagnostics, Oak Brook, IL), uses flow cytometry to combine detection of replication in a patient's cells by in situ hybridization with simultaneous immunophenotyping; it was compared with the Trofile assay in 288 HIV treatment-experienced patients (Abstract 1011). Vilchez and colleagues found that the number of inconclusive results was higher when reported by the Trofile assay (13% vs 6% for ViroTect assay) and that such inconclusive results were more likely to occur for patients with HIV RNA levels below 10,000 copies/mL and CD4+ counts above 200 cells/μL. Another study compared the SensiTrop II tropism assay (Pathway Diagnostics, Malibu, CA), which uses genotypic testing, with the Trofile assay in 252 treatment-naive patients (Abstract 1010). The SensiTrop II assay involves a combination of gp120 sequencing and heteroduplex complex formation. McCarthy and colleagues found that this new assay detects CXC chemokine receptor 4 (CXCR4) more frequently and can be accomplished more quickly than the Trofile assay can.

Deep sequencing for viral coreceptor tropism. Swenson and colleagues used deep sequence analyses to detect and quantify low-level X4 use within clinical HIV isolates that were not detected by standard sequence analysis but were found to have dual-tropic, or mixed (D/M), populations of HIV-1 by the Trofile assay (Abstract 680). They found that 18% of the 202 samples had X4 virus use of less than 10%. The samples were from a clinical trial of a CCR5 antagonist, maraviroc, in patients with D/M virus. Patients harboring HIV-1 with less than 10% use of X4 had greater viral load declines with a maraviroc treatment than did either placebo recipients or patients with HIV-1 populations with greater than 10% X4 use. This suggests that CCR5 antagonists may be used in patients with D/M virus with a relatively low frequency of X4 use. Archer and colleagues used pyrosequencing to analyze samples from 3 patients with R5 virus detected by the Trofile assay prior to initiation of maraviroc treatment but who demonstrated emergence of D/M virus with maraviroc treatment (Abstract 679). In all 3 patients, ultradeep sequencing detected X4 virus at low frequencies (0.5%, 1.5%, and 6%) prior to initiation of maraviroc treatment and higher frequencies after treatment (81%, 99.9%, and 82%).

Treatment of Acute Infection

The clinical and immunologic benefits of treatment during acute HIV infection are controversial. Nonrandomized studies have shown conflicting results. Steingrover and colleagues presented an analysis of the Dutch Primo-SHM embedded, acute-HIV-treatment cohort, comparing time off antiretroviral therapy in patients with primary HIV infection between 2003 and 2008 who were randomly assigned to no treatment or to treatment for 6 months or for 15 months (Abstract 70bLB). Of those enrolled, 102 were included in the analysis; 47 were untreated and 55 were treated. Pretreatment CD4+ count and viral load levels were similar in the 2 groups. Corrected Kaplan-Meier analysis, adjusted for time on therapy, showed that untreated patients started antiretroviral therapy after 126 weeks (95% CI, 104–150), whereas patients who initiated and then interrupted antiretroviral therapy remained off therapy for a mean of 181 weeks (95% CI, 161–201; $P < .001$).

The French ANRS (National Agency for Research on AIDS and Viral Hepatitis) Primo Cohort investigators described those persons in the primary HIV infection cohort who, in the absence of treatment, spontaneously controlled the virus to plasma HIV RNA levels below 400 copies/mL for at least 12 months (Abstract 513). Of the 661 patients enrolled overall, 211 were untreated and 8 of these individuals spontaneously controlled viral replication. The median time from infection to HIV RNA level below 400 copies/mL was 7.0 months (range, 1.7–14.0). In 2 patients, viral control was lost at 4.0 years and 4.4 years after primary infection, and the remaining 6 patients maintained viral control until the last follow-up visit. Of the 8 controllers, none had viruses that harbored genotypic resistance, all had R5 virus, and 7 had subtype-B virus. Four of the 8 patients had HLA-B*57 or -B*27. Viral load during primary HIV infection was statistically significantly lower in controllers (3.0 $\log_{10}$ copies/mL) than in noncontrollers (4.7 $\log_{10}$ copies/mL; $P < .001$), and controllers had statistically significantly higher CD4+ counts than noncontrollers during primary HIV infection.

Outcomes From Treatment Cohorts in Non–Resource-Limited Settings

Two investigations applied novel analytic approaches to determine the optimal time to begin antiretroviral treatment using data from longitudinal cohorts of people living with HIV disease. In the first, Kitahata and colleagues took observational data from 60 geographic regions in the United States and Canada from the NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) and tested the hypothesis

that initiation of antiretroviral therapy at CD4+ counts above 500 cells/μL improves survival (Abstract 71). Their analysis included 9155 study patients and 28,032 person-years of follow-up for HIV-infected individuals with CD4+ counts above 500 cells/μL who had active follow-up between 1996 and 2006. They excluded patients with prior antiretroviral therapy or AIDS-defining illnesses. The investigators attempted to mimic a randomized controlled trial by dividing participants into 2 groups, those who "deferred" treatment until CD4+ counts were below 500 cells/μL and those who initiated treatment with CD4+ counts above 500 cells/μL. Patients who did not initiate antiretroviral therapy within 1.5 years of reaching their target CD4+ count for antiretroviral therapy initiation were censored but not excluded. Inverse probability weights and adjusted Cox regression analysis allowed for control of time-varying, confounding, pretreatment differences between patients initiating or deferring treatment and for the informative censoring described above.

Within the cohorts, 2616 patients initiated antiretroviral therapy with CD4+ counts above 500 cells/μL, and 6539 deferred antiretroviral therapy. The percentage of patients initiating antiretroviral therapy with CD4+ counts above 500 cells/μL peaked in 1998 at 16% of the total cohort and decreased to less than 10% by 2003, reflecting standard-of-care treatment practices. Thus, the majority of patients in the early antiretroviral therapy subgroup received non–ritonavir-boosted PIs. Using inverse probability weighted Cox regression multivariate analysis, the relative hazard of death for those deferring antiretroviral therapy until their CD4+ count was below 500 cells/μL was 1.6 (95% CI, 1.3 – 1.9; $P < .001$) compared with those who initiated antiretroviral therapy with CD4+ counts above 500 cells/μL. These results were not altered by restriction of the inclusion criteria to patients with data on injection drug use and hepatitis C virus coinfection. They conducted a sensitivity analysis to demonstrate that an unmeasured confounder with a relative hazard of mortality of 4.0 would reduce the relative hazard of death for deferral only from 1.6 to 1.3 and concluded that their findings were robust.

Sterne and colleagues asked a similar question using data from the ART-CC (Antiretroviral Therapy Cohort Collaboration), a consortium of 15 cohorts from Europe and North America (Abstract 72LB). Prior data from this cohort collaboration showed increased rates of AIDS and death for patients initiating antiretroviral therapy with CD4+ counts below 250 cells/μL compared with rates in patients who initiated antiretroviral therapy with CD4+ counts above 350 cells/μL. The investigators extended these findings, using statistical techniques proposed by Cole and colleagues[3] to estimate distributions of lead time bias and unseen events that are unmeasured in the ART-CC, impute lead time and unseen events for each individual deferring antiretroviral therapy to a lower CD4+ count range, and account for the error in these estimates with multiple imputation. The prepotent antiretroviral therapy era data on 21,247 patients and 68,253 person-years of follow-up were derived from 7 observational cohorts that followed up patients between July 1989 and December 1995. The investigators restricted their dataset to non–injection-drug-using, AIDS-free individuals but did not control for other confounders.

Comparing data from patients initiating antiretroviral therapy with CD4+ counts of 351 cells/μL to 450 cells/μL with that of patients initiating at 451 cells/μL to 550 cells/μL, the HR for AIDS or death, adjusted for lead times and unseen events, was 0.99 (95% CI, 0.76 – 1.29). Comparing results from CD4+ count at initiation ranges of 0 cells/μL to 100 cells/μL with those of 101 cells/μL to 200 cells/μL showed a HR of 3.35 (95% CI, 2.99 – 3.75). Using this analysis for all 100-cell/μL ranges between 0 cells/μL and 500 cells/μL suggested that patients who defer antiretroviral therapy initiation to CD4+ count ranges below 350 cells/μL had an increased risk of AIDS or death. Similar comparisons for all-cause mortality alone did not show clear evidence that deferring antiretroviral therapy until CD4+ counts dropped below 250 cells/μL led to increased mortality rates. The investigators proposed that only a randomized, controlled trial could control for both measured and unmeasured confounders, but they concluded that delaying treatment until CD4+ counts are below 350 cells/μL confers an increased, through relatively small, absolute risk of AIDS and death.

Rosenblum and colleagues examined the relationship between antiretroviral therapy adherence, virologic failure, and the duration of continuous viral suppression among participants in the REACH (Reaching for Excellence in Adolescent Care and Health) cohort of HIV-infected homeless and marginally housed individuals receiving antiretroviral therapy in San Francisco (Abstract 583). They included 221 participants receiving antiretroviral therapy who achieved plasma HIV-1 RNA levels below 50 copies/mL and agreed to monthly, unannounced pill counts. Using a marginal structural model that controlled for nadir CD4+ count, regimen characteristics, past adherence, age, sex, depression, ethnicity, and drug or alcohol use, the investigators compared the probability of virologic failure immediately after achievement of virologic suppression to that after 12 consecutive months of virologic suppression. There was a statistically significant decrease in the risk of failure between these 2 time points for all individuals with at least 50% adherence to antiretroviral therapy. The estimated decrease in risk of failure was 0.39 (95% CI, 0.29 – 0.52) for those 90% to 100% adherent, 0.25 (95% CI, 0.05 – 0.50) for 75% to 89% adherence, and 0.45 (95% CI, 0.28 – 0.70) for 50% to 74% adherence. The authors concluded that the level of antiretroviral therapy adherence, correlating with the level of drug exposure necessary to maintain virologic suppression, decreases with increasing duration of virologic control but note that they cannot rule out selection bias in this observational study.

Lodwick and colleagues compared the risk of triple-class virologic failure among patients initiating either PI- or NNRTI-based regimens observed in 28 European longitudinal cohorts as a part of COHERE (Collaboration of Observa-

tional HIV Epidemiological Research Europe) (Abstract 585). The analysis was restricted to patients who were 16 years old or older, were followed up for at least 4 months, and initiated therapy with 2 nRTIs and either a PI or NNRTI. The authors defined virologic failure of an antiretroviral agent as occurring in individuals with a plasma HIV-1 RNA level above 500 copies/mL after at least 4 months of continuous use of that agent. Triple-class virologic failure was defined as failure of at least 2 nRTIs, 1 NNRTI, and a ritonovir-boosted PI. Overall, 45,937 people met inclusion criteria and started an initial antiretroviral regimen, 64% of whom received an NNRTI-based regimen. Of these, 980 (2.1%) experienced triple-class virologic failure, with the cumulative proportion of patients developing triple-class virologic failure rising from 3.4% (95% CI, 3.1–3.6) at 5 years from the start of antiretroviral therapy to 8.6% (95% CI, 7.5–9.8) at 9 years from antiretroviral therapy start. Using data from 2042 people who initiated PI-based regimens after the failure of NNRTI-based regimens, the investigators found that the risk of subsequent triple-class virologic failure was higher in patients who had lower CD4+ counts and higher plasma HIV-1 RNA levels, and lower for patients who spent less than 3 months taking antiretroviral therapy and had a plasma HIV-1 RNA level above 500 copies/mL. The authors noted that the rate of virologic failure did not decrease over time, which has implications for the need for future third-line treatment options in RLS.

Pharmacokinetic Considerations

Antiretroviral Drugs in Pregancy

Atazanavir/ritonavir and tenofovir. Mirochnick and colleagues reported on atazanavir levels without and with tenofovir coadministration in pregnant women (Abstract 941). Women received atazanavir 300 mg with ritonavir 100 mg once daily; 13 were receiving concomitant tenofovir and 14 were not. The investigators found the area under the curve (AUC) and trough concentrations were reduced during the third trimester compared with those at 6 weeks to 12 weeks postpartum in both groups. The AUC and trough concentrations were lower in the group receiving tenofovir, as expected. The cord blood levels of tenofovir were approximately 20% that of maternal blood levels. The authors recommended increasing the dosage of atazanavir to 400 mg daily with ritonavir during pregnancy to assure adequate levels of the drug.

Lopinavir/ritonavir. Kiser and colleagues evaluated lopinavir/r pharmacokinetics in the second and third trimesters of pregnancy (Abstract 946). They made individual dose adjustments based on intensive pharmacokinetic sampling. They found that lopinavir and ritonavir were less protein bound during pregnancy. Eight of 10 women required a dose increase in the second trimester to achieve lopinavir concentrations consistent with historical control patients. Only 2 women required a further dose increase in the third trimester. This suggests that the dose of lopinavir/r should be increased in the second trimester, not the third trimester, as current guidelines advise.

Nelfinavir. Fang and colleagues presented data on nelfinavir in pregnancy (Abstract 943). They compared plasma levels of nelfinavir and M8, an active metabolite, in 16 pregnant, HIV-infected women in the second and third trimesters with those in women 6 weeks postpartum. The trough concentration of nelfinavir was 36% and 54% lower in the second and third trimesters, respectively, than concentrations in postpartum women. Trough M8 levels were undetectable in more than 50% of women during pregnancy. This suggests that, as in nonpregnant patients, nelfinavir is not the optimal PI for use in pregnancy.

Antiretroviral therapy drugs in breast milk. Investigators evaluated 8 mother-and-infant pairs in whom the mother was receiving zidovudine, lamivudine, and lopinavir/r (Abstract 947). Breast milk concentrations of zidovudine and lamivudine were 1.86 times and 5.6 times that of the mother's plasma, respectively, whereas lopinavir and ritonavir concentrations were each 11% that of the plasma. No lopinavir, ritonavir, or zidovudine was detected in the infant's plasma. A very low concentration of lamivudine, 1% that of the mother's plasma, was detected in infants. The authors concluded that the low-to-undetectable antiretroviral drug concentrations found in the infants suggest that these drugs pose minimal risk of toxicity for infants. They also suggest that further studies should evaluate whether the low lopinavir/r concentration found in breast milk is associated with detectable HIV RNA in breast milk.

Other Pharmacokinetic Considerations

Efavirenz in hair samples. Gandhi and colleagues from the Women's Interagency HIV Study presented data on efavirenz concentrations in hair samples (Abstract 692). Drug measurement in hair samples reflects the long-term exposure to a drug, unlike a single plasma sample, which measures very recent drug exposure. The authors found that efavirenz levels in hair samples were the strongest predictor of achieving virologic success on an efavirenz-based regimen. Self-reported adherence was not predictive. The authors suggested that this technique is a promising method to assess long-term exposure to antiretroviral drugs.

Atazanavir and raltegravir. Zhu and colleagues evaluated raltegravir monotherapy 400 mg twice daily, atazanavir monotherapy 300 mg twice daily, and the combination of atazanavir and raltegravir in 22 HIV-uninfected adults (Abstract 696). They noted that the raltegravir and atazanavir combination is a potential nRTI-sparing regimen that does not require ritonavir. Atazanavir trough concentrations were reduced by 29% when coadministered with raltegravir. However, all participants had trough concentrations above the accepted atazanavir target concentration of 150 ng/mL. Raltegravir trough concentrations were increased by 48% with coadministration. Electrocardiograms showed a QRS widening of 11 ms with atazanavir twice-daily therapy

compared with pretreatment values. The clinical relevance of this effect is unknown.

Very low dose ritonavir and saquinavir. Van Der Lugt and colleagues examined saquinavir and ritonavir pharmacokinetics in 20 Thai HIV-infected patients (Abstract 697). All participants had virologic suppression with an antiretroviral regimen including saquinavir 1500 mg and ritonavir 100 mg given once daily. After a pretreatment pharmacokinetic assessment, patients received a reduced ritonavir dose of 50 mg and after 7 days underwent a second pharmacokinetic assessment. The authors found that ritonavir levels were statistically significantly lower after the dose adjustment but that saquinavir levels were not affected. These investigators used a liquid formulation of ritonavir and suggested that the strategy is not feasible in clinical practice until a more acceptable formulation reaches the market.

Nevirapine and fluconazole. Wakeham and colleagues compared nevirapine concentrations in 49 patients enrolled in a randomized, placebo-controlled trial of fluconazole for primary prophylaxis of cryptococcal disease (Abstract 700). The median nevirapine trough concentrations were increased in the presence of fluconazole, 5116 mg/mL in the treated group versus 3709 ng/mL in the placebo group (P = .007). However, no increase in hepatoxicity among the larger study population was observed.

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12. Limits and Realities of ART Scale-up. Alex Coutinho.

13. A Neglected Epidemic—HIV in Men Who Have Sex with Men: Lower-Middle Income Countries. Carlos Caceres.

14. The Effect of HIV Treatment on Transmission. Christophe Fraser.

18. Responding to the HIV Epidemic in Soweto, South Africa. Glenda Gray and J McIntyre.

20. Immune Effects at HIV-infected Mucosal Surfaces. Daniel Douek.

23. Characterization of TRN-SR2-mediated Nuclear Import of HIV. Frauke Christ, W Thys, A Bulek, O Taltynov, J De Rijck, R Gijsbers, and Z Debyser.

24. Analysis of HIV-1 Uncoating in Cells Using Fluorescent Microscopy. Amy Hulme, O Perez, and T Hope.

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35. Once-daily Nevirapine vs Efavirenz in the Treatment of HIV-infected Patients with TB: A Randomized Clinical Trial. Soumya Swaminathan, C Padmapriyadarsini, P Venkatesan, G Narendran, R Kumar, S Iliayas, D Pooranaganga, M Dilip, R Sakthivel, and R Ramachandran.

36a. Initiating ART during TB Treatment Significantly Increases Survival: Results of a Randomized Controlled Clinical Trial in TB/HIV-co-infected Patients in South Africa. Salim Abdool Karim, K Naidoo, A Grobler, N Padayatchi, G Nair, S Bamber, J Pienaar, G Friedland, W El-Sadr, and Q Abdool Karim.

36bLB. Novel Regimens for Treating Latent TB in HIV-infected Adults in South Africa: A Randomized Clinical Trial. Neil Martinson, G Barnes, R Msandiwa, L Moulton, G Gray, J McIntyre, H Hausler, M Ram, and R Chaisson.

36cLB. Early vs Delayed ART in the Treatment of Cryptococcal Meningitis in Africa. Azure Makadzange, C Ndhlovu, K Takarinda, M Reid, M Kurangwa, V Chikwasha, and J Hakim.

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49LB. Cell-free Virus in Seminal Plasma is the Origin of Sexually Transmitted HIV among Men Who Have Sex with Men. David Butler, M Lakdawala, D Richman, S Little, and D Smith.

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52bLB. Reduction of HIV Transmission Risk and High Risk Sex while Prescribed ART: Results from Discordant Couples in Rwanda and Zambia. Patrick Sullivan, K Kayitenkore, E Chomba, E Karita, L Mwananyanda, C Vwalika, M Conkling, N Luisi, A Tichacek, and S Allen.

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74. Cellular Co-factors of HIV Integrase—from Target Identification to Drug Discovery. Zeger Debyser.

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97. Mortality and Virological Outcomes of 2105 HIV-infected Children Receiving ART in Soweto, South Africa. H Moultrie, M Yotebieng, L Kuhn, and Tammy Meyers.

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138. Comparison of Home- and Clinic-based HIV Counseling and Testing among Household Members of Persons Taking ART: Uganda. E Lugada, S Jaffar, J Levin, B Abang, J Mermin, G Namara, H Grosskurth, E Mugalanzi, Sundeep Gupta, and R Bunnell.

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144. Evaluation of the WHO Immunologic Criteria for ART Failure among Adults in Rakai, Uganda. Steven Reynolds, G Nakigozi, K Newell, A Ndyanabo, R Galiwongo, I Boaz, T Quinn, R Gray, M Wawer, and D Serwadda.

145. Association between Modifiable and Non-modifiable Risk Factors and Specific Causes of Death in the HAART Era: The Data Collection on Adverse Events of Anti-HIV Drugs Study. Colette Smith and D:A:D Study Group.

146. HIV Infection Is an Independent Risk Factor for Atherosclerosis Similar in Magnitude to Traditional Cardiovascular Disease Risk Factors. Carl Grunfeld, J Delaney, C Wanke, J Currier, R Scherzer, M Biggs, S Sidney, J Polak, D O'Leary, R Kronma, and FRAM Study.

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152. Abacavir and Cardiovascular Risk. Peter Reiss.

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