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Highlights of the 17th Conference on Retroviruses and Opportunistic Infections

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Announcements

Topics in HIV Medicine®

Continuing Medical Education

This entire issue, which highlights presentations from the *17th Conference on Retroviruses and Opportunistic Infections*, is selected for CME credit.

Instructions

This Continuing Medical Education (CME) activity provides a review of new data presented at the 17th Conference on Retroviruses and Opportunistic Infections (CROI). It offers a maximum of 6 CME credits. To complete the activity, the learner is instructed to:

- Read the article
- Review a selection of the references
- Reflect on how the information might be applied to the clinical practice
- Apply relevant parts of the new information to the clinical practice
- Take the posttest
- Complete the CME claim form and send it to the IAS–USA office along with payment of $50.

Objectives

Upon completion of this activity, learners will be able to describe results of new research presented at the 17th CROI and the potential clinical implications for their HIV-infected patients in the following subject areas:

- Advances in basic science
- HIV vaccine development
- HIV epidemiology, testing strategies, and prevention interventions
- Neurologic disorders in HIV disease and their treatment
- Infections and metabolic complications of HIV disease and antiretroviral treatment
- Advances in antiretroviral therapy, including prevention of mother-to-child transmission and HIV resistance to antiretroviral drugs

Accreditation Statement

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The International AIDS Society–USA designates this activity for a maximum of 6 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Intended Audience

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

Author Financial Disclosures

Dr Stevenson has served as a consultant to Merck & Co, Inc.

Dr Watkins has served as a consultant to Pfizer Inc.

Dr Buchbinder has no relevant disclosures to report.

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Dr Hammer has served as a scientific advisor for Merck & Co, Inc, and Progenics Pharmaceuticals, Inc, has served on a Data Monitoring Committee for Bristol-Myers Squibb, and holds stock options and is a member of the Board of Directors of SIGA Technologies, Inc.

This CME activity is offered from May 25, 2010, to May 25, 2011. Participants who complete the activity posttest and submit the registration form and fee are eligible to receive 6 credits. Physicians (MDs, DOs, and international equivalents) may receive CME credit for completing this activity. Nonphysician health care practitioners will receive a certificate of attendance.

Posttest Questions

Circle the single best answer to each of the questions below.

1. The viral accessory protein, Vpu, has evolved principally to:
- **A.** Allow interaction of the virus with cell surface receptors
- **B.** Facilitate viral integration
- **C.** Counteract a cellular restriction
- **D.** Activate viral gene expression

2. A retrovirus has recently been linked to chronic fatigue syndrome in humans. It is:
- **A.** HIV-2
- **B.** Human T-cell lymphotropic virus-2
- **C.** Xenotropic murine leukemia virus–related virus
- **D.** Equine infectious anemia virus

3. It is difficult to produce an effective vaccine for HIV because:
- **A.** HIV hides in B cells
- **B.** HIV replicates in mucosal tissues
- **C.** Vaccines have not been able to induce neutralizing antibodies
- **D.** There is no good animal model

4. In the recent Thai trial, vaccinees acquired HIV at a rate of __% of the rate of control subjects.
- **A.** 11
- **B.** 24
- **C.** 31
- **D.** 44

5. In the United States, 12% of the population is black, but more than half of persons with newly diagnosed HIV infection are black. This racial disparity occurs in both men and women. Among men who have sex with men (MSM), which of the following factors is most likely to account for this higher rate of HIV acquisition among black MSM than among white MSM?
- **A.** Larger number of sex partners
- **B.** Higher rates of unprotected anal sex
- **C.** Lower rates of adequate HIV treatment among infected men
- **D.** Higher rates of "barebacking" (intentional sex without a condom)

6. Estimates are that approximately 25% of the US HIV-infected population are unaware of their status and that this group may account for 54% to 70% of new HIV transmissions. In Africa, 75% of HIV-infected persons are unaware of their infection, and more than 90% of transmissions likely come from this population. Thus, great attention is focused on increasing HIV testing rates and referring HIV-infected persons for treatment. Although no direct data yet address whether treatment will decrease the risk of HIV transmission, an observational study of serodiscordant couples found that the risk of HIV transmission in partnerships in which the HIV-infected person initiated treatment was decreased by approximately what amount?
- **A.** No decrease
- **B.** 25%
- **C.** 50%
- **D.** >90%

7. Which of the following statements is most correct?
- **A.** HIV-associated neurocognitive disorders directly result from HIV infection of neurons. As a result, treatment of HIV infection in the central nervous system requires only antiretroviral drugs that penetrate across the blood–brain barrier in therapeutic concentrations.
- **B.** HIV infects glial cells in the brain, which leads to injury of neurons via indirect mechanisms (ie, mechanisms other than HIV infection of neurons). As a result, treatment of HIV-associated neurocognitive disorders requires suppression of HIV replication in the nervous system and silencing of immune activation and other pathogenic events in the brain.
- **C.** HIV-associated neurocognitive disorders are common among antiretroviral drug–treated individuals and results from drug toxicity.
- **D.** Antiretroviral drug failure solely in cerebrospinal fluid is common and warrants routine lumbar puncture in the clinic.

8. Reports from the 2010 CROI conference found that the H1N1 strain of influenza A in HIV-infected patients:
- **A.** Requires a different antiviral treatment than in HIV-uninfected patients
- **B.** May be associated with longer shedding of influenza virus and more gastrointestinal symptoms than in HIV-uninfected patients
- **C.** Is associated with the same serologic response to vaccination as in HIV-uninfected patients
- **D.** Consistently causes more severe disease than in HIV-uninfected patients

9. The interleukin-28B C/C genotype was reported to be associated with:
- **A.** Higher rates of HIV infection
- **B.** Poor outcomes with hepatitis B virus treatment
- **C.** Abacavir hypersensitivity
- **D.** Higher rates of spontaneous clearance of hepatitis C virus (HCV) and favorable responses to HCV treatment

10. Which of the following statements correctly describes the results of AIDS Clinical Trials Group A5202, the randomized controlled trial comparing efavirenz with atazanavir/ritonavir?
- **A.** Efavirenz led to statistically significantly better suppression of plasma HIV-1 RNA than did atazanavir/ritonavir
- **B.** Atazanavir/ritonavir was discontinued more often than efavirenz
- **C.** Resistance developed more commonly in patients receiving efavirenz than in patients receiving atazanavir/ritonavir
- **D.** More serious adverse events occured with efavirenz than with atazanavir/ritonavir

11. Cobicistat is an investigational drug with properties of drugs in which category?
- **A.** HIV-1 integrase inhibitors
- **B.** Inhibitors of cytochrome P450 without anti-HIV activity
- **C.** Histone deacetylase inhibitors
- **D.** Nonnucleoside analogue reverse transcriptase inhibitors

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Advances in Basic Science

Mario Stevenson, PhD

Basic science continues to occupy a substantial portion of the program at the Conference on Retroviruses and Opportunistic Infections. At the 17th conference this year, presentations focused on advances in our understanding of cellular factors that regulate the interplay between the virus and the host cell and, in particular, cellular defenses such as tetherin (or BST-2) that antagonize viral replication. Research into basic mechanisms of primate lentiviral pathogenicity was also an area of great interest at the conference. An analysis of the evolution of lentiviral and primate genomes highlights the conflict between the virus and its host and illustrates the considerable gyrations that lentiviruses have undergone to acquire the ability to replicate within their primate hosts. It is now apparent that all 4 accessory proteins of lentiviruses are in some way involved in overcoming natural antiviral restrictions in primate cells. Therefore, because lentiviruses such as HIV-1 are hard pressed to avoid the intrinsic antiviral defenses of the cell, there is strong rationale for the development of strategies that harness the antiviral capacity of these natural cellular restrictions.

Cellular Factors Influencing the Interplay Between Virus and Host Cell

All viruses must commandeer cellular factors to replicate within the host. In the case of the immunodeficiency viruses, research over the past 2 decades has revealed the existence of cellular factors that are required for various steps in the viral replication cycle. This progress is best illustrated by the receptor and coreceptor molecules that primate lentiviruses use to gain access to the interior of the cell. Research into the interaction between the viral envelope glycoprotein and the receptor and coreceptor molecules on the cell surface has led to the development of novel small-molecule inhibitors like maraviroc that target the interaction between viral envelope glycoprotein and the CC chemokine receptor 5 (CCR5) coreceptor.

Research featured at the 17th conference revealed that it may be possible to therapeutically target not only the viral function but also the cellular cofactors upon which the viral function is dependent. The viral integrase is an enzymatic protein against which small-molecule inhibitors have most recently entered the clinic. Integrase processes viral and cellular DNA for ligation that leads to the establishment of the integrated provirus. Detailed biochemical information on the end processing and ligation reactions promoted the discovery of integrase inhibitors like raltegravir that are now widening treatment options for people living with HIV-1 infection (eg, Abstracts 263, 514, 515).

Furthermore, a high-resolution crystal structure for integrase has recently been determined,[1] which will further aid in the development of an expanded list of integrase antagonists. Although integrase is necessary for the integration of viral with host cell DNA, it is not sufficient. Research from Debyser's group in 2003 identified lens epithelium-derived growth factor p75 (LEDGF/p75) as a cellular protein that strongly binds to HIV-1 integrase.[2] Since that time, research from several groups has revealed that the ability of integrase to catalyze the integrase reaction depends upon its interaction with LEDGF/p75. When LEDGF/p75 expression is reduced by RNA interference, viral integration and replication is inhibited.

The crystal structure of the integrase core domain in complex with the integrase binding domain of LEDGF/p75 has been resolved; it reveals an interface to which small-molecule inhibitors might be directed.[3] Abstract 49 described the structures of first-in-class inhibitors of the LEDGF/p75 interaction. These 2-(quinolin-3-yl)acetic acid derivatives are micromolar inhibitors of the integration step that compete with LEDGF/p75 for integrase interaction. These agents were found to inhibit HIV-1 replication at micromolar concentrations and importantly, were active against raltegravir- and elvitegravir-resistant HIV-1 variants. This research points the way to the development of a new class of antiretroviral drugs that targets a cellular cofactor of integrase and raises the attractive possibility of targeting viral replication simultaneously on the viral and on the cellular interfaces of the integration reaction.

It was originally thought that primate lentiviruses like HIV-1 integrate randomly within chromatin. However, advances in the technology used to identify integration sites have revealed that HIV-1 preferentially integrates within actively transcribed genes. At present, it is not clear how the selective integration of HIV-1 within actively transcribed genes might impact or be advantageous to viral replication. In vivo studies have shown that depletion of LEDGF/p75 reduces the frequency of integration events into active genes. Therefore, LEDGF/p75 may function as a molecular tether to link integrase to sequences within transcriptionally active genes.

Abstract 145 presented evidence that it may be possible to reroute the HIV-1 genome to heterochromatic, gene-poor regions of chromatin. The authors fused the integrase-binding domain of LEDGF/p75 to the heterochromatin-binding protein CBX1. The authors then reduced expression of endogenous LEDGF/p75 and infected

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cells with HIV-1 and equine infectious anemia virus (EIAV). This CBX1 fusion protein was able to rescue HIV-1 and EIAV integration in LEDGF/p75-depleted cells. Active genes were disfavored by integration sites in cells expressing CBX1 fusion protein. Therefore, the normal integration site preferences exhibited by HIV-1 were reversed in the presence of this CBX1–LEDGF/p75 fusion protein.

These results underscore a model in which LEDGF/p75 supports integration by tethering integrase to chromatin and LEDGF/p75's tethering activity selectively targets active genes. One possible practical application of this research is that it might be used to retarget lentiviral vectors away from active genes, thereby reducing the probability of insertionally activating oncogenes in gene therapy trials. It would also be interesting to know whether retargeting of HIV-1 to heterochromatin might increase the probability of latent infection (see also Abstracts 251 and 252 for host factors that influence HIV integration site selection).

The capsid protein (CA) forms a cone-shaped core that protects genomic viral RNA in the extracellular viral particle. Mutations in capsid can affect capsid assembly and morphology of the core as well as core stability. In addition, the cellular factor TRIM5α from rhesus macaques can affect stability of the incoming core and greatly impact virus infectivity. Therefore, assembly, morphology, and stability of the capsid core are all essential for HIV-1 infectivity.

Abstracts 50 and 495 described the identification of compounds that can bind to capsid and affect viral core morphology and that exhibit antiviral activity. Both research groups used cell-free capsid assembly assays to screen small-molecule libraries. Compounds emerging from the inhibitor screens were found to affect viral core morphology or to prevent the formation of virions. In some cases, virions produced in the presence of inhibitor were non-infectious. Inhibitor-resistant variants (Abstract 50) could be generated by serial passage of virus in the presence of the inhibitors. Resistance was correlated with the presence of mutations in highly conserved residues at the N-terminal domain of capsid and within the C-terminal domain of capsid. Cell-free capsid assembly assays offer a strong opportunity for high-throughput screening and identification of novel inhibitors of capsid assembly and core morphology.

Intrinsic Cellular Defenses

Some cellular factors such as LEDGF/p75 and CCR5 are co-opted by the virus in its replication cycle, whereas other cellular factors antagonize viral replication. These antiviral cellular proteins, commonly referred to as cellular restrictions, are able to potently antagonize viral replication. Cellular restrictions acting at various points in the viral life cycle have been identified. Because of the existence of these cellular restrictions, primate lentiviruses have been forced to evolve defense strategies that counteract the antiviral action of cellular restrictions.

It is now apparent that the viral accessory proteins (Vif, Vpu, Nef, Vpr/Vpx) are all, in some way, involved in the antiviral defense against cellular restrictions. The Vif protein, which is encoded by all primate lentiviruses, counteracts the antiviral activity of APOBEC 3 cellular cytidine deaminases. The cytidine deaminase APOBEC 3G causes G-to-A substitutions in nascent viral complementary DNA (cDNA) and inhibits reverse transcription of viral cDNA. The viral Vif protein overcomes this defense by targeting APOBEC 3 for proteasomal degradation.

Abstract 90 presented evidence that deamination of viral cDNA by APOBEC 3 may contribute to the acquisition of drug resistance mutations. The authors hypothesized that some Vif alleles may harbor mutations that compromise their ability to neutralize the antiviral effects of APOBEC 3 proteins. The authors identified a Vif mutant that appeared to be associated with virologic failure. This Vif mutant (K22H) exhibited impaired viral replication in the presence of APOBEC 3. Patients harboring K22H viruses exhibited a greater propensity to harbor drug-resistant mutations resulting from G-to-A substitutions. The authors propose that polymorphisms that impact the ability of Vif to neutralize APOBEC 3G can lead to an increase in the G-to-A mutations that promote the emergence of drug resistance mutations.

Tetherin (also known as BST-2 or CD317) is an interferon-inducible cell protein that inhibits the detachment of nascent virions from the surface of infected cells.[4,5] The Vpu protein that is encoded by HIV-1 and some simian immunodeficiency virus (SIV) strains opposes the action of tetherin/BST-2. Abstract 144 presented evidence that the ability of Vpu to counteract tetherin/BST-2 correlated with its ability to down-regulate tetherin/BST-2 from the cell surface. The authors observed that Vpu transmembrane domain mutants that down-regulated tetherin/BST-2 from the cell surface were able to enhance virion release, whereas a Vpu mutant that did not down-regulate cell-surface tetherin/BST-2 lacked the ability to enhance virion release. The ability to enhance virion release by Vpu was found to be independent of ion channel activity, which has previously been hypothesized to underscore Vpu's biologic activity. The authors propose that Vpu and tetherin/BST-2 interact within post–endoplasmic reticulum endosomal membranes and that this interaction mislocalizes tetherin/BST-2 away from sites of virus budding. Similar results underscoring a role for tetherin/BST-2 internalization by Vpu were presented in Abstract 213.

Although the Vpu protein specifically counteracts the antiviral activity of tetherin/BST-2, Vpu is not encoded by HIV-2 and most SIV strains. Therefore, these viruses have evolved different mechanisms to counteract the antiviral activity of tetherin/BST-2. Research groups led by Evans and Bieniasz have recently demonstrated that SIV Nef can counteract restriction by rhesus macaques' tetherin/BST-2.[6,7]

In Abstract 142, the authors presented a fascinating story of the evolutionary changes in tetherin/BST-2 that drove the evolution of Vpu and Nef functions. The authors examined tetherin/BST-2 evolution in primates using

a maximum-likelihood approach. They observed strong signals of positive selection within the cytoplasmic tail of tetherin/BST-2, which is also the site of Nef interaction. However, the selection predated modern Vpu-encoding primate lentiviruses, suggesting that the evolution in tetherin/BST-2 was driven by selection from ancient viruses. In HIV-1 that encodes both Vpu and Nef, Vpu antagonizes tetherin/BST-2 but Nef is inactive against tetherin/BST-2. Conversely, in the ancestors to HIV-1 (chimpanzee SIV, SIVcpz), Nef antagonizes the host's tetherin/BST-2 but Vpu in these viruses is inactive against tetherin/BST-2. Therefore, as HIV-1 adapted to humans, the ability to counteract tetherin/BST-2 was lost in Nef and acquired in Vpu. However, the *nef* gene has been functionally retained by HIV-1, indicating that *nef* harbors other functions required for virus replication.

Data in Abstract 220 support the model in which tetherin/BST-2 is physically incorporated into HIV-1 virions. The authors visualized the location of tetherin/BST-2 using correlative fluorescence and electron microscopy. Virion incorporation of tetherin/BST-2 was evaluated by a bead-based immunocapture assay and by immunoblotting of tetherin/BST-2 in partially purified virions. By immuno-electromicroscopy, the authors visualized tetherin/BST-2 among and between virions as well as between virions and the plasma membrane. Virions tethered to the cell surface by tetherin/BST-2 could be released by proteolysis with subtilisin. The authors propose a model in which cell-associated and virion-associated tetherin/BST-2 molecules interact with each other to restrict virion release.

Several groups have presented evidence that myeloid lineage cells harbor an antiviral restriction that is active against HIV-1, HIV-2, SIV, and murine leukemia virus (MLV).[8,9] This restriction is specifically counteracted by the Vpx protein that is encoded by HIV-2 and most SIV strains. However, to date, there is no direct evidence that the Vpr protein of HIV-1 and SIV is able to counteract this restriction even though the restriction is active against HIV-1. Data presented in Abstract 223 mapped the active domain in Vpx to the amino-terminus of Vpx. Collectively, the aforementioned data underscore the notion that cellular restrictions exert profound effects on the biology of primate lentiviruses and that accessory genes have evolved in these viruses primarily to counteract the antiviral activity of cellular restrictions.

Viral Replication and Pathogenicity

Infection of the cell is initiated when envelope glycoprotein on the surface of the virion binds to receptor and coreceptor molecules on the cell surface. This step is followed by a fusion event between viral and cellular membranes that deposits the viral core in the cytoplasm of the target cell. By comparison, many other viruses enter the cell by endocytosis and subsequently fuse with the membrane of the endosome in a process that requires low pH. For HIV-1, the fusion event at the plasma membrane does not require low pH.

Abstract 120 presented evidence that challenged the fundamental view that HIV-1 cannot enter cells by endocytosis (see also Miyauchi et al[10]). The authors employed time-resolved imaging of single virions as well as a beta-lactamase assay to follow virus–cell fusion. The authors froze the entry process at different stages with the use of specific fusion inhibitors at various intervals following virus–cell incubation. They observed that the majority of viral particles acquired resistance to membrane-impermeable inhibitors before acquiring resistance to low temperature that blocks fusion events. This evidence suggested that HIV-1 enters endosomal compartments before fusing with the cell membrane. Dynasore, a dynamin inhibitor that blocks endocytosis, was found to be active against HIV-1 infection. Collectively, these results indicate that HIV-1 can infect primary T cells and cell lines via receptor- and coreceptor-mediated endocytosis and subsequent pH-independent fusion with endosomes.

In the transmission of virus particles between cells, transmission can occur by cell-free virus particles or during cell–cell contact in the form of a virologic synapse. Data presented in Abstract 121 examined the factors that impact the transmission of virus between cells during the formation of a virologic synapse. Specifically, the authors examined whether the antiviral restriction tetherin/BST-2 localized to virologic synapses. They compared the ability of wild-type and Vpu-deleted HIV-1 variants to be transmitted between cells in contact. The authors found that in virus-producing cells expressing tetherin/BST-2, wild-type virus was transmitted efficiently, whereas Vpu-deleted viruses did not transmit at the virologic synapse.

This evidence was consistent with the accumulation of viral Gag protein at the virologic synapse in tetherin/BST-2–expressing cells containing a Vpu-deleted virus. Tetherin/BST-2 did not directly inhibit the formation of virologic synapse; rather, it specifically localized to the membrane contacts at the virologic synapse. Curiously, when fluorescent viral particles were followed at the virologic synapse, wild-type viruses were transmitted as discreet, small dots that faded over time. In contrast, Vpu-deleted virus particles were localized in large patches of membrane and were transmitted as such. However, the fluorescent signal did not diminish over time, indicating that there was no fusion with the cell surface. These results indicate that tetherin/BST-2 has the potential to antagonize virus detachment and transmission, both in the cell-free state and during cell-to-cell transmission in the virologic synapse.

Xenotropic Murine Leukemia Virus-Related Virus

Xenotropic murine leukemia virus-related virus (XMRV) is a newly recognized human retrovirus first discovered in prostate tissues of cancer patients. XMRV is very similar to xenotropic viruses found in the mouse genome. Obviously, the presence of a new retrovirus recoverable from human tissue generates a lot of interest in the retrovirus research community, and a burning issue revolves around

whether XMRV is capable of infecting humans, whether it has a disease etiology, and whether action should be taken to control its replication. Goff presented a summary of the existing research on XMRV in a plenary lecture (Abstract 132). Recent studies have suggested a high degree of seroprevalence of XMRV in prostate cancer patients and in individuals with chronic fatigue (CF) syndrome. Much of the controversy surrounding the potential role of XMRV in human disease centers around the frequency with which XMRV can be detected in prostate cancer and in CF syndrome patients. The widely divergent prevalence rates reported in different studies may stem from several factors including methods used in the detection.

Goff reviewed the literature for and against a role of XMRV in the etiology of CF syndrome and prostate cancer and presented evidence on the infectiousness of XMRV for human cells. All isolates of XMRV characterized to date appear to be exceedingly similar to each other (eg, 0.3% sequence diversions were found between the most distant pairs). Because sequence evolution is an inevitable consequence of error-borne reverse transcription, this extreme similarity would suggest that XMRV undergoes very few cycles of replication or, alternatively, that upon infection of a new host, the virus is fixed by host immune pressure. XMRV is antagonized by mouse APOBEC genes and by human tetherin/BST-2, and because XMRV has no obvious Vif- or Vpu-like functions, its ability to spread within the host may be limited by these cellular restrictions, thereby explaining its limited sequence diversion. Aside from this controversy surrounding its involvement in CF syndrome and prostate cancer, several lines of evidence indicate that XMRV is a bona fide infectious virus. It is able to replicate within peripheral blood mononuclear cells (PBMCs) and in fibroblasts and exhibits broad mammalian tropism.

As to the origin of XMRV, the limited divergence of XMRV isolates taken from different locations within the United States at different times suggests a recent point of origin, and the relationship to xenotropic MLV further suggests recent cross-species transmission from mice. Because none of the xenotropic MLV variants has the exact sequence characteristic of XMRV, however, it is unlikely that xenotropic MLV is the immediate source. Rather, data are consistent with a relatively distant, signal cross-species transmission event followed by adaptation of the virus to humans and subsequent spread. Given that some MLV variants are transforming (via insertional activation), it is unclear as yet whether XMRV has transforming activity.

XMRV appears to be infectious for both B- and T-cell lines, and replication is associated with cytopathic effects. Abstracts 150LB and 151 described successful infection of rhesus macaques after intravenous inoculation with XMRV. Inoculation was followed by low-level transient plasma viremia and persistence of proviral DNA in circulating PMBCs for several weeks. XMRV-positive CD4+ T cells were detectable in most lymphoid organs including spleen, lymph nodes, and the gastrointestinal tract throughout the course of infection. Whereas complete XMRV dissemination had occurred by day 6 postinfection, prostate tissue was positive only during the acute phase of infection. Collectively, these studies indicate that lymphocytes are a primary target for replication in the absence of detectable plasma viremia. In addition, specific serologic markers were identified that can facilitate analysis of XMRV incidence in large-scale epidemiologic surveys.

Reservoirs and Mechanism of Viral Persistence

Antiretroviral therapy is able to sustain durable suppression of viremia. However, rapid recrudescence of viremia occurs if antiretroviral therapy is interrupted. Therefore, reservoirs exist that sustain HIV-1 persistence in the face of antiretroviral therapy. Some of these reservoirs are believed to harbor the virus in a latent state, one that is invisible to immune surveillance. How this state is established is a topic of great interest. In particular, identification of mechanisms that permit interruption of latency is of interest because such understanding could lead to strategies to purge latently infected cells from the infected individual.

Abstract 253 examined HIV-1 integration sites in a primary CD4+ T-cell model of latency. In latently infected cells, the majority of integration sites were active genes, which were transcriptionally active according to serial analysis of gene expression. Furthermore, the orientation of the latent HIV-1 genome was the same as that of the upstream transcriptionally active gene. This orientation preference was not apparent in acutely or persistently infected cells. The authors hypothesized that transcriptional interference may play an important role in maintenance of HIV-1 latency.

Abstract 257 presented evidence for establishment of latency in both naive and central memory T cells in a primary CD4+ T-cell model of HIV-1 latency. Previous studies have hypothesized that HIV-1 latency is established primarily in activated central memory T cells that enter a latent state upon return to quiescence. In these studies, resting naive CD4+ T cells were found to be relatively resistant to HIV-1 infection in vitro. Studies with lymphoid histocultures and studies in SIV macaque models have demonstrated infection in both naive and central memory cells. These results would argue that proliferation of the host cell is not required for the formation of a latent provirus.

CD4+ T cells from healthy donors were infected with HIV-1 NL4-3 and sorted into naive and memory cell subsets, which were then evaluated for integrated viral DNA by polymerase chain reaction and for replication-competent virus by limiting dilution coculture. Although central memory cells contained 2-fold more viral DNA than did naive cells, they were found to harbor up to 8-fold greater replication-competent virus. This evidence suggests that whereas both naive and central memory cells can become infected, many infection events in naive cells result in proviruses that are un-

able to promote replication upon cell stimulation.

Abstract 287 extended on this theme and demonstrated that X4-tropic but not R5-tropic viruses infect and integrate within naive CD4+ T cells, whereas R5-tropic viruses were able to infect and integrate only within memory cells. X4-tropic-infected naive cells produced low levels of Gag protein but did not release infectious virions while in the resting state. However, activation of these cells led to the production of infectious virus, suggesting that they harbor a latent infection. Furthermore, the authors found integrated viral DNA in sorted naive cells of 2 of 3 patients receiving antiretroviral therapy. These studies suggest that the naive CD4+ T-cell subset may be a long-lived reservoir of latent HIV-1 infection in vivo.

Abstract 258 presented evidence that myeloid dendritic cells engender signals to resting T cells that allow them to be infected and establish a latent infection. Resting CD4+ T cells were cocultured with myeloid dendritic cells and then infected with HIV. The number of latently infected cells that could be established in this coculture was over 20-fold higher than that achieved upon infection of resting CD4+ T cells alone. Increased CD69 expression was detected in CD4+ T cells after coculture with dendritic cells, but there was no evidence for expression of activation markers including HLA-DR or CD38. Separation of myeloid dendritic cells from resting CD4+ T cells using a semipermeable membrane before the CD4+ T cells were infected statistically significantly reduced the frequency of latently infected cells. However, the frequency was higher than that obtained with CD4+ T cells alone, suggesting the presence of soluble factors in dendritic cell–induced latency.

Abstract 259 presented the results of studies aimed at reactivating latent HIV-1 using a Jurkat cell-line model of HIV-1 latency. This latently infected cell line was used to screen 640 natural products for compounds that activate HIV-1 expression in this cell line. Nine compounds from 6 structurally diverse classes were found to reactivate the expression of latent HIV-1. The mechanism by which these natural products reactivate latent HIV is under investigation. An important consideration in these experiments is how well the Jurkat cell-line model of latency recapitulates physiologic latency as it exists in resting CD4+ T cells in vivo.

Abstract 260 evaluated the ability of histone deacetylase inhibitors to reverse HIV-1 latency. Chromatin-associated transcriptional suppression is believed to be a mechanism to maintain transcriptional dormancy of the integrated HIV-1 genome. The investigational drug ITF2357 is an orally active histone deacetylase inhibitor approved for clinical trials in humans. Investigators used latently infected U1 and ACH2 cell lines, which have been shown previously to maintain HIV in a latent state, to evaluate the effects of ITF2357 on viral p24 production. ITF2357 was found to be highly active in inducing HIV-1 gene expression (as evidenced by p24 production) at clinically relevant concentrations. Therefore, this compound has the potential for purging HIV-1 reservoirs. However, as with the research presented in Abstract 259, the question remains as to whether U1 and ACH2 cell lines are valid models for viral latency as it exists in vivo.

While considerable effort has focused on characterization of the latent reservoir that persists during antiretroviral therapy, a continuing debate centers on whether ongoing viral replication may persist during antiretroviral therapy in some individuals. Ongoing viral replication would have the potential to replenish viral reservoirs including latent reservoirs. Sessions 26, 47, 64, and 65 contained studies that evaluated the impact of treatment intensification on viral reservoirs that persist during antiretroviral therapy. The rationale behind such studies is to evaluate whether treatment intensification can perturb such reservoirs.

Although studies addressing this question have been hampered by a lack of sensitive assays with which to probe the viral reservoirs, investigators have been employing a variety of surrogate markers including immune activation, ultrasensitive viremia assays, and assays of unintegrated viral DNA. The original studies of Giorgi and colleagues presented evidence that immune activation is an accurate surrogate of viral replication and T-cell depletion in HIV-1-infected individuals.[11] Pathogenic lentivirus infection is associated with elevated levels of immune activation that is reduced but not normalized by suppressive antiretroviral therapy. However, it is not known whether the elevated immune activation that persists during suppressive antiretroviral therapy is a result of ongoing viral replication.

A number of studies have revealed that most HIV-1-infected individuals receiving suppressive antiretroviral therapy exhibit a low level of viremia—several copies of viral RNA per milliliter of plasma. The origin of this low-level viremia is unclear, including whether it is a result of ongoing viral replication or the steady production of viral particles from persistent reservoirs. Data presented in Abstracts 279 and 280 indicated that antiretroviral therapy intensification with the integrase inhibitor raltegravir did not change the level of persistent low-level viremia in HIV-1-infected individuals receiving suppressive antiretroviral therapy. Similarly, Abstracts 101LB, 282, and 283 failed to observe an impact of raltegravir (Abstract 101LB) or maraviroc (Abstracts 282, 283) intensification on immunologic responses including immune activation markers (CD38+ or HLA-DR+ CD8+ cells). Therefore, these studies suggest that persistent immune activation in patients receiving antiretroviral therapy is unlikely to be the result of ongoing viral replication.

In contrast, Abstract 100LB presented evidence that raltegravir intensification of a suppressive antiretroviral therapy regimen reduced the extent of immune activation (measured by CD38+ or HLADR+ CD8+ cells) and impacted episomal viral cDNA dynamics in approximately 30% of patients. However, there was no effect of intensification on low-level viremia in these individuals. Episomal viral cDNA is a dead-end product of viral infection. However, these viral cDNA forms are

dynamic and turn over in vivo. As such, they are indicative of recent infection events. Upon intensification with raltegravir, there was a dramatic and transient increase in the frequency of episomes by 2 weeks to 4 weeks postintensification.

Because the formation of episomal cDNA requires de novo infection and reverse transcription, this evidence indicates that infection continues despite antiretroviral therapy in a statistically significant percentage of infected individuals. Furthermore, individuals with detectable episomal cDNA were more likely to have elevated levels of activated CD8 cells, suggesting that ongoing viral replication might be a contributing factor to immune activation in patients receiving antiretroviral therapy. Although these observations are provocative, they require confirmation in other cohorts undergoing suppressive antiretroviral therapy.

Abstracts 284 and 285 presented evidence that intensification with a coreceptor antagonist (maraviroc) reduced the size of the latent reservoir and residual viremia (Abstracts 284) and reduced the level of immune activation markers on both CD4 and CD8+ cell subsets (Abstracts 284 and 285). The basis for the effect of maraviroc on the latent reservoir is unclear. One hypothesis is that maraviroc engenders a signal through CCR5 that reverses viral latency. The ability to detect an increase in viremia as well as episomal cDNA in some of these individuals after maraviroc intensification is consistent with this hypothesis because reversal of viral latency and production of infectious virus could promote new infection events. Regardless of the mechanism, if these studies are reproduced, CCR5 inhibitors could represent one possible approach to purging the reservoirs that persist in the face of antiretroviral therapy.

Mechanisms of Immunopathogenesis

Studies investigating underlying mechanisms governing pathogenic lentivirus infection continue to remain a strong component of the conference. In his plenary presentation (Abstract 73), Silvestri provided an update on factors that distinguish pathogenic and nonpathogenic lentivirus infections. Pathogenic lentivirus infection, as exemplified by HIV-1 infection of humans or SIV infection of rhesus macaques (SIVmac), involves high-level viral replication, accelerated CD4+ T-cell turnover, and elevated levels of immune activation. Studies from several groups have demonstrated that nonpathogenic infection, as exemplified by SIV infection of sooty mangabeys (SIVsm) or African green monkeys (SIVagm), exhibits all of the characteristics of pathogenic infection with the exception of immune activation.

Studies over the past several years have focused on processes that drive immune activation. The consensus is that loss of mucosal integrity, as a result of virus replication, permits translocation of bacterial products (lipopolysaccharides, LPS), which drives immune activation and further enhances conditions for viral replication. Previous studies by groups led by Brenchley, Douek, and others[12,13] have suggested that infection and depletion of T_H17 cells, which are essential in host immunity against microbial pathogens, are direct causes of impaired mucosal integrity. In nonpathogenic infection, there is no apparent loss of T_H17 cells.

Silvestri presented evidence that the acute infection phase is remarkably similar in pathogenic and nonpathogenic infections. After acute infection, there is a generalized immune activation and massive viremia that lead to rapid depletion of gut CD4+ T cells. Silvestri presented data that similar events occur in the nonpathogenic infection of sooty mangabeys. However, analysis of cellular transcriptome profiles indicated that a number of cellular genes involved in immune activation are upregulated in both pathogenic and nonpathogenic infections. This activation profile was resolved following the acute infection phase in sooty mangabeys but persisted in pathogenic infection. Silvestri proposed that the rapid resolution of immune activation following the acute phase of infection contributes to the nonpathogenic state.

Silvestri also presented evidence that central memory T cells, which are a self-renewing source of T effector memory cells targeted by the virus, are protected from infection in natural SIV hosts. Studies from the research group led by Picker have suggested that the depletion of T central memory cells is crucial for progression to AIDS in SIV-infected rhesus macaques. Silvestri presented evidence that CCR5 expression on central memory T cells from sooty mangabeys is extremely low relative to CD4+ T cells from nonnatural hosts. These cells were also found to be relatively resistant to SIV infection compared with T central memory cells from rhesus macaques. These results support a model in which both rapid resolution of immune activation after acute infection as well as target cell restriction may be contributing factors that protect natural hosts of SIV from CD4+ T-cell depletion and AIDS.

Continuing with this theme, Abstract 44 presented evidence that increased microbial translocation and loss of natural killer (NK) cells are associated with rapid SIV disease progression in pigtail macaques. The authors measured peripheral and gastrointestinal tract lymphocyte function, activation, and turnover as well as microbial translocation in the gastrointestinal tract of pigtail macaques and rhesus macaques at various stages of disease progression.

The degree of damage to the gastrointestinal tract was found to correlate strongly with the LPS level in the colon, which in turn correlated with the amount of immune activation in the colon. Colon NK cells were able to produce interleukin-17 (IL-17), which is important for maintenance of gut enterocytes and mucosal integrity. The frequency of IL-17-producing NK cells was found to correlate negatively with the extent of damage to the colon. These data indicate that continued damage to gut epithelia may drive rapid disease progression after SIV infection and further suggests that local NK cells within the gut are necessary to maintain mucosal integrity. Therefore,

NK cells may be crucial to preserving gut integrity and limiting microbial translocation and immune activation.

Abstract 96LB presented evidence for the existence of defective CCR5 molecules in sooty mangabeys that did not support SIV infection. The authors identified a novel 2-base-pair deletion in the sooty mangabey CCR5 gene that results in a frame shift of the fourth transmembrane domain. This mutant CCR5 molecule was not expressed at the cell surface, nor did it support SIV entry. There appeared to be little selection pressure for or against the mutant allele in sooty mangabeys from the Yerkes National Primate Research Center, where the allele was detected at a frequency of approximately 25%. Because sooty mangabeys support robust HIV infection, these results indicate that CCR5-independent entry pathways are being used by SIVsmm in sooty mangabeys. The use of alternative pathways may play a role in protecting critical target cells that restrict pathogenesis in natural SIV infection.

Data presented in Abstract 93 suggest that the whey acidic protein family member WFDC1/ps20 is an HIV-1 permissivity factor on CD4+ T cells. The authors demonstrated that CD4+ T cells can be segregated into $ps20^{high}$ and $ps20^{low}$ subsets and that $ps20^{high}$ clones were preferentially susceptible to HIV-1 infection. To determine whether preferential infection and depletion of $ps20^{high}$ CD4+ T cells in vivo could lead to a drop in circulating ps20 levels, the authors examined plasma levels of ps20 in infected and uninfected individuals. Statistically significant differences in ps20 levels were observed between healthy volunteers and HIV-1-seropositive individuals; statistically significantly lower ps20 levels were found in control subjects versus infected individuals and in elite controllers versus chronic HIV-1-seropositive individuals. Therefore, HIV-1 infection is associated with a reduction in levels of circulating ps20, and plasma ps20 level is a novel correlate of viremia. It remains to be determined whether ps20 levels can be normalized after antiretroviral infection and whether reduction in ps20 levels correlates with other immunologic markers of AIDS progression.

Financial Disclosure: Dr Stevenson has served as a consultant to Merck & Co, Inc.

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HIV Vaccine Development

David I. Watkins, PhD

Updates on the Thai clinical vaccine trial, the discovery of additional neutralizing antibodies, and several new, nonhuman primate vaccine studies were presented at the 17th Conference on Retroviruses and Opportunistic Infections this year. Interestingly, the vaccine effect observed in the Thai trial diminished with time and was most effective in individuals who reported low-risk behavior. Two new neutralizing monoclonal antibodies were reported that were more potent and broadly reactive than the previously described monoclonal antibodies, giving the neutralization field an important boost. New studies were presented in macaques showing that a DNA prime modified vaccinia virus Ankara boost regimen can reduce acquisition of infection after a low-dose mucosal challenge with a heterologous pathogenic simian immunodeficiency virus (SIV) strain. Data suggesting that attenuated SIV vaccines can induce cellular immune responses that control viral replication were also discussed. Finally, and perhaps most encouragingly, vaccination with cytomegalovirus-expressing SIV antigens provided robust levels of protection against the highly pathogenic SIVmac239 viral isolate. All of these promising results should serve to energize the HIV vaccine field.

Most classic vaccines induce neutralizing antibodies that prevent or control viral replication. However, given the diversity of the HIV envelope and its glycan shield, it has been difficult to develop neutralizing antibodies against this virus. Many investigators have therefore been trying to develop alternative strategies to induce effective HIV-specific immune responses by vaccination. Encouraging results from antibody studies were expanded upon at the 17th Conference on Retroviruses and Opportunistic Infections this year, and new data from nonhuman primates gave the field hope that it might indeed be possible to make a vaccine against HIV.

Human Vaccine Trials

Michael described new post hoc analyses from the Thai clinical vaccine trial (Abstract 74). He urged that these post hoc analyses be treated with caution, however. Despite a paucity of vaccine-induced cellular immune responses, vaccinees acquired HIV at a lower rate (31%) than individuals given placebo, but the vaccine had no effect on viral load or CD4+ counts in vaccinees once they became infected. Interestingly, Michael presented data showing that vaccine efficacy dropped over time. Although most vaccinees had binding antibodies, titers collapsed after 24 weeks.

Fauci discussed the Thai vaccine trial results, urging researchers to try to understand the correlates of protection in vaccinated individuals who avoided infection in this trial (Abstract 19). He suggested that new vaccines should be designed to try to prevent acquisition rather than control viral replication after infection. Furthermore, in future HIV vaccine trials, researchers should strive for an efficacy rate higher than 60%. Both Fauci and Michael urged further studies with this vaccine approach.

In a follow-up to the Step (HIV Vaccine Trials Network/Merck 023) trial, Rolland tested whether adenovirus serotype 5 (Ad5)-induced T cells can affect viral evolution in infected vaccinees (Abstract 75). She presented data from the Step Trial Study Group showing that vaccinees exerted statistically significant selective pressure on cytotoxic T-lymphocyte (CTL) epitopes, largely in Nef sequences. In viral proteins that were not used in the vaccine, there was no evidence for selection. These results suggest that the vaccine-induced CTLs exerted some measure of selection on the regions of the virus that encoded CTL epitopes.

HIV Pathogenesis Studies With Relevance to Vaccine Studies

Alter discussed the possible role of natural killer (NK) cells in controlling HIV replication (Abstract 178). It has previously been shown that certain NK cell receptors paired with particular HLA types can affect the rate of progression to AIDS after HIV infection.[1] Individuals with the activating killer immunoglobulinlike receptor (KIR) allele 3DS1 paired with HLA-Bw4 progress to AIDS more slowly than individuals without the 3DS1 allele. Alter presented data showing that during early infection, 50% of peripheral blood mononuclear NK cells secreted cytokines. Furthermore, individuals who express KIR3DS1 and HLA-B48 suppressed viral replication better than others. Alter also showed emerging data suggesting that NK cells can select for mutations in several different regions of HIV. Thus, it is possible that vaccination to induce NK cells might prove to be a novel and useful avenue for exploration in HIV vaccine development.

Burton presented encouraging data from the field of neutralizing monoclonal antibodies (Abstract 67). Before 2009, only 4 neutralizing antibodies had been isolated from HIV-infected individuals. Burton described 2 new antibodies, PG9 and PG16, that were more potent and of higher affinity than those previously described. He also reiterated that lower concentrations of these neutralizing antibodies in vivo might be required to achieve neutralization than described earlier. Overall, he painted a hopeful scenario for the field.

Dr Watkins is professor in the Department of Pathology and a member of the AIDS Vaccine Research Laboratory at the University of Wisconsin Madison.

Results From Nonhuman Primate Vaccine Studies

Robinson presented encouraging results from a DNA prime/modified vaccinia virus Ankara (MVA) boost vaccination regimen in which they used granulocyte macrophage colony-stimulating factor (GM-CSF) as an adjuvant in half of the vaccinated animals (Abstract 79LB). The vaccine constructs expressed the proteins Gag, protease (PR), reverse transcriptase (RT), and envelope (Env) of the simian immunodeficiency virus strain mac239 (SIVmac239) and prevented infection in 5 of 7 vaccinated animals (using the adjuvant GM-CSF) from a repeated low-dose heterologous mucosal challenge. In the group of animals that did not receive the adjuvant, 4 of 7 were protected. By contrast, all 9 naive control animals became infected after 12 low-dose weekly challenges with the heterologous challenge isolate SIVsmE660. Robinson noted that the GM-CSF group had developed antibodies with enhanced neutralizing titers against a neutralization-sensitive variant of SIVsmE660.

Johnson presented a comprehensive overview of the state of knowledge regarding vaccine protection induced by attenuated live SIV (Abstract 179). Vaccination of macaques with SIVmac239 from which the *nef* region was deleted (SIVmac239Δnef) confers sterilizing immunity against challenge by the highly pathogenic homologous SIVmac239. However, protection against heterologous intravenous challenge has proved to be less robust. Johnson presented new results from Reynolds showing that the attenuated vaccine can prevent acquisition of a heterologous low-dose mucosal challenge. These data suggested that attenuated SIV might indeed be effective against a heterologous isolate using a challenge that more closely mimicked human HIV exposure. Johnson then presented new data from Schmitz indicating that B-cell depletion does not affect protection after challenge with SIVmac239.

Similarly one of Johnson's colleagues, Desrosiers, who first described the protection induced by SIVmac239Δnef, showed that manipulating the envelope in the vaccine had little effect on protection. The majority of animals vaccinated with SIVmac239Δnef expressing the envelope (Env) protein of SIVsmE543 were protected from SIVmac239 challenge, suggesting that Env-specific antibodies were not playing a role in control of viral replication because the envelopes of these 2 viruses are very different. Johnson also presented data suggesting that ongoing viral replication likely plays a role in this protection. Vaccination of animals with single-cycle SIVmac239 that undergoes only a single round of replication is not as effective as with SIVmac239Δnef. Finally, Johnson presented data showing that if animals are challenged vaginally 5 weeks after vaccination with SIVmac239Δnef, they reduce viral replication by 1 $\log_{10}$ in the acute infection phase, but no protection is noted in the chronic phase. These results confirm earlier studies suggesting that SIVmac239Δnef–induced protection needs time to develop.

Picker presented follow-up studies (Abstract 181) to his previously published work.[2] Here the researchers used a cytomegalovirus (CMV)-vectored vaccine to induce immune responses that afforded protection in 4 of 12 vaccinees after repeated mucosal challenge with the highly pathogenic SIVmac239 clone. Interestingly, these 4 monkeys showed small "blips" of viral replication and subsequently developed T-cell responses against Vif, a region of the virus that was not used in the vaccine phase. Thus, these animals had clearly been infected with the challenge virus but had effectively controlled replication. Picker credited this remarkable protection in the 4 vaccinees to the effector memory CD8+ T cells induced by the chronic CMV vector.

Picker described a new study in which 6 of 12 animals vaccinated with CMV showed the same type of control as previously reported.[2] One animal had a peak of 40 million copies/mL, after which viral replication was controlled to undetectable levels. Half of the CMV-vaccinated animals showed no control of SIVmac239 replication, and their viral loads were indistinguishable from those of the naive, unvaccinated animals. Picker also presented a new correlative analysis showing that peak frequency of SIV-specific CD8+ T cells in the vaccine phase was the only factor that correlated with the ability to withstand challenge. Importantly, 33 weeks after infection, 12 of 24 vaccinees were still controlling viral replication, with only 1 animal having lost control. Picker also presented data showing that 7 years after CMV-Gag vaccination, high frequencies of effector memory T cells were still present in the liver, spleen, and bone marrow. Finally, Picker suggested that there may be 3 levels of protection—antibodies, effector memory T cells, and central memory T cells. Understanding why this CMV vector is so efficient at controlling replication of the highly pathogenic SIVmac239 challenge should give important insights into how to make an effective HIV vaccine.

Financial Disclosure: Dr Watkins has served as a consultant to Pfizer Inc.

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Human Papillomavirus-Related Anal Squamous Cell Dysplasia and Carcinoma in HIV Infection

John Koeppe, MD, and Steven C. Johnson, MD
Level: All

Human papillomavirus (HPV) infection of the anus and HPV-related anal dysplasia are prevalent among HIV-infected persons. This COW activity discusses the risk of anal squamous cell carcinoma (SCC) in HIV-infected persons with anal dysplasia that is detected on cytologic screening. The use and limitations of digital rectal examination and anal Papanicolaou testing for screening of anal dysplasia and anal SCC are considered, and available treatment options for anal dysplasia are compared. This activity also discusses the use of condoms, HPV vaccines, and antiretroviral therapy to prevent anal dysplasia and anal SCC.

Common Drug Interactions in Patients Receiving Antiretroviral Therapy

John J. Faragon, PharmD, BCPS, David Condoluci, DO, and Cindy M. Hou, DO, MBA
Level: Basic

Drug interactions are an increasing challenge for practitioners who treat HIV-infected patients. To the typical 3-drug antiretroviral regimen additional drugs may be added for comorbid conditions and as prophylaxis for opportunistic infections. Treatment is further complicated in patients in whom numerous antiretroviral regimens have failed, because such patients often require the use of more complex regimens to suppress HIV. This activity describes the effects of antiretroviral drugs and other drugs on the cytochrome P450 enzyme system and presents strategies for preventing interactions between antiretroviral drugs and selected coadministered drugs used in primary care settings.

Non–AIDS-Defining Cancers in Patients with HIV Infection

Roger J. Bedimo, MD, MS
Level: Advanced

Despite a substantial decline in the incidence of AIDS-defining cancers that has occurred with the use of antiretroviral therapy, the incidence of malignancies not known to be associated with immunosuppression, the non–AIDS-defining cancers, has increased. This presentation discusses changes in the spectrum of cancers among HIV-infected patients, the role immunodeficiency plays in the incidence of non–AIDS-defining cancers, and the management and prognosis of selected non–AIDS-defining cancers.

Management of an HIV-Infected Patient After Initial Antiretroviral Regimen Failure

Warangkana Sangchan, MD, and Lisa M. Chirch, MD
Level: Basic

Although the management of HIV has undergone dramatic improvement in recent years, failure of an initial antiretroviral regimen remains a common clinical challenge. In this activity, learners will identify the clinical and laboratory characteristics of an initial antiretroviral regimen failure and the possible causes of such failure. The presentation discusses management strategies for patients with first-regimen failure and appropriate antiretroviral regimens for treatment-experienced patients.

The Use of Chemokine Receptor Antagonists in Antiretroviral Treatment Failure

David M. Margolis, MD, and Gretchen Shaughnessy Arnoczy, MD
Level: Advanced

HIV engages in complex interactions with host cell-surface receptors to gain cellular entry and begin viral replication. The use of entry inhibitors such as chemokine receptor antagonists offers the potential for achieving virologic suppression in highly drug-experienced patients in whom suppression was previously difficult to attain. This activity discusses the interpretation and significance of HIV tropism assay results and the implementation of a chemokine receptor antagonist in a treatment-experienced patient with numerous treatment failures.

End-Stage Renal Disease in the HIV-Infected Patient

Christina M. Wyatt, MD
Level: Advanced

HIV-infected patients are at heightened risk of kidney disease related to HIV, coinfections, and the direct toxicity of antiretroviral therapy and concomitant medications. This expertly developed activity discusses current recommendations for the screening and management of chronic kidney disease (CKD) and end-stage renal disease (ESRD) in HIV-infected patients. Issues unique to the diagnosis and management of CKD in the HIV-infected are discussed as are criteria for identifying HIV-infected patients with ESRD who may be eligible for kidney transplantation.

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HIV Epidemiology, Testing Strategies, and Prevention Interventions

Susan Buchbinder, MD

As the HIV epidemic has matured, a substantial proportion of new infections worldwide may be occurring within stable partnerships. Within the United States, blacks are disproportionately affected by HIV disease, and the drivers of this epidemic involve behavioral and structural factors. The 17th Conference on Retroviruses and Opportunistic Infections highlighted new insights into drivers of HIV infection in both of these populations. The conference also focused on new strategies to track the epidemic and to prevent HIV infection, including scale-up of HIV testing and of treatment of HIV-seropositive persons, and the use of oral and topical antiretroviral drugs to prevent HIV acquisition among HIV-uninfected persons.

Populations With High Incidence Rates of HIV Infection

Serodiscordant Couples

In session 3, Bunnell highlighted the high rates of HIV transmission globally that occur in stable partnerships (Abstract 14). For example, it is estimated that 74% of new infections in Uganda occur in married or recently married persons, and 30% to 53% of new infections in Thailand occur in the previously seronegative partners in serodiscordant couples. Similarly, data from the United States and Europe suggest that a high proportion of new infections in men who have sex with men (MSM), perhaps up to two-thirds, occur in steady partnerships.[1] Mwangi and colleagues (Abstract 38) and Kaiser and colleagues (Abstract 40) presented data from Kenya's nationally representative, population-based survey. Of more than 2700 couples interviewed for whom HIV-testing results were available, 5.9% were serodiscordant. Applied at a population level, this result suggests that there are 344,000 serodiscordant couples in Kenya. Among married HIV-infected Kenyans, the vast majority (89%) did not know their own or their partner's HIV serostatus. Factors associated with serodiscordance included older age in women, larger number of lifetime partners in women, lack of male circumcision, herpes simplex virus type 2 (HSV-2) positive concordance, and lack of knowledge of HIV serostatus. These studies suggest that prevention strategies should target both testing of and treatment for couples.

Bunnell outlined a number of strategies to identify serodiscordant couples and provided successful examples of these diverse strategies. For example, in Uganda, family members of HIV-seropositive patients were offered HIV testing. Of 2300 family members offered home-based testing, 99% accepted. Importantly, 43% of spouses of HIV-infected adults were found to be HIV-seronegative, and 99% of these partners had not previously been HIV tested, providing an important opportunity to prevent new HIV transmissions.

In Kenya, a program was initiated to identify HIV infection among persons with tuberculosis (TB), and then testing was offered to their partners. Among stable partners of nearly 42,000 patients coinfected with HIV and TB, 49% were HIV-seronegative, again highlighting important opportunities for HIV prevention. In Uganda, health care practitioners initiated testing among their patients and their partners. Overall, 19% of the couples were found to be serodiscordant, and all were unaware of their serodiscordant status. Rwanda has had an impressive program of testing the male partners of pregnant women to reduce HIV transmission rates in postpartum women and their partners, in whom HIV incidence is exceptionally high. These efforts have increased rates of testing in male partners from 16% in 2003 to 84% in 2009.

Another strategy to increase the uptake of testing in couples is with door-to-door testing. In Kenya, the home-based testing program has received widespread acceptance, with uptake rates in excess of 85%. Two-thirds of adults in couples were tested together, and 85% of cases were previously undiagnosed; the median CD4+ cell count was 450/µL, substantially higher than has been seen in US populations of newly diagnosed cases of HIV infection. A mass testing program in Larambi, Kenya, successfully tested more than 47,000 persons in 7 days (approximately 80% of the total population). Of this population, 82% had never been tested.

Bunnell also pointed out that a substantial minority of infections in serodiscordant couples may occur from outside the partnerships. For example, 2 African studies suggested that 13% to 29% of HIV-uninfected partners in serodiscordant couples who later seroconverted were infected with HIV that was not genetically linked to the HIV from the seropositive partner, suggesting that these infections occurred outside of the primary serodiscordant relationship. Campbell and colleagues presented data on 151 seroconversion events in a longitudinal study of HIV-serodiscordant couples (Abstract 970). Of these, 26.5% were determined to be unlinked. This study demonstrates the importance of sequencing viral isolates from both partners in serodiscordant-couple studies, to understand factors that may drive infection within stable partnerships, and to accurately assess the efficacy of interventions that target the HIV-infected person within these partnerships.

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Disparities in HIV Disease in the United States

Smith presented a comprehensive overview of disparities in HIV incidence, morbidity, and mortality in blacks in the United States (Abstract 72). Although blacks make up 12% of the US population, they comprise more than half of newly diagnosed cases of HIV infection. Smith explained that this phenomenon is not new, as more than half of the children and women receiving AIDS diagnoses in the mid-1980s were black. However, public health campaigns and public perception, including within the black community, were inadequately focused on this burgeoning epidemic in the early years of the HIV epidemic. These disparities have continued to grow, with higher AIDS case rates and mortality in blacks than in any other racial or ethnic group in the United States.

Smith explored some of the underlying drivers of these health disparities, including behavioral factors (eg, risk practices, overlapping sexual networks, substance use) and environmental factors (eg, poverty, limited health care access, health illiteracy, and incarceration). A number of studies in heterosexuals have demonstrated that normative sexual behaviors can lead to disproportionately high incidence rates of HIV infection if the HIV prevalence in the partner pool is substantially higher than in other communities. For example, a study of HIV-infected persons in Washington, DC, found that nearly half of the HIV-seropositive women had only 1 sexual partner. A similar situation occurs in the acquisition of other sexually transmitted diseases (which may, in turn, increase the risk of HIV acquisition); among young people with lower-risk behavioral characteristics, blacks were 25 times more likely than whites to acquire a sexually transmitted disease. High rates of incarceration (higher in blacks in the United States than in blacks in South Africa during apartheid) also disrupt social relationships and may lead to HIV transmission within and outside of prisons and jails, within more intertwined sexual networks. Adimora and colleagues reported that the 2002 National Survey of Family Growth found higher rates of sexual concurrency (partnerships that overlap in time) among black women, women with nonmonogamous partners, and women with various drug and alcohol patterns (Abstract 968).

Numerous studies have found similar or lower rates of sexual risk taking among black MSM compared with white MSM. For example, Magnus and colleagues reported that among MSM participating in the National HIV Behavioral Surveillance survey in 2008, MSM of color were statistically significantly less likely to report 4 or more sex partners in the past 12 months (42% vs 61%; $P < .05$), unprotected anal intercourse (receptive in 31% vs 56%; $P < .05$; insertive, 30% vs 51%; $P < .05$), and to have ever engaged in "barebacking" (sex without a condom, 58% vs 73%; $P < .05$) (Abstract 972). Despite lower reported risk, HIV prevalence was statistically significantly higher among MSM of color (20% vs 8%; $P < .001$), who were also statistically significantly more likely to be newly diagnosed (8% vs 3%; $P < .001$). As Smith pointed out, this leads to a situation in which there is "no room for error" for HIV-uninfected black MSM if they are likely to choose other black MSM partners. Despite lower levels of risk, their sexual partners may be more likely to be HIV-seropositive, be unaware of their seropositive status, have higher rates of sexually transmitted diseases, and be less likely to be adequately treated, leading to higher transmission rates.

Smith also pointed to the considerable health disparities among HIV-infected blacks in the United States, who may be less likely to access care, less likely to be given antiretroviral drugs early in the course of the disease, and more likely to experience treatment failure if adherence is poor. She urged that public health messages move away from the focus on risk practices to concentrate on populations; encouraged clinical investigators to include more diverse populations in prevention and treatment trials; and challenged clinicians to begin treatment earlier, improve adherence, rapidly link patients into care, and build culturally competent relationships that address misperceptions and mistrust.

Molecular Epidemiology to Track the Spread of Infection

Investigators have begun to use viral sequencing data to track clusters of sexual and injection-drug-use transmission among populations, leading to new insights about transmission patterns. Weinert and colleagues presented a phylogenetic analysis of HIV transmission among MSM in the United Kingdom (Abstract 449). Of nearly 15,000 subtype-B HIV samples tested, nearly 100 clusters of similar viral strains infecting 10 or more individuals were found, accounting for 1673 individuals. Patterns of transmission suggest that infections have moved out of London into Manchester and Brighton, with further outward migration from these 3 urban epicenters. A similar study in Belgium among 506 patients receiving diagnoses between 2001 and 2009 found that patients belonging to transmission clusters were more likely to be white, younger, and MSM (Abstract 450). These 2 studies point to the influence of sexual networks on the rapid spread of HIV among MSM populations globally.

Phylogenetic analysis among injection drug users (IDU) in Sargodha, Pakistan, identified a single cluster of highly related sequences among 151 IDU, suggesting the recent introduction of a single source of infection in this population (Abstract 451). The authors of each of the studies suggest that phylogenetic analyses may provide useful information about transmission patterns that could help in developing and targeting interventions.

Strategies to Increase HIV Testing

Several investigators presented data on programs to increase HIV testing rates, demonstrating major strides in the rollout of testing strategies while pointing to as-yet-unfilled need. Althoff and colleagues reported on more than 35,000 HIV-infected patients in the United States and Canada participating

in the 11 cohorts in the NA–ACCORD (North American–AIDS Cohort Collaboration on Research and Design) study (Abstract 982). From 1996 to 2007, the median CD4+ cell count at first presentation increased from 234/µL to 327/µL ($P < .01$), with increases seen in all risk groups. Although the proportion of persons with a CD4+ cell count of at least 350/µL at first presentation also increased (34% vs 47%; $P = .01$), more than half of HIV-infected persons in these cohorts did not present until their CD4+ count was below the recommended threshold for treatment.

A number of strategies are being tested to increase HIV testing rates in populations at risk. Castel and colleagues presented encouraging data from a public health initiative to increase HIV testing and linkage to care throughout Washington, DC, one of the most heavily affected cities in the United States (Abstract 34). HIV testing increased 3.7-fold from 2004 to 2008, increasing from fewer than 20,000 tests to more than 72,000 tests over that time. This led to a 17% increase in newly identified HIV-seropositive patients, and the proportion receiving a viral load measurement within 3 months of their first positive HIV test result increased from 62% to 67% over that time. Median CD4+ cell counts increased from 216/µL to 343/µL. More work needs to be done, however, as 33% of persons were not receiving timely viral load measurements, and of the persons with newly diagnosed AIDS cases, 61% had still first tested HIV seropositive within 12 months of receiving their diagnosis.

Calderon and colleagues presented an approach to increasing HIV testing in hospital emergency departments by using a multimedia tool to deliver prevention messages in addition to providing access to an HIV-test counselor (Abstract 1004). During the 2 years of this demonstration project, nearly 29,000 patients were tested. Patient satisfaction was high, with 89% reporting they had learned a moderate to large amount of new information about HIV. Only 101 HIV infections were newly identified or confirmed, but 86% of these patients were linked to outpatient care, with a mean of 7 days to the time of their first appointment.

Daskalakis and colleagues presented data on an HIV-testing program delivered to MSM attending commercial sex venues (Abstract 1005). From February 2006 to August 2009, nearly 1000 unique clients were tested, yielding 2.7% newly diagnosed cases of HIV infection, 30% of which were acute or recent infections. Polk and colleagues described a program using mobile vans to provide HIV testing in high-risk neighborhoods in Baltimore (Abstract 1007). They recruited more than 1000 participants at 40 venues and identified 21 non-IDU heterosexuals with HIV infection. Wohl and colleagues presented data on an opt-out HIV testing program in the North Carolina state prison system (Abstract 1006). The proportion agreeing to testing increased from 57% to 91% after the program was implemented. Testing is an essential first step for prevention strategies, so the lessons learned from these pilot programs are important in planning scale-up of testing strategies.

Cherutich discussed the role of HIV testing in treatment and the use of innovative home-based testing in Africa to increase knowledge of HIV serostatus (Abstract 61). Published data suggest that in the United States, the approximately 25% of persons unaware of their HIV infection may contribute from 54% to 70% of new sexually transmitted infections.[2] In Africa, where 75% of HIV-infected persons are unaware of their infection, more than 90% of HIV transmission likely stems from this lack of knowledge.

Cherutich described 2 innovative programs of home-based testing in which door-to-door testing attempts to achieve broad coverage of all persons, or targeted testing is attempted in which household members of known HIV-infected persons are offered testing. These programs have been highly successful. In Uganda, a study in 2300 families of HIV-infected persons found that 37% of adults and 19% of children under the age of 5 years had undiagnosed HIV infections, and 39% of those without previous testing were eligible for antiretroviral treatment. In Kenya, door-to-door testing programs have achieved 60% to 77% coverage of individuals offered testing, and 76% to 91% have accepted testing. Among HIV-infected persons, 85% to 90% were unaware of their HIV infections; median CD4+ cell counts were 411/µL, representing a major achievement in identifying persons early in HIV infection and increasing opportunities for both prevention and treatment. Both household-member testing and door-to-door testing have been found to be cost-effective, with estimates ranging from $6 to $14 per person tested, and $84 to $232 per HIV infection detected.

Brown and colleagues found that a partner-notification program of patients with newly diagnosed HIV infection more than doubled the proportion of partners who received HIV counseling and testing (from 24% to 51%; $P < .001$), nearly two-thirds of whom were found to be HIV-seropositive (Abstract 960). Substantially more research is needed to optimize the operational components of these testing programs, determine the optimal frequency of home-based testing, and develop the most cost-effective strategies to reduce HIV incidence, morbidity, and mortality.

HIV Treatment as Prevention

Mathematic Models of Expanded HIV Testing and Treatment

There has been great interest in the possibility that increasing HIV testing, linkage to care, and early initiation of antiretroviral therapy could substantially reduce or eventually eliminate new HIV transmissions, the so-called "test-and-treat" or "test, linkage-to-care, plus antiretroviral therapy (TLC plus)" approach. Fauci pointed out that with an estimated 2.7 million new infections each year, for every person receiving treatment, approximately 2.5 new persons become infected, suggesting that we need more effective prevention approaches than we currently have (Abstract 19).

Williams and Dye (Abstract 13) and their colleagues Granich and coinvestigators (Abstract 965) presented several

mathematic models to evaluate the impact of widespread HIV testing and antiretroviral therapy for HIV-infected persons in South Africa. A model that would provide universal, annual HIV testing and antiretroviral treatment for all HIV-infected persons would reduce HIV incidence by 80% compared with a program that begins antiretroviral therapy at CD4+ T-cell counts below 200/μL. Although the cost of such programs is high in the first 5 years to 10 years, the overall cost over the life of the program is similar to that of current strategies because of savings from infections averted.

Bendavid and colleagues presented a model of universal testing and treatment showing a 35% reduction in new infections over 10 years with this approach (Abstract 999). The addition of enhanced linkage to and retention in care led to an additional 73% reduction in infections over that time period.

Two models addressed the role of enhanced testing with or without treatment among MSM in the United States. Charlebois and colleagues presented a mathematic model of this universal testing and treatment strategy among MSM in San Francisco, a high-prevalence (23%) population with high rates of awareness about HIV serostatus (Abstract 996). These models suggest that the addition of annual HIV testing and treatment regardless of CD4+ cell count would lead to an 81% reduction in new HIV infections over 10 years compared with current practice.

Golden and colleagues presented a model that explored the relative importance of primary HIV infection, chronic undetected HIV infection, and chronic untreated HIV infection in driving new HIV infections in MSM in King County, Washington (Abstract 1001). Although more than half of new infections in his model were transmitted by persons unaware of their HIV infection, more than half of those (greater than one quarter of the total) were MSM with primary HIV infection, which may not be detected in standard testing strategies. Another substantial source of new infections in this model were those transmitted from persons aware of their HIV infection but not yet receiving antiretroviral therapy. These investigators are now pilot testing a program to link known HIV-infected persons into care and to address questions and concerns about antiretroviral therapy with these patients.

Other mathematic models focused on the potential impact of more widespread HIV testing and treatment using the new international guidelines for initiating treatment at CD4+ cell counts at or below 350/μL. One model presented by van de Vijver and colleagues assumed HIV testing annually for at most 20% of the population in Macha, a rural area in southern Zambia (Abstract 963). Even with this assumption, in this model, the median HIV incidence would decrease in 10 years by 62% (range, 56% – 67%), with much of the remaining infections the result of transmission from acutely infected persons. Reducing the annual number of sexual partnerships and implementing strategies to identify newly infected persons could lead to further substantial declines in HIV incidence.

Scott and colleagues modeled the impact of testing every year versus every 3 years and initiating antiretroviral therapy at CD4+ cell counts at or below 350/μL or at diagnosis (Abstract 964). Compared with current practice, annual screening and treatment led to a 17% reduction in new infections in 5 years but also to a paradoxic increase of 11% of lifetime cases of secondary HIV transmission. Blower and colleagues also sounded a cautionary note about the potential risk of increases in antiretroviral drug resistance with universal testing in South Africa (Abstract 966). However, Montaner and colleagues showed data from British Columbia, Canada, that refuted these concerns about resistance (Abstract 88LB). In their experience, widespread use of antiretroviral therapy has led to reductions in viral load and substantial reductions in the prevalence of antiretroviral drug resistance within the community.

Overall these models suggest that more aggressive guidelines for HIV testing and treatment could have widespread beneficial impact, with continued attention needed for issues like linkage to and retention in care and further reductions in behavioral risk. However, empiric data will be essential to develop and validate these modeling projections. Palombi and colleagues presented data on treatment responsiveness and survival from the DREAM (Drug Resource Enhancement against AIDS and Malnutrition) study throughout sub-Saharan Africa as an example of how data from observational cohorts can inform mathematic models (Abstract 998).

Temporal Trends in HIV Incidence in the Effective Antiretroviral Therapy Era

Several studies examined temporal trends in HIV incidence around the time of scale-up of antiretroviral therapy programs. Rehle and colleagues reported on HIV incidence and risk practices in South Africa from 3 national household surveys conducted in 2002, 2005, and 2008 (Abstract 37). South Africa has made enormous progress in rollout of antiretroviral therapy, with only 33,000 receiving treatment in January 2005, increasing to nearly 750,000 in March 2009. From 2002 to 2008, HIV incidence declined, particularly among women aged 15 years to 24 years, in whom incidence had fallen from 5.5 per 100 person-years to 2.2 per 100 person-years. Overall, self-reported risk practices have decreased (condom use at most recent sexual encounter increased from 31% to 65% from 2002 – 2008), and knowledge of HIV serostatus has increased from 25% to 56%. Wanyama and colleagues confirmed that antiretroviral therapy use was associated with a reduction in risk activities, including increased condom use and a reduction in sex with multiple partners in the 12 months after antiretroviral therapy initiation in patients of an infectious diseases clinic in Kampala, Uganda (Abstract 975).

Montaner and colleagues presented an ecological analysis that demonstrated that concomitant with an increase in rollout of antiretroviral therapy for HIV-infected persons in British Columbia, Canada, was a decline in the plasma viral levels throughout the province (ie, "provincial, or community, viral load")

and a decrease in new HIV diagnoses (Abstract 88LB). These declines were seen particularly among IDU, who experienced a 50% reduction in new diagnoses. Das-Douglas and colleagues conducted a trend analysis of the mean viral load among HIV-infected persons in San Francisco, California, from 2004 through 2008. Mean viral load decreased overall from approximately 24,000 copies/mL to 15,000 copies/mL and was associated with a drop in the annual number of newly diagnosed HIV infections (from 798 to 434 infections) (Abstract 33). However, an analysis to assess the relationship of mean viral load with a decrease in estimates of HIV incidence was not statistically significant, perhaps because of the uncertainty of incidence estimates from cross-sectional samples. These trends are encouraging and suggest that continued effort to increase HIV testing, linkage to care, and treatment may result in lower HIV infection rates within populations.

A cautionary note was sounded by Jansen and colleagues, who presented data from the Amsterdam Cohort Study (Abstract 35). HIV-related risk practices substantially increased in MSM 30 years of age or younger, accompanied by substantial increases in HIV incidence rates. This result may suggest that increases in sexual risk may be able to overwhelm any reduction in HIV incidence that occurs as a result of any scale-up in antiretroviral therapy.

In addition to these ecological analyses, Donnell and colleagues presented observational data from the Partners in Prevention trial indicating very low rates of HIV transmission among couples initiating antiretroviral therapy (Abstract 136). Of 3381 serodiscordant couples, 349 HIV-seropositive partners initiated antiretroviral therapy during the 12-month to 24-month follow-up period. HIV incidence was 2.24 per 100 person-years among the couples not receiving antiretroviral therapy and 0.37 per 100 person-years of follow-up. After adjusting for time on study and CD4+ T-cell counts, the relative risk of HIV infection was 0.08 (95% confidence interval, [CI], 0.002 – 0.57), a 92% reduction in the risk of HIV transmission. Incidence rates were particularly high among untreated couples with CD4+ cell counts below 200/µL, with no infections in treated couples with these low CD4+ counts, suggesting that even initiating treatment in persons under previous international guidelines could have a substantial impact on reducing HIV transmission rates.

However, all of these ecological studies and this observational study data provide indirect evidence that have the potential for confounding. Data will be available in the future from a randomized controlled trial of standard versus early initiation of antiretroviral therapy in serodiscordant couples (HIV Prevention Trials Network [HPTN] 052) to inform future directions in treatment as prevention·

Prevention Approaches for HIV-Seronegative Populations

Condoms and Male Circumcision

Two known, effective interventions to reduce the spread of HIV infection, male condoms and male circumcision, are currently underutilized. Warner reviewed the challenges with increasing condom use (Abstract 60). Consistent condom use is relatively low in many surveys of populations in the United States and internationally, including among known serodiscordant couples. Although condom use has been increasing over time, rates still remain below 50% in many populations, including those with multiple partners in high-prevalence countries. Barriers to condom use include access to condoms, device-specific challenges (eg, reduced sensation, difficulty maintaining erection), and partnership-related issues (eg, difficulty negotiating use, concerns that condom use implies mistrust). Warner called for more research into new condom technologies that address some of the current limitations and help individuals overcome these barriers to use.

Dickson and Farley presented an overview of the scale-up of male circumcision in Africa (Abstract 62). Three randomized controlled trials demonstrated a 60% reduction in HIV acquisition among HIV-uninfected men undergoing male circumcision. In 2007, a set of recommendations was developed to scale-up male circumcision in high-prevalence areas with low rates of male circumcision, and 13 priority countries were identified in eastern and southern Africa. Modeling exercises suggest that if 80% of adult men and newborn boys could be circumcised in 14 African countries by 2015, more than 4 million adult infections could be averted in 15 years. A $4 billion (US) investment to scale-up male circumcision could lead to more than $20 billion in savings. A number of countries have begun scale-up of male circumcision, although challenges remain, including development of service-delivery systems that can support scale-up through task shifting and task sharing between health professions.

Microbicides

McCormack presented data (for Chisembele et al, Abstract 87LB) from the MDP (Microbicides Development Programme) 301 Phase III vaginal microbicide trial. The results demonstrated that a gel, naphthalene sulfonate microbicide polymer (PRO 2000; Indevus Pharmaceuticals, Lexington, MA), did not protect women against HIV infection. The summary results of the trial were announced in December 2009, but the presentation at this year's conference was the first presentation of these data at a large scientific meeting. This trial was particularly important because it followed a number of trials of unsuccessful microbicide products based on non–HIV-specific approaches to protection, including nonoxynol-9, C31G (Biosyn, Inc, Philadelphia, PA), Carraguard (Population Council, New York, NY), and cellulose sulfate. However, at the 2009 conference, Karim presented data on the 0.5% naphthalene sulfonate polymer microbicide gel from a trial, HPTN 035, that found a statistically nonsignificant trend toward lower HIV acquisition (30%) among women receiving the gel.[3] In subgroup analyses, however, HIV incidence was further reduced in the

subgroup of women who were highly adherent to gel use and not using condoms, the group most likely to benefit from a topical microbicide. This had suggested that the product might be efficacious but required a larger trial with more women to definitively address this question.

Thus, the field eagerly awaited the results of the MDP 301 trial, in which more than 9300 women were enrolled in Uganda, Tanzania, Zambia, and South Africa. Women were randomly assigned to receive 2% naphthalene sulfonate polymer microbicide gel, 0.5% gel, or placebo gel administered prior to sexual intercourse; follow-up was for 52 weeks (or up to 104 weeks in Uganda). The 3 trial groups were balanced in baseline demographic and risk characteristics, and retention was comparable between groups. Overall, 95% of the women had at least 1 follow-up visit, but only 84% of the total duration of follow-up was available in the modified intention-to-treat analysis, which excluded time that women were not using gel because of pregnancy. The 2% trial arm was stopped early for futility in February 2008, at which point the infection incidence was 4.7 per 100 women-years (wy) in the 2% gel group and 3.9 per 100 wy in the placebo group (hazard ratio [HR], 1.21; 95% CI, 0.88 – 1.68). At the end of the trial, there was also no statistically significant difference in HIV incidence between the 0.5% gel group (4.5/100 wy) and the placebo group (4.3/100 wy; HR, 1.05; 95% CI, 0.82–1.34). This trial definitively ruled out any statistically significant protective effect for either the higher- or lower-dose regimen of naphthalene sulfonate polymer microbicide gel, and it is widely seen as the end of an era of development of nonspecific microbicides. In their place, investigators have been developing and testing topical formulations of antiretroviral agents, discussed in greater detail below.

Preexposure Prophylaxis

Antiretroviral drugs hold great promise in the prevention of HIV infections. The use of antiretroviral treatment of HIV-infected persons to lower HIV transmission rates is summarized above. The remainder of this article focuses on oral and topical use of antiretroviral drugs to prevent HIV acquisition among HIV-seronegative persons.

Mayer summarized the suite of clinical trials now under way that are evaluating tenofovir-based regimens (Abstract 63). Several of these trials are expected to yield data later in 2010, and others should provide data over the next several years. The 3 clinical trials sponsored by the US Centers for Disease Control and Prevention (CDC) (a biomedical and behavioral safety trial of tenofovir in US MSM; an efficacy study of tenofovir/emtricitabine stopped early for operational futility in young heterosexuals in Botswana; and an efficacy study of tenofovir in IDU in Thailand) may all provide data later in 2010 or 2011. CAPRISA 004 (Centre for the AIDS Programme of Research in South Africa 004), an efficacy trial of 1% tenofovir gel used vaginally pre- and postcoitally among women in South Africa, may have results in summer 2010. The iPrEx (Chemophrophylaxis for HIV Prevention in Men) study, an efficacy trial of oral tenofovir/emtricitabine in MSM in North and South America, South Africa, and Thailand may also have efficacy results later this year.

Three other efficacy trials are expected to have results available by 2012 or 2013. The Partners PrEP (Preexposure Prophylaxis) trial is an efficacy study of oral tenofovir versus oral tenofovir/emtricitabine versus placebo in serodiscordant heterosexual couples in Africa. The Fem-PrEP (Study to Assess the Role of Truvada [tenofovir/emtricitabine] in Preventing HIV Acquisition in Women) trial is evaluating oral tenofovir/emtricitabine among women at high risk in Africa. Finally, the VOICE (Vaginal and Oral Interventions to Control the Epidemic) trial will evaluate oral tenofovir versus oral tenofovir/emtricitabine versus topical tenofovir versus placebo among women at high risk in Africa. In combination, these trials will enroll more than 20,000 participants and will address questions about the efficacy of daily oral tenofovir or tenofovir/emtricitabine and daily or coitally dependent, topical tenofovir-based regimens.

All of the regimens in the first generation of efficacy trials require regular dosing of oral or topical agents. To correctly interpret trial results, investigators will need an understanding of the patterns of pill and gel use by study participants. Liu and colleagues presented data on the correlation of various biomarkers of tenofovir use with pill count and self-reported adherence measures in the US CDC-sponsored PrEP trial (Abstract 86). The biomarkers measured included tenofovir levels measured in plasma, peripheral blood mononuclear cells (PBMCs) and hair. Given the long intracellular half-life of tenofovir diphosphate, plasma levels are thought to reflect tenofovir use in the past few days, whereas PBMC and hair levels reflect tenofovir use in the past month. Hair has the added advantage of being easy and inexpensive to collect, store, and transport to the laboratory.

In this study, all 3 measures demonstrated very high levels of sensitivity and specificity with treatment assignment. For example, 46 of 47 men randomly assigned to receive daily tenofovir had detectable levels of tenofovir in hair, but only 1 of 42 men in the placebo group had detectable levels of tenofovir in hair. This man also had tenofovir detected in his plasma and PBMCs, suggesting that he may have been exposed to the drug outside of the study. Correlation of the biomarkers with pill counts was modest, and correlation with self-reported adherence measures was poor. More work is being done to assess factors affecting the dynamic range of these biomarker measures and to evaluate their correlation with protection in efficacy trials.

Less frequent administration of PrEP would be less expensive and potentially safer than daily PrEP. Garcia-Lerma and colleagues[4] have been investigating coitally dependent systemic administration of tenofovir/emtricitabine in a low-dose, repeated-rectal-challenge model in rhesus macaques (Abstract 83). They reported that intermittent PrEP, when given up to 7 days before and 2 hours after each challenge, can provide partial or complete protection against sim-

ian-HIV (SHIV) strain 162p3 infection in the rhesus macaque model. However, the postexposure dose is an essential element to achieve protection, an important insight to be taken into account in future clinical trials.

They also presented data on drug levels of tenofovir and emtricitabine in plasma, PBMCs, and rectal secretions in macaques. In these studies, tenofovir diphosphate persists in PBMCs for prolonged periods, with a half-life of 115 hours (5 days), whereas emtricitabine triphosphate has a half-life in PBMCs of approximately 24 hours. Both tenofovir and emtricitabine levels peaked in rectal secretions at 24 hours. However, emtricitabine was detectable in rectal secretions within 2 hours after dosing, whereas tenofovir was undetectable at the 2-hour and 5-hour time points but was detected at 24 hours. These data suggest that the combination of tenofovir/emtricitabine may provide an advantage over single-drug use by providing coverage both early and late in rectal secretions and PBMCs. Moreover, these drugs are synergistic.

Additional data presented by Garcia-Lerma and colleagues raised a cautionary note in predicting efficacy based on pharmacokinetic and pharmacodynamic data. Their group evaluated the tenofovir prodrug GS7340 for protection from SHIV challenge in their rectal-challenge macaque model. This prodrug was believed to be more potent than tenofovir because of results indicating 100-fold-increased levels of tenofovir diphosphate in PBMCs and earlier and higher levels of drug penetration in rectal secretions in macaques. However, the prodrug completely failed to protect macaques against rectal challenge. Additional studies are needed to explore the reasons for the failure of this prodrug to provide protection. Further validation of all nonhuman primate challenge models awaits the results of clinical trials.

Another presentation from this group, by Dobard and colleagues, evaluated 1% tenofovir gel for protection against vaginal SHIV challenge in their rhesus macaque model (Abstract 949). The investigators had previously demonstrated that tenofovir gel provided complete protection when administered 30 minutes before each vaginal challenge. In this study, they administered 2 weekly challenges, one 30 minutes after and the other 3 days after a single weekly vaginal administration of 1% tenofovir gel. This regimen provided a 7-fold reduction in SHIV infection ($P = .01$ in proportional hazard model), suggesting that the long half-life of tenofovir may provide prolonged protection. Validation of this model also awaits clinical trial results.

Several investigators evaluated the potential of CC chemokine receptor 5 (CCR5) inhibitors for PrEP. Moore presented results of a study (Veazey et al, Abstract 84LB) in which maraviroc tablets were dissolved to create a topical gel that could be applied in a macaque vaginal challenge model. The investigators demonstrated the dynamic range of drug required to protect against SHIV 162p3 and suggested that the doses required could be substantially lower than required for oral administration. During the question-and-answer session, questions were raised about the decreased potency of maraviroc against cell-associated virus. These animal challenge models use cell-free virus challenges, but the relevance of these challenges to human transmission is unknown.

Brown and colleagues presented data from a clinical trial of oral maraviroc administration in HIV-seronegative men (Abstract 85). Unlike studies in women, in which maraviroc appeared to be concentrated at higher levels in genital secretions, in this study in men, semen concentrations were approximately half those in blood plasma. However, maraviroc was highly concentrated in rectal secretions, reaching an 8-fold increase in the area under the curve after a single dose and a 28-fold increase after repeated dosing. Brown speculated that fecal elimination of the drug may lead to high drug levels in rectal secretions, although the relevance of this to protection against rectal challenge is unknown. These data also suggest that studies of drug concentration in genital secretions should include both men and women, as results between sexes may be discordant.

Concerns have been raised about widespread usage of PrEP before data are available from clinical efficacy trials. Mansergh and colleagues reported on data from a study in 1011 MSM substance users in Chicago, Los Angeles, New York City, and San Francisco (Abstract 957). In this sample, 2% of HIV-seronegative men reported taking PrEP, and 3% of HIV-seropositive men reported giving their partners antiretroviral drugs for PrEP, confirming that current use appears low in this population.

The current generation of nonvaccine prevention trials focus largely on strategies to increase HIV testing, to increase uptake of antiretroviral drugs for treatment, and for the use of oral or topical antiretroviral drugs for prevention in HIV-seronegative persons. Additional work is needed to understand the social and behavioral drivers of HIV transmission and acquisition, to develop strategies to address HIV transmission in couples, and to prepare to make PrEP feasible to deliver, should it prove effective.

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A list of all cited abstracts appears on pages 93-99.

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Neurologic Complications of HIV Disease and Their Treatment

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Findings on the nervous system complications of HIV disease and their impact on people living with HIV continue to accumulate. New reports at the 17th Conference on Retroviruses and Opportunistic Infections this year confirmed that HIV-associated neurocognitive disorders (HAND) are common, even among effectively treated individuals. Risk of HAND correlated with nadir CD4+ cell counts and with cerebrospinal fluid (CSF) viral loads that were at least as high as plasma viral loads. Other new data regarding risk factors for HAND implicated vascular disease, apolipoprotein E and mannose binding lectin genotypes, reduced resting cerebral blood flow, and HIV mutants that cause macrophages to shed the HIV gp120 protein. Two analyses linked worse neurocognitive performance to use of efavirenz, raising concerns about neurotoxicity. Analyses comparing differences in estimated distribution of antiretroviral drugs into the central nervous system (CNS) to neurocognitive outcomes using the 2008 version of the CNS penetration-effectiveness (CPE) ranking system did not support a hypothesis of neurotoxicity but did have mixed results, some supporting a benefit and some supporting no effect. Of note, a revised version of the CPE ranking system was presented that was more strongly associated with CSF viral loads than the 2008 version. Reports also estimated that primary CSF virologic failure occurs in 3% to 10% of treated individuals, although the clinical consequences of this remain uncertain. New data on common coinfections in people with HIV identified that a specific strain of Treponema pallidum *may be more neurovirulent than other strains, that hepatitis C virus Core protein may be neurotoxic, and that hepatitis B virus may replicate in the nervous system. The extensive data presented will inform new research and clinical decisions in the coming year.*

Introduction

Research on the central and peripheral neurologic complications of HIV infection continues to expand, answering some important questions but raising new ones as well. New reports on the correlates of neurocognitive impairment should help clinicians identify at-risk patients. A newly revised central nervous system (CNS) penetration-effectiveness (CPE) ranking system was presented that is more strongly associated with cerebrospinal fluid (CSF) viral loads than the older approach. Also, the frequency of primary CSF virologic failure was estimated, neurovirulent HIV mutations were identified, and a new animal model for HIV-associated sensory neuropathy was described. Summaries of these and other reports are presented below in 5 sections: Central Nervous System Complications, Pathogenesis and Biomarkers of Nervous System Disease, Brain Imaging, HIV-Associated Peripheral Neuropathy, and Other Infections of the Nervous System.

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Central Nervous System Complications

Reports from North America and Europe

Work presented at prior conferences has shown that HIV-associated neurocognitive disorders (HAND) continue to be common, even among many people taking effective antiretroviral therapy with immune recovery (eg, Heaton et al[1]). Several explanations for these findings are possible, and one is that brain injury acquired during advanced immunosuppression might be only partially reversible with antiretroviral therapy. Because HAND is more common in people with advanced immune suppression, its incidence or severity might be reduced when antiretroviral therapy is initiated at higher CD4+ cell counts. If initiation of antiretroviral therapy at higher CD4+ cell counts prevents HAND, this would be an important added benefit because HAND is associated with unemployment, worse quality-of-life, reduced antiretroviral therapy adherence, and earlier death.

To examine whether earlier initiation of antiretroviral therapy might be associated with lower risk of HAND, Ellis and colleagues evaluated the relationship between the lowest reported or observed CD4+ cell count (ie, the nadir) and neurocognitive impairment in 1525 individuals enrolled in the CHARTER (CNS HIV Antiretroviral Therapy Effects Research) cohort, a prospective, multicenter study that incorporated comprehensive neurocognitive and medical assessments (Abstract 429). Neurocognitive impairment and HAND diagnoses were defined according to the Frascati criteria,[2] and comorbid conditions contributing to impairment were evaluated by a single, experienced neuropsychologist. Just over half of this mostly antiretroviral therapy–experienced cohort was neurocognitively impaired, in most cases at mild to moderate levels.

Table **1.** Revised Central Nervous System Penetration-Effectiveness Ranking

Antiretroviral Drug Class	4	3	2	1
Nucleoside analogue reverse transcriptase inhibitors	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Tenofovir Zalcitabine
Nonnucleoside analogue reverse transcriptase inhibitors	Nevirapine	Delavirdine Efavirenz	Etravirine	
Protease inhibitors	Indinavir/ritonavir	Darunavir/ritonavir Fosamprenavir/ritonavir Indinavir Lopinavir/ritonavir	Atazanavir Atazanavir/ritonavir Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir/ritonavir Tipranavir/ritonavir
Entry/fusion inhibitors		Maraviroc		Enfuvirtide
Integrase strand transfer inhibitors		Raltegravir		

Note: Larger numbers reflect estimates of better penetration or effectiveness in the central nervous system (eg, a ranking of 4 indicates the best penetration or effectiveness). Based on data from Abstract 172.

The principal findings were that participants who had a nadir CD4+ cell count below 50/mL had the greatest risk of neurocognitive impairment (222 of 387 patients; 57.4%) and, compared with this reference group, the odds of impairment diminished at successively higher nadir CD4+ cell count strata, with the lowest risk in those with nadir CD4+ cell counts above 350/mL (130 of 287 patients; 45.3%). In the subgroup of individuals who were taking antiretroviral therapy and had plasma HIV RNA levels below 50 copies/mL, this difference was even greater (60.5% vs 45.6%). When analyzed as a continuous predictor, a graded decrease in neurocognitive impairment risk was observed across the entire range of nadir CD4+ cell counts. The influence of nadir CD4+ cell count on neurocognitive impairment was similar in multivariable analyses adjusting for demographic and clinical covariates that might affect neurocognitive performance, including age, duration of HIV infection, and suppression of plasma viral loads from antiretroviral therapy.

Another possible explanation for persisting HAND among effectively treated individuals (ie, with suppressed plasma viral loads) is limited distribution of these drugs into the CNS. Several presentations compared estimated distribution of antiretroviral therapy into the CNS to CSF viral loads, neurocognitive performance, or neuroimaging findings. Letendre and colleagues presented cross-sectional CSF and plasma viral load data from 1221 individuals enrolled in the CHARTER cohort (Abstract 172). Eight hundred forty-two of these individuals were taking antiretroviral therapy, and 135 (16%) had a CSF HIV RNA level above 50 copies/mL (ie, detectable). Multivariable analysis identified that detectable CSF viral loads were associated with higher plasma viral loads, current CD4+ cell counts below 200/mL, estimates of lower antiretroviral therapy distribution into the CNS using a revised version of the CPE ranking system (CPE 2010; Table 1), worse adherence (taking fewer than 95% of doses in the 4 days preceding assessment), and nonwhite ethnicity. This revised version of the CPE ranking method incorporated data from recent pharmacokinetic and pharmacodynamic analyses and was more strongly associated with CSF viral loads than the older CPE 2008 method.[3]

A report from the 16th conference in 2009 described 10 neurologically symptomatic individuals, all of whom had viral loads higher in CSF than in plasma.[4] This report did not include a denominator, making it impossible to estimate the frequency of primary CSF virologic failure (ie, detectable viral loads in CSF but not in plasma while taking antiretroviral drugs) in a clinic population. In the cross-sectional CHARTER analysis, this frequency was determined by identifying the proportion of neurocognitively symptomatic and asymptomatic persons who were taking antiretroviral therapy and had plasma HIV RNA levels that were suppressed below 50 copies/mL: 14 of 463 CHARTER participants (3%) had CSF HIV RNA levels above 50 copies/mL (Abstract 172). In another cross-sectional analysis focused specifically on CSF virologic failure, Edén and colleagues identified that 7 of 67 (10.4%) neurocognitively asymptomatic individuals who were taking antiretroviral therapy and had plasma HIV RNA levels suppressed below 50 copies/mL also had CSF HIV RNA levels above 50 copies/mL (Abstract 432), confirming that primary CSF virologic failure may be relatively infrequent. Cross-sectional studies, however, are inherently limited in their ability to accurately estimate population event frequencies, particularly uncommon ones.

Longitudinal designs can typically better estimate event frequencies, al-

though most cohort studies sample participants relatively infrequently (eg, every 6 or 12 months). In a longitudinal analysis of 346 CHARTER participants who were taking antiretroviral therapy and whose CSF HIV RNA levels were suppressed below 50 copies/mL at their first visit, 67 (19%) persons experienced failure (defined as CSF HIV RNA level > 50 copies/mL) after a median of 9.3 months. Shorter times to loss of viral response (TLOVRs) in CSF were associated with baseline CD4+ cell counts below 200/mL, younger age, and worse neurocognitive performance (Abstract 430).

Two statistical interactions were also present in this analysis: older people taking antiretroviral drugs with estimates of better penetration had longer TLOVRs in CSF than did other participants, and black people who had impaired neurocognitive performance had shorter TLOVRs in CSF than did other participants. Of note, neither of these interactions was present in a parallel analysis of TLOVR in plasma among persons whose plasma viral loads were suppressed at their first visit. Because the effects were present in the CSF analysis but not in the plasma analysis, they may reflect conditions specific to control of HIV in the nervous system. An important limitation of this analysis is that it did not observe initiation of antiretroviral therapy in any of the participants (ie, all participants were already taking antiretroviral drugs by the time of their first visit).

Several other abstracts reported new findings on the frequency and correlates of HAND. Starace and colleagues reported data from 45 virally suppressed individuals to determine if "neuroactive" antiretroviral drug regimens (defined as those with a CPE 2008 rank ≥ 2) were associated with better neurocognitive performance (Abstract 433). They administered the Cotugno Mini Battery, a set of 6 neuropsychologic tests of verbal memory span, auditory verbal learning, verbal fluency, executive function, speeded information processing, and walking ability. Overall, 31 of 45 (69%) participants had HAND, with 26 having asymptomatic neurocognitive impairment and 5 having minor neurocognitive disorder (MND). Those taking neuroactive antiretroviral drugs were less likely to have HAND and had better performance on 3 of the 6 administered tests (verbal memory span, verbal fluency, speeded information processing). Of note, performance on the other 3 tests also was better in the neuroactive antiretroviral therapy group, although the differences did not reach statistical significance.

Garvey and colleagues reported results of a retrospective review of a much larger sample (nearly 20,000 persons) who initiated antiretroviral therapy between 1996 and 2007 and enrolled in the multicenter UK CHIC (United Kingdom Collaborative HIV Cohort) project (Abstract 427). In this analysis, the investigators determined the correlates of severe CNS disorders and mortality. A total of 224 individuals developed a severe CNS disorder during the observation period; these included disorders that commonly afflict people with AIDS, such as cryptococcosis, toxoplasma, JC virus infection, and HIV encephalopathy. For the purposes of this analysis, all severe CNS disorders were grouped together. In this longitudinal study, the initial and most recent CPE 2008 ranks for the antiretroviral regimens were evaluated, and the investigators grouped regimens into categories that differed substantially in size (ranking < 1, 1560 [7.9%]; ranking 1–1.5, 8444 [42.6%]; ranking 2–2.5, 9386 [47.3%]; ranking > 2.5, 438 [2.2%]).

The investigators identified that subjects in the 2 minority CPE 2008 groups (rankings < 1 or > 2.5) were more likely than others to develop a severe CNS disorder over approximately 5 years of observation, although these groups also had lower CD4+ cell counts than the majority groups. Multivariable analysis identified associations between the occurrence of severe CNS disorders and lower baseline or current CD4+ cell counts, higher plasma HIV RNA levels, shorter durations of antiretroviral therapy, and heterosexual risk behavior—but not CPE 2008 category. Among these correlates, the association with heterosexual activity (relative risk, 3.2 compared with men who have sex with men) is unexpected and deserves further epidemiologic investigation to determine why persons who engage in unprotected heterosexual activity may be at risk. An even more important finding may have resulted from the multivariable mortality analysis: very low or very high CPE 2008 ranks were associated with higher mortality. This analysis did not account for the number of antiretroviral drugs in each regimen, an important limitation because highly treatment-experienced individuals who take more than 3 antiretroviral drugs will have higher CPE 2008 ranks and may have a poor prognosis. Despite this, these findings add to existing data supporting that antiretroviral drug penetration may influence survival.[5,6]

Although these findings add to evidence supporting the potential benefits of better penetrating antiretroviral therapy, not all studies agree. For example, Muñoz-Moreno and colleagues did not find an association between estimates of antiretroviral therapy penetration into the CNS and neurocognitive performance (Abstract 416). These investigators used a classification and regression tree approach to analyze data from a single clinic population of 172 individuals. Among the 142 antiretroviral therapy–experienced individuals, neurocognitive impairment was associated with shorter duration of the current antiretroviral therapy regimen (< 32.2 months), longer duration since initiation of antiretroviral therapy (> 13.5 years), older age (> 32 years of age), and higher peak plasma HIV RNA level (highest ever > 4.8 $\log_{10}$ copies/mL) but not with estimate of worse antiretroviral therapy penetration into the CNS using the CPE 2008 method.

Ciccarelli and colleagues also did not find an association between estimates of worse antiretroviral therapy penetration and impaired neurocognitive performance (Abstract 417). This study assessed 136 consecutive clinic patients using a comprehensive neurocognitive test battery. Antiretroviral therapy pen-

etration into the CNS was again estimated using the CPE 2008 method (< 1.5 vs ≥ 1.5). The 70 individuals who had impaired neurocognitive performance in this study were not more likely to take "worse-penetrating" antiretroviral therapy regimens, but they were more likely to take efavirenz (odds ratio [OR], 5.37; $P = .004$). Although this finding raises concerns about long-term efavirenz neurotoxicity, no abstracts reported associations linking better antiretroviral therapy penetration to worse neurocognitive performance, which would have been evidence of neurotoxicity across a broader spectrum of antiretroviral drugs.

The report by Winston and colleagues highlighted the challenge of interpreting associations between estimates of antiretroviral therapy penetration, possible neurotoxicity, and imaging or neurocognitive outcomes (Abstract 434). This multicenter project, the ALTAIR (Alternative Antiretroviral Strategies: a Comparison of Three Initial Regimens) study, randomly assigned 30 participants to 1 of 3 open-label regimens (tenofovir/emtricitabine/efavirenz [CPE 2008 = 1.0]; tenofovir/emtricitabine plus atazanavir/ritonavir [CPE 2008 = 1.0]; or tenofovir/emtricitabine plus zidovudine plus abacavir [CPE 2008 = 2.5]. All subjects were neurocognitively asymptomatic at initiation of antiretroviral therapy and were longitudinally assessed using computerized neurocognitive testing and proton magnetic resonance spectroscopy (MRS).

After 48 weeks, persons receiving tenofovir/emtricitabine plus zidovudine plus abacavir had better performance than those taking tenofovir/emtricitabine/efavirenz on tests of 2 cognitive abilities, speed-of-information processing and executive functioning. In contrast to the neurocognitive differences, people taking tenofovir/emtricitabine/efavirenz had changes considered beneficial on MRS, with increases in *N*-acetyl aspartate (NAA) to creatine (Cr) ratios (a neuronal indicator) and declines in myoinositol (MI) to Cr ratios (an inflammation indicator). Although the pretreatment asymptomatic status of the participants of this study is an important limitation, this combination of findings supports that efavirenz-containing regimens may better lead to normalization of the HIV-infected nervous system (via improvements in both neuronal and neuroinflammatory indicators) but, despite this, may still lead to worse neurocognitive performance.

To better understand the possible neurotoxicity of antiretroviral treatment, Liner and colleagues exposed fetal rat cortical neuronal cultures to increasing concentrations (from 0.01 to 300 µg/mL) of 15 individual antiretroviral drugs and 6 antiretroviral drug combinations over 1 week (Abstract 435). Neuronal pathology and cell death were assessed by microtubule-associated protein 2 staining, calcium signaling in response to glutamate, and mitochondrial membrane potential using fluorescent microscopy. Based on the findings, the investigators constructed concentration-effect curves and calculated median toxic concentrations for each drug. The investigators identified that the median toxic concentrations of several antiretroviral drugs fell within the range of concentrations reported in plasma or CSF with standard clinical dosing, including for abacavir, amprenavir, atazanavir, didanosine, efavirenz, lamivudine, nevirapine, tenofovir, and zidovudine.

These findings implicate nearly all currently used antiretroviral drugs as potentially neurotoxic to fetal rat cortical neurons, making the findings difficult to apply to clinical decision making, but they also lay the groundwork for additional analyses and reinforce the concept of a therapeutic window in the nervous system. The therapeutic window concept would dictate that antiretroviral drug concentrations be sufficiently high to reliably inhibit HIV replication but not so high that they put patients at risk of neuronal injury. This concept is also supported by the analysis by Garvey and colleagues (Abstract 427) that identified that severe CNS disorders were more common in the approximately 10% of persons who were taking antiretroviral regimens that had either very low or very high CPE 2008 ranks, although this association was only statistically significant in univariate analyses. Defining the upper and lower limits of the nervous system therapeutic window will be challenging and may require therapeutic drug monitoring, at least in individuals who have neurocognitive impairment that does not resolve with antiretroviral therapy.

A non–mutually exclusive alternative to optimizing antiretroviral therapy penetration into the CNS for treatment of HAND, a strategy being investigated in controlled clinical trials, is intensification of antiretroviral therapy regimens with additional antiretroviral drugs. Yilmaz and colleagues explored the effect of antiretroviral therapy intensification on residual, low-level CSF viral loads and CSF immune activation biomarkers (eg, neopterin, β_2-microglobulin) (Abstract 431). They assessed 10 individuals who were taking at least 3 antiretroviral drugs and had HIV RNA levels suppressed below 50 copies/mL in CSF and in plasma but detectable levels in CSF using an assay with a detection limit of 2 copies/mL. All participants added to their existing regimen 1 of 3 antiretroviral drugs, either 1 of 2 "good" penetrators (maraviroc or lopinavir/ritonavir) or 1 "poor" penetrator (enfuvirtide). The findings during 8 weeks of antiretroviral therapy intensification and an additional 16 weeks of observation failed to demonstrate consistent decreases (or increases) in low-level viral loads or levels of immune activation biomarkers regardless of whether a "good" or "poor" penetrating antiretroviral drug was added to the existing regimen. Because no neurocognitive assessments were presented, no conclusions could be reached about whether adding antiretroviral drugs to an existing regimen leads to clinical change, either improvement or worsening.

Reports from Resource-Limited Settings

Depression is common in patients with HIV infection in high-resource settings in the United States and Europe and is associated with delayed initiation of, poorer adherence to, and lower rates

of HIV suppression with antiretroviral therapy compared with patients without a mental illness. Patients who have their depression treated, however, are equally likely to initiate antiretroviral therapy as patients without a mental illness and have improved antiretroviral therapy adherence, providing a strong rationale for identifying and treating depression. To date, research on the correlates and consequences of depression in HIV-infected patients in resource-limited settings (RLS) has been sparse. Four studies addressed aspects of these issues in sub-Saharan Africa.

The first study identified that depression was common among 1268 adults living in Botswana (Abstract 1010). Nearly one-third of men (31.4%) and one-fourth of women (25.3%) met criteria for depression on the Hopkins Symptoms Checklist for Depression. Risk of depression in men was associated with being unmarried and not living with a partner, rural residence, worse health status, more frequent visits to health care practitioners, intergenerational sex (sex with women > 10 years younger), and fear of HIV or AIDS stigma. For women, the associated risk factors were lower education, higher income, and lack of control of sexual decision making. Although this project was designed to estimate depression prevalence in the general population, it implies that depression could affect clinical care of the substantial subgroup of people living with HIV infection in Botswana.

This inference from Botswana was applied in an analysis of 412 persons observed for 2 years in the Ugandan AIDS Rural Treatment Outcomes (UARTO) cohort (Abstract 1011). Adherence, as judged by self-report of number of missed doses per month and number of interrupted days per month, was remarkably high (92.6%), with 87% achieving plasma virologic suppression (< 50 copies/mL). Depression as measured by the Hopkins Symptoms Checklist for Depression contributed to poor adherence and failure of HIV suppression. Other contributors to poor adherence were male sex, younger age, being unmarried, lower socioeconomic status, distance to clinic, tobacco and alcohol use, and shorter duration of treatment. In a separate report from the same cohort, severe food insecurity was also associated with symptoms of depression in women but not men (Abstract 1012).

The effects of depression and excessive alcohol use on adherence were examined in HIV-infected Nigerian patients either receiving antiretroviral therapy (n = 222) or untreated (n = 177) (Abstract 1013). The Alcohol Use Disorders Identification Test assessed alcohol use, and the Center for Epidemiological Studies Depression Scale measured depression. Untreated patients were more likely to use alcohol excessively and be depressed. In multivariable analyses, depression was associated with low socioeconomic status and failure to disclose HIV serostatus to anyone. Depression, but not excessive alcohol use, was associated with worse adherence, as measured by medication refill rates.

Another topic that gained greater exposure was the long-term impact of HIV infection on children. Compared with norms for HIV-seronegative children (0 – 6 years old), HIV-infected children in Uganda were more likely to have derangements in visual reception and receptive and expressive language (Abstract 860). Despite the introduction of antiretroviral therapy, however, no statistically significant improvement was seen in neurocognitive scores, raising concerns about the irreversibility of these deficits. Supporting that these early deficits are reversible, however, was a multicenter study of older children (7 – 16 years old) in the United States and Puerto Rico that did not observe overall differences in neurocognitive performance scores compared with those of HIV-seronegative control subjects (Abstract 861). In this analysis, children with a history of advanced immune suppression were more likely to have neurocognitive deficits. Thus, similar to supportive findings in adults, earlier initiation of antiretroviral therapy in children may better maintain CD4+ cell counts and reduce the risk of neurocognitive impairment. Many of these studies evaluating CNS disorders are summarized in Table 2.

Pathogenesis and Biomarkers of Nervous System Disease

HIV Characteristics

A major question in HIV neurology research is whether neurovirulence differs between viral subtypes of HIV-1. Subtype-D HIV has been implicated as being more neurovirulent than other subtypes in adults, based in part on clinical data showing a difference in the frequency of HAND reported in Ugandan adults: 8 of 9 persons (89%) with subtype-D HIV had HAND compared with 7 of 33 (24%) persons with subtype-A HIV.[7] Because subtype-D HIV is also associated with more rapid immune disease progression, and advanced disease in turn is associated with HAND, distinguishing the impact of subtype-D HIV infection on the immune and nervous systems is an important focus for future research.

The impact of subtype-D HIV on the developing brain has not been previously reported but was expected to be similar to the relationship observed in adults. In a cross-sectional study of 102 Ugandan treatment-naive children aged 6 years to 12 years (Abstract 175), HIV subtype was determined by a real-time polymerase chain reaction assay with subtype-specific probes in 5 regions (*gag*, *pol*, *vpu*, *env*, or *gp41*). Based on consistent subtypes from at least 2 regions, 37 children had subtype-A HIV, 24 had subtype D, and 9 had recombinant subtypes (32 were indeterminate), a distribution similar to adults in Kampala.

Those with subtype-A HIV infections had higher plasma viral loads but no other demographic or disease-related differences. In contrast to the data for adults, children with subtype-A HIV had worse—not better—scores on neurocognitive tests of sequential processing ($P = .04$), simultaneous processing ($P = .04$), and learning ($P = .03$) than did children who had subtype D, but they did not have worse planning and reasoning, attention, or motor task scores. None of these differences persisted, however, after adjusting for the difference in plasma viral loads in the primary analysis. In a subanalysis

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

Abstract No. Authors	Location	Sample Size	Findings	Correlates of Findings
Abstract 429 Ellis et al	USA	1525	52% global neurocognitive impairment	Lower nadir CD4+ cell count
Abstract 172 Letendre et al	USA	1221	51% global neurocognitive impairment	CSF viral load ≥ plasma viral load
Abstract 432 Edén et al	Sweden	67	Neurocognitively asymptomatic cohort	Primary CSF failure occurred in 10.4%
Abstract 430 Letendre et al	USA	346	53% global neurocognitive impairment	Worse neurocognitive performance associated with shorter times to loss of viral response in CSF and plasma
Abstract 433 Starace et al	Italy	45	69% HAND	Lower CPE 2008 rank
Abstract 427 Garvey et al	UK	19,828	224 severe CNS disorders; 1256 deaths	Lower CPE 2008 rank associated with death, not severe CNS disorders
Abstract 416 Muñoz-Moreno et al	Spain	172	60% HAND	Shorter duration of current antiretroviral therapy; longer duration of total antiretroviral therapy; older age; highest ever plasma viral load; not lower CPE 2008 rank
Abstract 417 Ciccarelli et al	Italy	136	52% global neurocognitive impairment	Efavirenz use; not lower CPE 2008 rank; lower nadir CD4+ cell count
Abstract 434 Winston et al	England, Canada, China, Thailand	30	Neurocognitively asymptomatic before randomization	Efavirenz associated with less neurocognitive improvement but higher NAA:Cr and lower MI:Cr ratios on MRS
Abstract 860 Brahmbatt et al	Uganda	187	HIV-seropositive children performed worse	*0–6 years:* visual reception; receptive language; expressive language *7–14 years:* sequential processing; expressive language
Abstract 861 Smith et al	North America	461	HIV-seropositive children performed worse	CDC C class HIV diagnosis
Abstract 1011 Bangsberg et al **Abstract 1012** Tsai et al	Uganda	456 (combined)	Depression: more common in women	Worse adherence; treatment failure; food insecurity
Abstract 1013 Farley et al	Nigeria	399	Depression: 13% (CES-D ≥ 16)	Lack of antiretroviral therapy; lower socio-economic status; failure to disclose HIV serostatus

CDC indicates Centers for Disease Control and Prevention; CES-D, Center for Epidemiological Studies Depression Scale; CPE 2008, central nervous system penetration-effectiveness ranking system[3]; CSF, cerebrospinal fluid; MI:Cr, myoinositol to creatine ratio; MRS, magnetic resonance spectroscopy; NAA:Cr, *N*-acetyl aspartate to creatine ratio.

of children whose subtype determination included the *env* region (n = 53), however, the differences between sequential and simultaneous processing did remain statistically significant after adjusting for plasma viral loads as well as other demographic and social characteristics. Thus, in the small number of children examined with a limited number of neurocognitive tests, the expected order of neurovirulence in HIV clades A and D was reversed compared with adults. Although this finding may be related to differences in HIV replication between groups, the subanalysis indicates that it is not.

Neurotropic or neurovirulent strains of subtype-B HIV have been identified in a number of studies, although no consensus has emerged about the genetics of these strains and the mechanism by which HIV adapts to and injures the brain. Brain-derived HIV strains are more likely to be macrophage-tropic, to use CC chemokine receptor 5 (CCR5) for entry into macrophages, to cause fusion of cells to form syncytia, and to promote neuronal apoptosis. A new phenotypic characteristic of neurotropic strains that may contribute to brain damage, shedding of soluble gp120, and its genetic correlates were investigated in brain tissue from people dying with HIV-associated dementia (HAD), the most severe form of HAND (Abstract 176). Two mutations in the beta-3 strand of the bridging sheet between the V1 and V2 regions of HIV *gp120* (D197 and T200) were found to be associated with neurotropism (T200) and HAD (both D197 and T200). In vitro studies of brain-derived HIV strains into which these envelope mutations were introduced showed that these mutations contributed to increased infection of macrophages and greater shedding of soluble gp120 from a transfected human embryonic kidney cell line (293T).

Because soluble gp120 can cause neuronal apoptosis, this characteristic may contribute to the neurovirulence of these variants. Together, the combination of reduced CD4 dependence and increased shedding of gp120 may identify particularly neurotropic and neurovirulent viruses that could greatly increase risk of HAND. The frequency of these mutations and their characteristics in living HIV-infected individuals, however, remain unknown.

Possible clinical evidence of neuroadaptation was presented from a study comparing CSF viral loads to neurocognitive performance in 379 untreated individuals (Abstract 172). Higher CSF viral loads were associated with higher plasma viral loads, lower current and nadir CD4+ cell counts, and older age. Higher CSF viral loads were not associated with worse neurocognitive performance; however, the 14% of individuals who had CSF viral loads at least as high as their plasma viral loads (a putative indicator of neuroadapted HIV) had substantially worse neurocognitive performance (Cohen's d = 0.65; $P = .001$), even after adjusting for age, nadir CD4+ cell count, and other measures reflecting disease severity and comorbid conditions. No genotype data were presented, however, to support the hypothesis that individuals who have very high relative CSF viral loads are more likely to have compartmentalized HIV.

Host Characteristics

The role of vascular disease, either coronary or cerebral, in the development of HAND is unclear. Vascular disease could provide a mechanism that explains the impact of accelerated aging and the metabolic syndrome on the persisting high prevalence of HAND in antiretroviral therapy–treated individuals. In the neurologic substudy of the SMART (Strategies for Management of Antiretroviral Therapy) study, 292 HIV-infected participants with CD4+ cell counts greater than 350/mL underwent 5 neurocognitive tests before and 6 months after starting antiretroviral therapy (Abstract 415). Although only 3% of participants had evidence of coronary vascular disease, 3 vascular disease–related risk factors (history of coronary vascular disease, use of antihypertensive drugs, and elevated total cholesterol levels) increased the risk of impairment at baseline. The ORs for neurocognitive impairment were increased by coronary vascular disease history (OR, 6.1; $P = .02$) and total cholesterol (OR, 1.1 per 10 m/mL, $P = .05$) but not by use of antihypertensive drugs (OR, 1.6; $P = .40$). In this study, none of the HIV disease– or antiretroviral therapy–related risk factors predicted impairment, including AIDS, current or nadir CD4+ cell count, plasma viral load, or CPE 2008 rank. These participants differed from those previously reported as having several vascular disease–related, but no HIV-related, risk factors for neurocognitive impairment. Although the relatively early disease stage of these participants may account for this inconsistency, these findings indicate that the impairment of at least some patients is either mediated by or has risk factors in common with vascular disease.

Two host proteins, apolipoprotein E and mannose binding lectin, may provide links between risks of vascular disease and HAND. An analysis based on a cohort study of 203 HIV-infected individuals in Anhui province, China, identified that the 21% of individuals who had at least 1 *APOE* epsilon4 allele had 3-fold increased odds of having neurocognitive impairment at their first assessment (Abstract 414). This association held in multivariable analyses that adjusted for disease and treatment characteristics. Polymorphisms in the *MBL2* gene were not associated with neurocognitive impairment at the first testing but did predict neurocognitive decline over 12 months. Specifically, the neurocognitive performance of the 12% of participants who had the *MBL2* O/O genotype was more likely to decline over 12 months than for the 49% of participants who had the A/A genotype (OR = 3.6; $P = .004$). Of note, neurocognitive performance was not associated with polymorphisms or copy number variants in several other genes previously implicated in risk of AIDS or HAND, including *CCR2*, *CCR5*, *MCP-1*, and *CCL3L1*.

Cross and colleagues evaluated the unfolded protein response (UPR) in HIV-infected macrophages (Abstract 407). The UPR is a cellular adaptation to stressors such as heat shock and glucose deprivation that prevents congestion of the endoplasmic reticulum with

nonfunctional, misfolded proteins. Infected macrophages constitute a reservoir of infection in the CNS and other tissues in antiretroviral therapy–treated individuals. Also, macrophages generate soluble, excitatory neurotoxins that may contribute to neuronal injury and neurocognitive impairment. The investigators showed that HIV, by modulating the UPR pathway, helps keeps macrophages alive while they efficiently replicate virus. They also showed that it was possible to manipulate UPR function using various drugs, thereby inhibiting HIV replication. These findings raise the possibility of reducing the macrophage reservoir and blocking macrophage neurotoxicity by pharmacologic interventions directed at UPR pathways.

Brain Imaging

The role of neuroimaging in understanding the pathogenesis and clinical management of HAND continues to expand. Four techniques that were prominently displayed included morphometry, MRS, diffusion tensor imaging (DTI), and arterial spin labeling. Brain morphometric measures were assessed as part of the Neuradapt study (Abstract 400). Within a cohort of 169 HIV-infected subjects, people with HAND had larger subcortical (eg, putamen, thalamus, and globus pallidus) volumes than did either HIV-infected, unimpaired individuals or HIV-seronegative control subjects. These larger structural volumes were associated with increases in the MRS measure of the choline (Cho) to Cr ratio, a marker of inflammation, suggesting that HAND may continue because of persistent immune activation, which may in turn be caused by persistent low-level HIV replication.

The observed morphometric increases are similar to those from a prior study[8] but differ from others[9,10] in which decreases in volume were seen with HIV infection. In a cross-sectional multicenter study, investigators observed statistically significantly lower values for all MRS measures including ratios for NAA to Cho, MI to Cr, and Cho to Cr in asymptomatic HIV-infected individuals about to start antiretroviral therapy (Abstract 403). Observed reductions in inflammatory ratios (MI to Cr and Cho to Cr) are contrary to a published report[11] and could result from the earlier stage of the disease of the participants in the conference report.

The conference also highlighted an increasingly popular neuroimaging method, DTI. This technique measures the restricted diffusion of water within the brain in order to visualize neural fiber tracts. Two studies investigated the effects of HIV infection and other comorbid conditions on DTI measures. Structural changes were observed within the caudate (eg, a decrease in fractional anisotropy and an increase in mean diffusivity) in HIV-infected individuals with metabolic syndrome compared with those without metabolic syndrome (Abstract 401), identifying a macromechanism by which metabolic syndrome may lead to HAND (ie, disruption of neural fiber tracts).

Another analysis compared DTI findings of people with HIV monoinfection with those in people with HIV and hepatitis C virus (HCV) coinfection in a cohort, most of whom were taking antiretroviral therapy (Abstract 402). Coinfected individuals performed worse on brief neurocognitive testing but did not have worse fractional anisotropy or mean diffusivity measures with DTI, suggesting that HCV infection may injure the brain via a mechanism not evident with detailed imaging of neural fiber tracts. These reports suggest that DTI may help investigators distinguish the effects of comorbid conditions from the effects of HIV infection on brain pathology. However, larger, controlled studies are needed to fully evaluate the role of DTI and other modalities.

New data on the emerging method of arterial spin labeling were also shown. In a cross-sectional analysis, a statistically significant decrease in resting cerebral blood flow was seen in untreated HIV-infected individuals compared with antiretroviral therapy–treated, HIV-infected individuals and with HIV-seronegative control subjects (Abstract 171). Although treated individuals had better cerebral blood flow than untreated individuals, antiretroviral therapy did not seem to completely normalize cerebral blood flow, identifying another mechanism that might account for persistent HAND in treated individuals (ie, persistently abnormal cerebral blood flow). In a smaller longitudinal component, untreated HIV-infected individuals who initiated antiretroviral therapy had an improvement in resting cerebral blood flow. These results support a role for arterial spin labeling measurements of cerebral blood flow to evaluate the effectiveness of antiretroviral therapy in the nervous system. Once again, however, larger, controlled studies are needed because this technique is still in its infancy.

HIV-Associated Peripheral Neuropathy

Painful HIV sensory neuropathy (HIV-SN) continues to be a common problem despite successful virologic suppression with antiretroviral therapy. Taller individuals are more susceptible than shorter ones,[12] a phenomenon believed to result from the dependency of longer distal nerve segments on metabolic support from sensory nerve cell bodies in the dorsal root ganglion near the spinal cord. Mitochondria are distributed along the length of axons and are particularly important for energy production in these very long cell components. Mitochondria also play important roles in the management of oxidative stress that can occur with HIV infection and other conditions.

Axonal mitochondria are assembled in the sensory neuron cell body and transported down the axon in a relatively slow process that results in distal mitochondria being considerably "older" than those in the cell body. Lehman and colleagues evaluated a common 5-kilobase deletion mutation of mitochondrial DNA as a marker of mitochondrial "aging" along the length of the axon (Abstract 412). They found that sural nerves of HIV-infected individuals who died with neuropathy (provided by the National NeuroAIDS Tissue Consortium) had

higher levels of mitochondrial deletion mutations than did sural nerves of HIV-seronegative control subjects or HIV-infected individuals who died without neuropathy. Deletion mutations were more common in distal nerve segments than in the dorsal root ganglia of the same patients. The investigators also found evidence of mitochondrial dysfunction and abnormal oxidative stress in the sensory nerves of SIV-infected macaques treated with antiretroviral therapy.

Among the major risk factors for painful HIV-SN are low CD4+ cell count, older age, and exposure to certain nucleoside analogue reverse transcriptase inhibitors like stavudine and didanosine. Injury to small unmyelinated nerve fibers leads to pain, and previous studies have demonstrated that reductions in epidermal nerve fiber density (ENFD) can serve as measures to assess this damage. However, ENFD has not been systematically evaluated in neuropathy-free HIV-infected subjects not yet exposed to antiretroviral therapy.

Shikuma and colleagues evaluated baseline cross-sectional data from 87 antiretroviral therapy–naive Thai subjects in the SEARCH 003 (Southeast Asia Research Collaboration With Hawaii 003) clinical trial (Abstract 173). All subjects were free of HIV-SN as demonstrated by physical examination. Superficial skin biopsies from the proximal thigh and distal leg were assessed for unmyelinated nerve fibers according to an established method (protein gene product [PGP] 9.5 immunostaining). Mitochondrial functional integrity was assessed in peripheral blood mononuclear cells (PBMCs) from these same individuals by immunoassay for oxidative phosphorylation markers.

In these Thai subjects (average age, 36 years; mean CD4+ cell count, 153/μL; mean plasma HIV RNA level, 4.9 $\log_{10}$ copies/mL) the average ENFD values (fibers/mm of epidermis) were unexpectedly higher than published age-matched population normative values from the United States, both for both proximal thigh and distal leg. Nevertheless, in the Thai subjects, lower distal ENFD was associated with being older and taller and with having a lower CD4+ cell count and higher viral load. PBMC oxidative phosphorylation protein or activity level did not correlate with ENFD value in the subgroup of 38 individuals in whom these assessments were performed.

These findings suggest that, in addition to height and age, race or ethnicity may also substantially affect the density of small, unmyelinated pain nerve fibers. They also imply that nerve damage exists even in antiretroviral therapy–naive subjects with no signs or symptoms of neuropathy and that this damage is related to advanced HIV immunosuppression. Because the mitochondrial functional assays were performed in PBMCs rather than peripheral nerve tissue, they do not clearly exclude a role of mitochondrial dysfunction in HIV-SN.

An important limitation in research on HIV-SN is that no large–animal model is widely available to investigate this condition. Mankowski and colleagues attempted to address this important shortcoming by looking to SIV infection in macaques as a model for HIV-SN (Abstract 174). They collected samples of skin from distal leg as well as sural nerves and lumbar dorsal root ganglia from animals at asymptomatic and terminal stages of SIV infection. ENFD was measured by staining for the nerve marker PGP 9.5. Inflammatory responses in dorsal root ganglia were evaluated by immunostaining for macrophage activation.

Similar to HIV-infected humans, SIV-infected macaques showed loss of epidermal nerve fibers and infiltration of macrophages into the dorsal root ganglion. Dorsal root ganglia also showed neuronal loss and SIV replication in macrophages. Pain-sensing C-fiber conduction velocities in sural nerves were reduced, and these changes correlated strongly with the extent of dorsal root ganglia macrophage infiltration. These similarities between sensory neuropathies induced by SIV and those by HIV suggest that macaques may provide a valid large-animal model for HIV-SN, which in turn should lead to new research into pathogenesis and new treatments to prevent or ameliorate HIV-SN.

Other Infections of the Nervous System

Syphilis

HIV infection is associated with an increased risk of syphilis and appears to increase the risk of symptomatic CNS disease, but identification of characteristics of *Treponema pallidum* that could influence neurovirulence has remained elusive. Molecular methods were used to type *T pallidum* from 79 persons with syphilis in the Seattle area from 1999 to 2008 to describe the epidemiology and clinical phenotypes of *T pallidum* strains (Abstract 177). After amplification of *T pallidum* DNA from organisms isolated from either blood or CSF, strain type was determined using 3 methods: number of repeats in the acidic repeat protein gene, restriction fragment length polymorphism analysis of *T pallidum* subfamily II repeat protein genes, and sequence analysis of an 84-base-pair region of the *tp0548* gene. Of 79 individuals studied, 76 were men, 66 were HIV-infected, 73 had early-stage (primary, secondary, or early latent) syphilis, and 9 had late-stage syphilis or syphilis of unknown duration. By serologic criteria (positive CSF VDRL test result), 18 (23%) had neurosyphilis.

Six *T pallidum* strains were identified among the 79 patients (types 4, 9, 10, 12, 13, and 20). One strain was particularly associated with neurosyphilis: strain 9 had a 36% rate of neurosyphilis compared with 8% in other strains combined. Both a previously established marker of neurosyphilis (rapid plasma reagin titer ≥ 1:32; OR = 2.2) and strain 9 (OR = 8.6) contributed to a model for discriminating neurosyphilis, suggesting that strain typing could contribute to diagnosis of this condition. Extension of this study to other geographic regions and further study of strain 9 for factors associated with neuroinvasion promise to expand the understanding of neurosyphilis.

Hepatitis B Virus

HIV and HCV have been shown to adapt to the nervous system, but no such data exist for hepatitis B virus (HBV). Duiculescu and colleagues investigated the presence and compartmentalization of HBV in the CSF of individuals with chronic HIV-HBV coinfection (Abstract 428). They did so by measuring HBV DNA in CSF from 18 patients with detectable plasma HBV DNA and, in a subgroup of 5, by characterizing anti-HBV drug resistance–associated mutations using a reverse hybridization line probe assay. Eleven of the 18 individuals (61%) had detectable HBV DNA in CSF at levels approximately 2 $\log_{10}$ IU/mL lower than in plasma (mean 4.1 vs 6.0 $\log_{10}$ IU/mL).

Interestingly, HBV DNA levels correlated with HIV RNA levels in both fluids, suggesting a role for active HBV replication in regulation of HIV replication (or vice versa). Of 7 patients with undetectable plasma HIV RNA while taking lamivudine-containing antiretroviral therapy, none had detectable HBV DNA in CSF. Analysis of genetic variation between plasma and CSF HBV identified concordant profiles in 2 but discordance in the other 3. Of the 3 with discordance, 2 had HBV drug resistance–associated mutations present in CSF that were not present in plasma, suggesting that the nervous system might serve as either a source of or a refuge for HBV drug-resistant mutants. These data are sparse, however, and further investigations are needed to confirm these findings and to determine their clinical implications.

Hepatitis C Virus

Many published reports have identified that HCV can infect glial cells, can compartmentalize in the nervous system, and can worsen neurocognitive performance and neuroimaging findings. Few studies, however, have investigated whether HCV-encoded proteins are neurotoxic, similar to the effects of HIV-encoded Env and Tat. Vivithanaporn and colleagues hypothesized that HCV-encoded Core protein would be neurotoxic and investigated its effects on human fetal neurons with or without Core-treated human glia (Abstract 410). Building on their findings on the neurotoxicity of HIV-encoded Vpr,[13,14] they also concurrently exposed cultures to Vpr.

They found that Core protein reduced expression of 2 markers of neuronal viability, beta-tubulin and lipidated LC3-II, and that it induced expression of proinflammatory cytokines or chemokines in microglia and astrocytes. The Core protein's neurotoxicity was potentiated by the presence of Vpr protein. The investigators also studied the in vivo impact of Core protein in Vpr-transgenic mice by administering intrastriatal stereotactic implants of HCV Core. Core protein–treated mice showed evidence of pathologic behavior (worse ipsiversive rotary behavior after implantation) and, at necropsy, had evidence of fewer neurons and more microglia, further supporting that HCV infection of the brain can induce neuroinflammation and neuronal injury and that these effects may be additive to those of HIV infection.

Summary

As more data accumulate on the presence and treatment of the neurocognitive disorders associated with HIV disease, several trends are increasingly clear. First, advanced HIV disease confers an increased risk of neurocognitive impairment that may be either partially irreversible or only partially treatable with the antiretroviral therapy regimens commonly in use. Second, better-penetrating antiretroviral therapy better reduces HIV in the nervous system, but HIV suppression below the detection range of commercial assays does not guarantee full cognitive recovery. Third, certain antiretroviral drugs may have long-term neurotoxicity, but nearly all existing data support that better-penetrating antiretroviral therapy per se is not neurotoxic. Fourth, primary CSF virologic failure does occur but seems to be an infrequent event that can either be symptomatic or asymptomatic.

Together, these findings argue for new research into (1) strategies to prevent the neurocognitive complications of HIV infection, including new diagnostic methods to identify asymptomatic patients who are at risk, (2) new diagnostic methods to distinguish reversible from irreversible disease, (3) clinical strategies to distinguish neurocognitive symptoms attributable to HIV infection and persistent immune activation from antiretroviral therapy neurotoxicity or comorbid conditions, and (4) more effective therapeutic strategies once disease occurs.

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A list of all cited abstracts appears on pages 93-99.

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Complications of HIV Disease and Antiretroviral Therapy

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

There is growing interest in the pathogenesis, treatment, and prevention of long-term complications of HIV disease and its therapies. Specifically, studies focused on cardiovascular, renal, bone, and fat abnormalities were prominent at the 17th Conference on Retroviruses and Opportunistic Infections. Although enthusiasm about the effectiveness of current antiretroviral therapy remains strong, collectively, the ongoing work in the area of HIV disease and treatment complications appears to reflect concerns that these clinical problems will continue to remain important and possibly increase over time in the current therapeutic era. This year's conference also highlighted important data on prevention and optimal treatment of common coinfections that occur in HIV-infected individuals, including tuberculosis, influenza, and viral hepatitis.

Cardiovascular Disease

Risk Factors for Cardiovascular Events

Several current studies are focused on quantifying the contribution of host- and disease-related factors that contribute to cardiovascular risk in HIV infection. Elevated triglyceride levels are common in HIV-infected patients, caused both by untreated HIV infection and by ritonavir exposure, yet the independent role of triglycerides has not been evaluated in large studies. Analyses presented from the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study identified triglyceride levels as an independent risk factor for myocardial infarction (MI), with data from 33,308 patients and 580 MI events (Abstract 127). However, after adjustment for other known cardiovascular disease (CVD) risk factors and specifically high-density lipoprotein (HDL) and total cholesterol levels, the magnitude of the effect was reduced but remained statistically significant (relative risk [RR], 1.11; 95% confidence interval [CI], 1.01–1.23).

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Smoking remains a common and potentially modifiable risk factor for CVD. In another D:A:D study analysis, Petoumenos and colleagues demonstrated that the risk of CVD (with a composite endpoint including MI, invasive coronary artery procedure, carotid artery endarterectomy, stroke, or death from other coronary heart disease) was reduced in those who stopped smoking (Abstract 124). Compared with risk in current smokers, the incidence rate ratio of CVD statistically significantly decreased after 3 years since the cessation of smoking. Although these results are not surprising, they provide concrete evidence that HIV care practitioners can use when discussing the importance of smoking cessation in patients with HIV infection, and they highlight the need to identify effective strategies for smoking cessation for this population.

Visceral fat and lipoatrophy remain common problems for patients, especially those who have been receiving long-term HIV therapy. The contribution of visceral fat, as measured by single-slice computed tomography (CT) scan, to CVD events in HIV patients has not been well studied. Guaraldi and colleagues examined the relationship between CVD and visceral fat and contrasted this with measures of general adiposity (waist circumference and body mass index [BMI]) in a cohort of HIV-infected patients with prevalent coronary heart disease (Abstract 703). In this cross-sectional study, visceral adipose tissue (VAT) but not BMI or waist circumference was associated with the prevalence of CVD in patients with fat accumulation or a mixed-phenotype lipodystrophy. Despite the limitations of this type of cross-sectional analysis, these results suggest that interventions to reduce the quantity of visceral fat hold promise for reducing rates of cardiovascular events.

There is great interest in the role of biomarkers in predicting cardiovascular (and other serious non–AIDS-related) events in patients with treated HIV infection. Investigators from the National Institutes of Health examined the relationship between serum biomarkers and CVD events in a case-control analysis that included 52 events among nearly 2000 patients enrolled in clinical trials since 1995 (Abstract 713). Cases in this study included incident CVD events (MI, silent MI, acute coronary syndrome, coronary revascularization, stroke, or peripheral artery bypass). Serum samples from 2 years and 3 months before the event were included in the analysis. After adjustment for traditional cardiac risk factors, D-dimer levels were higher in cases than in control subjects at both time points.

In contrast to previous studies,[1] no relationship between serum C-reactive protein (CRP) levels and incident CVD was observed. Several other factors were examined (vascular cell adhesion molecule 1 [VCAM-1], intercellular adhesion molecule 1 [ICAM-1], amyloid A, and tumor necrosis factor alpha [TNF]-α) and not found to be associated with cases versus control subjects. Although these results are not strong enough evidence to promote routine monitoring of D-dimer levels in clinical practice, they do confirm earlier studies that demonstrated an association between D-dimer levels and all-cause mortality in patients with HIV[2] and highlight the potential role for disorders of coagulation to contribute to cardiovascular risk in HIV-infected patients.

Biomarker concentrations were correlated with Framingham risk scores (FRSs) in stored samples from a completed clinical trial (Abstract 702). Statistically significantly higher levels of the biomarkers high-sensitivity (hs)-CRP, interleukin-6 (IL-6), and lipoprotein-associated phospholipase A2 (Lp-PLA2) were seen in the subgroup with higher FRSs at baseline and during follow-up. Whether any of these biomarkers add to the predictive value of the FRS remains to be determined.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a marker for the diagnosis and prognosis of heart failure and a predictor of CVD in the general population. Investigators from the SMART (Strategies for Management of Antiretroviral Therapy) study performed a case-control study and found that higher baseline levels of NT-proBNP were predictive of CVD (Abstract 712). This relationship persisted after adjustment for baseline level of IL-6 but was no longer statistically significant when hs-CRP level was included.

Several groups presented data to try to elaborate a mechanism to explain the association between recent exposure to abacavir and the risk of MI observed in the D:A:D and SMART studies. Investigators from the STEAL (Switching to Tenofovir-Emtricitabine or Abacavir/Lamivudine) study compared changes in levels of biomarkers associated with CVD in patients randomly assigned to abacavir/lamivudine– or tenofovir/emtricitabine–based antiretroviral therapy (Abstract 718). The study examined markers of inflammation, coagulation and thrombosis, and endothelial function. Although higher levels of amyloid P were seen among abacavir recipients at week 24, there was no consistent pattern between any of the biomarkers and abacavir exposure.

In vitro studies using a human endothelial cell culture system suggested that abacavir exposure induces activation of the leukocyte integrin Mac-1, which then interacts with its ligand ICAM-1 (Abstract 716). This interaction between abacavir and leucocyte activation could potentially lead to leukocyte accumulation in the endothelium. However, as noted above, no statistically significant changes in the levels of ICAM-1 were seen in abacavir-exposed patients in vivo.

Finally, and possibly most important, an in vitro study suggested that the active metabolite of abacavir, carbovir triphosphate, competitively inhibits activity of soluble guanylyl cyclase, a negative inhibitor of platelet reactivity (Abstract 717). Platelet hyperreactivity in the setting of abacavir exposure is a plausible mechanism to explain the associations observed in clinical studies and merits further evaluation through in vivo studies of platelet function in the presence of abacavir therapy.

Incomplete immune recovery during antiretroviral therapy has been associated with poor long-term outcomes in some cohort studies, yet the relationship with immune recovery and CVD is less clear. Investigators from the ATHENA (AIDS Therapy Evaluation in the Netherlands) cohort compared the rates of CVD and non–AIDS-related events in a group of patients whose CD4+ cell count failed to increase above 200/µL despite an undetectable viral load. Patients in this group had a statistically significantly higher rate of CVD events (4.9% within 5 years) than did patients in other groups whose CD4+ cell count had increased to levels above 200/µL (1.9%) (Abstract 714). The mechanism that underlies this relationship remains poorly defined (see Subclinical Coronary Disease and Vascular Changes).

Subclinical Coronary Disease and Vascular Changes

A variety of noninvasive imaging modalities are currently used to investigate the pathogenesis of and identify risk factors for CVD in HIV-infected patients. The results may vary depending on which modality and specific measurements are used. Some of these modalities are limited to use in research settings, whereas others may have direct clinical applications.

Exercise stress testing is an accepted noninvasive means to screen patients thought to have an intermediate pretest probability for disease. In patients with HIV infection, it remains unclear whether conventional measures to categorize asymptomatic patients into risk groups apply. Stress testing with nuclear perfusion imaging was performed in 80 asymptomatic HIV-infected patients with a mean FRS of 9% and in 50 control subjects (Abstract 711). Surprisingly, 20% of the HIV-infected patients had abnormal radionuclide (technetium-99) exercise stress test results, leading to interventions such as angioplasty (n = 8), stent placement (n = 8), or coronary artery bypass graft (n = 3). Larger studies are needed to compare the utility of different noninvasive screening tests for clinical use in HIV-infected patients and to determine whether the current Framingham risk scoring system performs adequately in this population.

Inflammation, Immune Activation, Senescence, and Carotid Intima-Media Thickness

Several groups have utilized the noninvasive measurement of carotid intima-media thickness (IMT) as a surrogate marker for future cardiovascular events in HIV-infected patients. The studies vary in the segments of the carotid that are measured and the specific techniques, even when measuring the same segments. Although there are differences in these technical aspects, important findings have emerged from all of these studies.

At this year's conference, several groups focused on measures of inflammation and immune function and progression of carotid IMT in longitudinal studies. Hsue and colleagues confirmed their earlier findings of more rapid progression of carotid IMT in HIV-infected patients than in control subjects and again showed that hs-CRP level was associated with progression of IMT in HIV-infected patients (Abstract 125). In this study using a measurement protocol on 12 segments of the carotid artery, evidence for progression in the HIV-infected patients was strongest in the bifurcation region, and the association between hs-CRP level and progression was evident only at this location. A 3-year follow-up study

of 239 patients presented by Mangili and colleagues (Abstract 710) did not see an association with hs-CRP and IMT progression, although only common carotid segments were measured in this study. In the analysis, traditional risk factors were the strongest predictors of progression.

Kaplan and colleagues from the Women's Interagency HIV Study (WIHS) identified a relationship between T-cell activation as measured by CD38+HLA-DR+ markers on CD4+ and CD8+ T cells as well as a marker of T-cell senescence (CD57+CD28-) (Abstract 709). They found that markers of activation and senescence were associated with carotid artery distensibility and the presence of carotid lesions. Together these studies add further support for the hypothesis that ongoing inflammation, as well as traditional risk factors, may contribute to the risk of CVD in HIV-infected patients. An in vitro study of human coronary artery endothelial cells found evidence that exposure to ritonavir or lopinavir plus ritonavir was associated with increased expression of the senescence protein prelamin A, decreased nitrous oxide production, and increased oxidative stress, suggesting a possible mechanism through which these drugs could contribute to the development of early CVD in vivo (Abstract 699).

HIV Disease, Antiretroviral Therapy Exposure, and Intima-Media Thickness

Baker and colleagues in the SUN (Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy) research group measured common carotid IMT progression in a large 4-center study of 424 HIV-infected patients and found *lower* rates of IMT progression in patients who maintained a plasma HIV RNA level below 400 copies/mL throughout follow-up (Abstract 126). Additionally, they noted that among the HIV-infected patients, those who were receiving nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) therapy at baseline had lower rates of IMT progression. A combined analysis of 3 cross-sectional studies of common carotid IMT identified male sex, older age, low-density lipoprotein (LDL) cholesterol level, smoking, and duration of ritonavir exposure as factors associated with carotid IMT (Abstract 705), confirming observations from earlier longitudinal studies. These data add to the growing literature to suggest that suppression of plasma HIV RNA level, and possibly specific antiretroviral therapy regimens, may help reduce the longer-term risk of CVD.

Kidney Disease

Although uncontrolled HIV replication is detrimental to the kidneys, antiretroviral medications and host risk factors may also contribute to development of nephrotoxicity. Several cohort studies sought to elucidate the contribution of HIV treatment in general, as well as specific antiretroviral drugs, to the development or progression of renal impairment.

The Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort demonstrated an improvement in the rate of glomerular filtration rate (GFR) decline in patients with impaired renal function at baseline and in those receiving antiretroviral therapy without tenofovir or ritonavir (Abstract 735). This improved GFR slope was statistically significant only during the first year of antiretroviral therapy, after which GFR slope appeared stable. Individuals with normal kidney function at baseline showed an initial decline in GFR slope when measured by the Modification of Diet in Renal Disease (MDRD) equation but an increase in GFR slope when determined using the Cockcroft-Gault equation. Tenofovir with ritonavir was associated with a statistically significant initial decline in GFR slope by MDRD determination only during the first year of antiretroviral therapy and with stable GFR slope thereafter. However, tenofovir therapy alone was not associated with statistically significant changes by MDRD determination.

The Swiss HIV Cohort also reported tenofovir-containing antiretroviral therapy to be associated with a statistically significant decline in estimated GFR (eGFR) by MDRD determination compared with non – tenofovir-containing antiretroviral therapy, with an average decline in eGFR of 2.40 mL/min/1.73 m^2 over a median of 2.5 years (Abstract 740). However, initiation of antiretroviral therapy was generally associated with an increase in eGFR of 0.68 mL/min/1.73 m^2 during the same time period. In a cohort of individuals coinfected with HIV and hepatitis B virus (HBV), tenofovir treatment lasting up to 5 years was associated with decreased renal function, as evidenced by a small but statistically significant increase in mean serum creatinine level from 0.87 mg/dL to 0.93 mg/dL (P = .002) (Abstract 631).

The EuroSIDA investigators found an independent, statistically significant association of new renal impairment with several individual antiretroviral drugs, including tenofovir (incidence rate ratio [IRR], 1.16), indinavir (IRR, 1.12), atazanvir (IRR, 1.21), and lopinavir (IRR, 1.08), regardless of the method used for calculating renal impairment (Abstract 107LB). Although indinavir has a recognized association with renal insufficiency,[3,4] the atazanavir and lopinavir associations have not been previously reported. Atazanavir-related nephrolithiasis was suggested as a possible explanation of the observed renal toxicity. Considering that this was an observational cohort, it is possible that individuals with a higher risk of vascular disease were preferentially treated with atazanavir because of its reduced impact on lipids, leading to a channeling bias. The long-term impact of newer drugs such as maraviroc, raltegravir, darunavir, and etravirine on renal function could not be examined in this cohort.

Bone Disease

Osteopenia and Loss of Bone Mineral Density

More data on the rates of and risk factors for osteopenia and bone loss over time were reported this year (Abstracts 746–748). Several studies confirmed the association between loss of bone

mineral density (BMD) and use of tenofovir, both as initial antiretroviral therapy (Abstract 106LB) and in the switch setting (Abstract 723). The metabolic substudy of ACTG (AIDS Clinical Trials Group) 5202 demonstrated a higher percentage change in lumbar spine and hip BMD in patients who received tenofovir/emtricitabine than in those who received abacavir/lamivudine, and in patients who received efavirenz than in those who received atazanavir/ritonavir (Abstract 106LB). Two-year follow-up of a French cohort identified a high rate of pathologic bone loss over time and a high prevalence (76%) of vitamin D deficiency in the cohort (Abstract 747). A high prevalence of low BMD was described in a small group of patients with primary HIV infection and appeared to correlate with plasma HIV RNA level, at least for hip BMD (Abstract 745).

Fractures

This year, 3 groups reported data on risk factors for and rates of fractures in HIV-infected patients and compared these with data in control groups from the general population. Investigators from the HIV Outpatient Study compared age-standardized fracture rates among HIV-infected persons over time with population-based data (Abstract 128). They reported the fracture rate to be 4.3 times higher in the HIV-infected group than in patients from the National Hospital Discharge Survey in the time periods examined since 2002. Hepatitis C virus (HCV) coinfection, lower CD4+ count nadir, diabetes, and substance use were each found to be independent predictors of fracture risk.

In the Veterans Aging Cohort Study, using a contemporary control group observed in the same setting, HIV infection was found to be an independent predictor of fracture only among older male veterans (Abstract 129). Finally, investigators from the WIHS examined fracture rates for HIV-seropositive women compared with control subjects after an average of 5 years of follow-up (Abstract 130). They identified that whites, menopausal women, and renal insufficiency, but not HIV serostatus, were all predictors of fractures. Within the HIV-infected population, a history of AIDS, but not CD4+ cell count or antiretroviral therapy exposure, were associated with fractures. Collectively, these studies highlight the importance of monitoring fracture events in HIV-infected populations and identifying for targeted interventions those patients who may be at greatest risk.

Bone Disease in Children Exposed to Tenofovir in Utero

Tenofovir is increasingly used as a component of first-line antiretroviral therapy; however, there have been concerns about the potential for bone toxicity in the developing fetus based on animal studies. Vigano and colleagues used quantitative ultrasound to measure bone density (specifically, measuring tibial speed of sound [SOS] with ultrasound) and markers of bone turnover in tenofovir-exposed and -unexposed children (Abstract 926). The absolute values for the tibial SOS measures were lower in the tenofovir-exposed children; however, the *z* scores were the same, and there was no difference in the levels of bone alkaline phosphatase or C-terminal telopeptide of type I collagen in this relatively small study.

Vitamin D Deficiency

In addition to its well-known associations with bone disease, vitamin D deficiency is linked to a number of disease states important for people with HIV infection. These include cardiovascular disease, immunologic response to infection, malignancy, and obesity. Several studies at this year's conference addressed the issue of vitamin D deficiency in the setting of HIV infection from both resource-limited settings and in the context of current antiretroviral therapy.

Mehta and colleagues from Dar es Salaam and the Harvard School of Public Health have been studying the contributions of nutritional factors to HIV disease progression for many years. This year, they reported results from their examination of the relationship between vitamin D deficiency and HIV disease progression using stored samples from a cohort of pregnant women who participated in a study in Tanzania of multivitamin supplementation that did not include vitamin D (Abstract 753). They found that HIV-infected women with low vitamin D levels (serum 25-hydroxyvitamin D < 32 ng/mL) had a 25% higher risk of their disease progressing to AIDS than did those with adequate levels. In addition, women who were deficient in vitamin D were at higher risk of weight loss and of having a range of clinical problems develop, including upper respiratory infections, thrush, and mucosal ulcers. Vitamin D deficiency was also observed commonly among both HIV-seropositive and -negative US women in the WIHS, and it was associated with bacterial vaginosis, a finding previously described in pregnant women (Abstract 754).

Campbell and Spector presented in vitro studies suggesting that the addition of the active form of vitamin D, 1,25-dihydroxycholecalciferol ($1,25\text{-}[OH]_2D_3$), to monocyte-derived macrophages could inhibit HIV replication (Abstract 231). They postulate that this occurs through the effects of vitamin D on autophagy proteins that appear to be required for productive HIV infection. Given the low cost and simplicity of vitamin D supplementation, these results suggest the need for randomized trials to examine the benefit of routine supplementation.

The prevalence of vitamin D insufficiency (defined as a serum level of 25-hydroxyvitamin D [25[OH]D] < 30 ng/mL) was estimated to be 72% in the SUN investigation (Abstract 750). As expected, blacks, Hispanics, and those with lower levels of UV light exposure were at higher risk. In addition, lack of exercise and efavirenz exposure were also associated with an increased risk of having insufficient levels. In the SUN cohort, use of ritonavir and a GFR below 90 mL/min/1.73 m^2 were protective against lower vitamin D levels.

Swiss HIV Cohort Study investigators measured vitamin D levels in patients before and after starting anti-

retroviral therapy and reported lower 25[OH]D levels for injection drug users and patients receiving NNRTIs, whereas tenofovir exposure was associated with higher levels (Abstract 752). These results confirm earlier published data linking efavirenz exposure to lower levels of vitamin D.[5-7] The clinical importance of these results is not yet known.

Fat Accumulation and Lipoatrophy

Changes in body fat remain an important concern in the long-term management of HIV infection. Other than locally injectable fillers and modest effects from switching off stavudine or zidovudine, there are no proven interventions to reverse lipoatrophy. Previous studies suggested that supplemental uridine might improve mitochondrial function and reverse lipoatrophy associated with ongoing exposure to thymidine nucleoside analogue reverse transcriptase inhibitors (nRTIs).[8-10] A well-powered, randomized, placebo-controlled ACTG trial reported by McComsey and colleagues failed to demonstrate any improvement in lipoatrophy using a uridine supplement (Abstract 131). Although small improvements in lipoatrophy were noted in the uridine group at week 24, they did not persist over time. In addition, the supplement was not well tolerated; however, only 1 subject receiving treatment discontinued it because of protocol-defined toxicity.

Evaluations of body fat changes within randomized antiretroviral therapy trials continue to be an important means to determine the contributions of newer regimens to these problems. The superior lipid profile of raltegravir compared with efavirenz was demonstrated after 96 weeks of follow-up of patients randomly assigned to receive either of these drugs combined with tenofovir/emtricitabine (Abstract 720). Data from a small (n=55 per group) dual-energy x-ray absorptiometry (DEXA) substudy in this same trial showed comparable increases in limb, trunk, and appendicular fat in both groups. Regimens that spare nRTIs continue to be investigated as a potential means to prevent lipoatrophy from developing. Investigators from the MONOI-ANRS (French National Agency for Research on AIDS and Viral Hepatitis) 136 trial reported interim results of a DEXA substudy that compared rates of lipoatrophy among virologically suppressed patients who switched to darunavir/ritonavir monotherapy with rates among patients taking a triple-nRTI-containing regimen (Abstract 721). Results demonstrated that higher rates of lipoatrophy were observed in the nRTI-containing group (11%) than in the monotherapy group (1%).

Tuberculosis and Influenza Coinfections

Coinfections with tuberculosis (TB) and the H1N1 strain of influenza A were highlighted at this year's conference, with a focus on optimizing prevention of these diseases with treatment for latent TB and with influenza vaccination. Promising data were reported on the effect of extended courses of preventative TB therapy on TB incidence and mortality in different geographic regions of the world. Initial reports on the impact of the H1N1 influenza epidemic on HIV-infected populations and the efficacy of H1N1 vaccination in HIV-infected patients were presented.

Tuberculosis Coinfection

Prevention of TB was the focus of 3 oral presentations. Samandari and colleagues presented the results of the joint Botswana–USA Centers for Disease Control and Prevention Project, the BOTUSA trial, which evaluated 1995 HIV-seropositive adults living in Botswana randomly assigned to a 3- or 36-month course of isoniazid preventive therapy (IPT) (Abstract 104LB). In the intent-to-treat analysis, they found a 43% reduction in TB cases in the 36-month group versus the 6-month group. The protective effect of isoniazid was lost promptly after discontinuation of the drug in the 6-month group. Similar to previous studies, individuals testing positive on tuberculin skin tests (TST) had the greatest reductions in TB rates. Among TST-positive persons, the 36-month IPT group had a 92% reduction in TB rates compared with the 6-month group. Only a 14% reduction in the 36- versus 3-month IPT regimens was seen among TST-negative persons, which was not statistically significant. Among breakthrough TB cases in this trial, isoniazid resistance was detected in 17% of those in the 6-month group and 14% in the 36-month group.

The association of IPT with mortality was analyzed in a retrospective cohort study presented by Innes and colleagues (Abstract 102). The investigators evaluated survival outcomes in 3635 antiretroviral therapy–naive individuals receiving health care in a mining workplace program in South Africa. They found that the mortality rate was lower in those who received IPT than in those who did not (3.5 vs 9.8 per 100 person-years), with a hazard ratio of 0.37 (95% CI, 0.25 – 0.54). These reductions were still observed if patients previously treated for TB were excluded from the analysis. Whether mortality was a direct consequence of isoniazid preventing TB or isoniazid served as a surrogate for patients more actively engaged in care and likely to receive a prompt diagnosis of AIDS complications could not be discerned from the analysis. However, this report was reassuring in that it showed favorable outcomes for a program with large numbers of HIV-seropositive persons receiving IPT in a setting with a high prevalence of TB.

Swaminathan and colleagues presented the results of a second randomized study of efficacy of 2 TB preventive strategies among 712 HIV-infected adults in India (Abstract 103). This study compared 6 months of treatment with ethambutol plus isoniazid to 36 months of treatment with isoniazid for the prevention of TB. Rates of TB were not statistically significantly different between the 2 groups, with 2.4 TB cases per 100 patient-years in the short-course, 2-drug group and 1.6 TB cases per 100 patient-years in the isoniazid 36-month group. Execution of this study spanned the introduction of antiretroviral therapy in India; thus, the study included patients with low CD4+ cell counts who were not yet

receiving antiretroviral therapy. Consistent with other studies, rates of TB were higher in patients with low CD4+ cell counts. Although the trend favored greater benefits among TST-positive persons, it did not reach statistical significance. Among the patients with TB and isolates available for drug-susceptibility testing, isoniazid resistance was present in 6 of 16, and multidrug resistance was present in 2 of 16.

How should these seemingly differing results among the studies on IPT be reconciled? These data are actually consistent with an accumulating body of evidence that demonstrates that IPT can be delivered safely in resource-limited settings in the HIV-infected population, that the greatest reductions in TB rates are detected among those who are TST-positive, and that in places like sub-Saharan Africa, where ongoing and repeated episodes of TB occur among HIV-infected patients, longer durations of preventive therapy result in greater overall reductions in TB rates. The jury remains out regarding the effect of IPT on mortality. The relative contribution of antiretroviral therapy and IPT to the reduction in TB rates is also an area of current study. These data support the justification of the new World Health Organization (WHO) recommendations for IPT, for which duration of IPT depends on the epidemiologic setting.

One randomized TB–antiretroviral therapy trial was presented in an oral session by Kayanga on behalf of Walusimbi and colleagues (Abstract 105). This study evaluated whether a 6-month course of antiretroviral therapy (abacavir, lamivudine, zidovudine) given concurrently with TB therapy would improve outcomes in HIV-infected adults with CD4+ T-cell counts of at least 350/µL. This trial included 232 Ugandan adults with a median CD4+ count of 584 cells/µL. Subjects were randomly assigned to immediate (6-month punctuated course) or deferred antiretroviral therapy. All patients with a CD4+ cell count of 250/µL or less received antiretroviral therapy.

There was no benefit to short-course antiretroviral therapy in this population. There was, however, a demonstrable clinical benefit favoring immediate over deferred antiretroviral therapy at the 1-year follow-up point, supporting current WHO guidelines recommending antiretroviral therapy in all patients with TB regardless of CD4+ cell count. In addition, this study reported viral suppression rates of 86% at 6 months, no abacavir hypersensitivity reactions, and no immune reconstitution inflammatory syndrome among this group of patients, who may have limited options for antiretroviral therapy because of the toxicity profile of nevirapine and the teratogenicity of efavirenz.

The poster session on TB covered a wide range of topics, starting with TB screening. Danel and colleagues reported preliminary results from an IPT study enrolling HIV-seropositive persons with CD4+ cell counts in the range of 350/µL to 600/µL and no symptoms of TB, in whom isoniazid was to be initiated 1 month after enrollment (Abstract 774). The investigators found that 36 (7.7%) of the patients had symptoms of TB that prevented isoniazid initiation at 1 month; TB was confirmed in 14 of them. These data point to evolving strategies in which isoniazid is started 1 month to 3 months after antiretroviral therapy initiation to ensure that TB is not present at the start of IPT.

Studies from the United States and Africa support prior investigations indicating that TB rates increase the first 6 months after initiation of antiretroviral therapy but then decline over time to rates much lower than pre–antiretroviral therapy levels (Abstracts 777–779). Bliven and colleagues reported that 2-month TB sterilization rates do not differ between HIV-seropositive and HIV-seronegative populations and called for greater inclusion of HIV-seropositive patients in new TB drug treatment trials (Abstract 782). O'Donnell and colleagues reported outcomes for 60 patients (43 of whom were HIV-seropositive) with extensively drug resistant (XDR) TB in a referral hospital in South Africa (Abstract 787). Survival at 2 years was 50%. Of surviving patients, 11 were cured, 7 patients defaulted, and 12 experienced treatment failure. These data represent an improvement upon the abysmal outcomes reported from the recent outbreak in KwaZulu Natal,[11] but at the same time they demonstrate the need for rapid diagnosis, new TB drugs, and improved health systems for these patients.

Influenza A (H1N1) Coinfection

"Swine flu" swept through the world in 2009, and the HIV community braced itself accordingly. In a themed discussion, "Swine Flu Meets HIV," data on clinical presentation and outcomes from the 2009 epidemic were presented, and immune responses to the new influenza A (H1N1) vaccine were described. A series from Spain found that clinical symptoms associated with confirmed H1N1 influenza were similar among 567 HIV-seronegative adults and 56 HIV-seropositive adults, with the exception of more gastrointestinal symptoms in the HIV-seropositive influenza patients (Abstract 802LB). Pneumonia and respiratory failure were actually less common in HIV-seropositive (9%) than in HIV-seronegative (25%) patients, although after adjusting for comorbidities, which were higher in the HIV-seronegative group, there was no difference between the groups in this outcome.

Complications of influenza in the HIV-infected population were more likely to occur in the sicker patients and in injection drug users. Notably, oseltamivir use was higher in the HIV-seropositive than in the HIV-seronegative populations. As this was an observational study, it was difficult to compare clinical presentations between HIV-seropositive and HIV-seronegative populations because HIV-infected patients in care may receive more aggressive screening, detection, and treatment of disease than the HIV-seronegative population would.

A second series from Mexico City examined outcomes in 22 HIV-seropositive patients with H1N1 influenza (Abstract 803LB). Twelve of the patients were hospitalized, 7 required intubation, and 5 died. There appeared to be a delayed detection of serious influenza among the HIV-infected population in this case series, which was attrib-

uted to the observation that several patients had concomitant opportunistic infections. Interestingly, in a small subset of patients, this group reported that viral shedding among patients treated with oseltamivir persisted for as long as 11 days. They reported no detection of resistance mutations. In a study by Campos-Loza and colleagues, only 6 cases of HIN1 influenza were identified by polymerase chain reaction in an HIV program caring for 967 patients (Abstract 801). One patient with concomitant *Pneumocystis jiroveci* and cytomegalovirus pneumonia died.

H1N1 influenza vaccine efficacy was examined by several groups. Bickel and colleagues reported vaccine response rates to the adjuvanted H1N1 influenza vaccine in 160 HIV-infected adults (Abstract 805LB). Vaccine response rates (seroconversion) were 69% in this population. Bickel reported in the discussion that in unpublished observations, patients who received 2 doses of the vaccine had higher serocoversion rates. In the ANRS study, 237 HIV-seropositive adults were randomly assigned to receive 2 doses of the adjuvanted or 2 doses of the nonadjuvanted H1N1 influenza vaccine (Abstract 804LB). After the first vaccine dose, the seroconversion vaccination response rates were 92% with the adjuvanted vaccine and 72.1% in the nonadjuvanted vaccine.

Tebas and colleagues evaluated response to the nonadjuvanted H1N1 influenza vaccine in 120 HIV-infected adults (Abstract 806LB). They reported a 53% seroconversion rate in patients with no preexisiting antibody at week 3. Lower current and nadir CD4+ cell count was associated with poorer response. Nachman and colleagues reported the results of H1N1 influenza vaccination of 130 HIV-infected pregnant women (Abstract 808LB). The vaccine schedule was 2 vaccine doses separated by 21 to 28 days. There were no grade 3 adverse events, and immune studies are ongoing.

Much of the needed additional clinical research in this area is now stalled as the result of the fortunate waning of the H1N1 influenza epidemic. At least in the most recent round, H1N1 influenza did not appear dramatically worse in the HIV-infected population, and not surprisingly was more serious in the most immune-compromised patients. Vaccination was well tolerated, although response rates even with the adjuvanted vaccine were quite variable and generally lower than in the HIV-uninfected population. Data are needed to determine if 2 doses are better than 1, and to determine optimal vaccine preparations and dosing schedules in all populations, including pregnant women and children.

Hepatitis Coinfections

This year's conference highlighted the morbidity and mortality benefits of curative HCV therapy as well as the increasingly recognized nonhepatic complications associated with HCV coinfection. Several host factors were demonstrated to be linked with improved response to therapy, such as the interleukin-28B (*IL28B*) C/C genotype and lack of insulin resistance. Presentations on HIV-HBV coinfections focused on the efficacy of tenofovir for control of viral replication and the potential consequences of ongoing HBV replication despite nRTI treatment.

Hepatitis C Virus Coinfection

At the 2009 conference, the GESIDA (Grupo de Estudio de SIDA) investigators demonstrated that attaining a sustained virologic response (SVR) with HCV treatment was associated with reduced liver-related complications and mortality. This year, the GESIDA group reported that SVR with interferon plus ribavirin therapy was also associated with decreased AIDS progression as well as non–liver-related death (Abstract 167). In a regression analysis adjusted for fibrosis, nadir CD4+ cell count, and HIV disease stage, the adjusted hazard ratio of nonhepatic mortality and new AIDS-defining conditions was 3.78 (95% CI, 1.48 – 9.65) in patients without SVR versus those with SVR.

Similarly, data from the Veterans Aging Cohort Study Virtual Cohort highlighted the nonhepatic complications of HCV infection, demonstrating an increased risk of stroke in patients with HIV infection (HR, 2.13) and HCV monoinfection (HR, 1.44), as well as HIV-HCV coinfection (HR, 2.21), in comparison with uninfected control subjects (Abstract 668). The increasingly recognized proinflammatory effects of HCV replication may contribute to the observed HCV-associated vascular disease and AIDS progression. HCV infection was associated with elevated levels of the endothelial dysfunction markers soluble ICAM and soluble VCAM (Abstract 667), increased CD14+ monocyte activation (Abstract 672), and increased Fas-induced CD4+ apoptosis (Abstract 673).

Selecting the optimal timing for HCV therapy remains challenging, as timely treatment of HCV must be balanced with the knowledge that better HCV therapeutic options are in development. Sulkowski and colleagues reported that a baseline hepatic biopsy fibrosis score of 2 or greater (on a Metavir scale of 0–4) was independently associated with hepatocellular carcinoma, end-stage liver disease, and death over a median of 5.4 years in their HIV-HCV coinfected cohort (Abstract 166). The incidence rate of these clinical outcomes jumped from a range of 20.9 to 26.8 per 1000 person-years for patients with fibrosis stages 0 to 1 to a nearly doubled incidence rate of 50.1 per 1000 person-years for patients with fibrosis stage 2. Incidence rates continued to rise to 59.2 and 71.4 per 1000 person-years with stages 3 and 4, respectively. These findings may caution against waiting for newer treatment options, particularly if a fibrosis stage of 2 or greater is demonstrated. Once disease has progressed to cirrhosis, the mortality rate was 5.8% per year, as shown in a Madrid cohort study of compensated HIV-infected patients with cirrhosis, who were evaluated by ultrasound elastography (Abstract 684). This rate is higher than that previously reported in HIV-uninfected cirrhotic patients.[12,13] Of note, only half of the deaths reported in this cohort were liver related.

Given the lower-than-desired response rates to interferon plus ribavi-

rin–based HCV treatment, selecting the best patients for HCV treatment and optimizing individual factors that may boost response are priorities. There was a proliferation of data on the *IL28B* gene as a predictor of spontaneous HCV clearance and favorable response to HCV treatment. The *IL28B* C/C genotype was associated with high rates (90%) of spontaneous HCV clearance (Abstract 163), as well as favorable response to interferon plus ribavirin therapy. The C/C genotype was associated with an SVR rate with interferon therapy of 75% compared with 38% in non-C/C genotypes (Abstract 165LB), and an adjusted odds ratio of SVR of 5.05 ($P < .001$) (Abstract 656). An additional abstract reported an association of the *IL28B* C/C genotype with SVR; however, this association was no longer statistically significant after multivariate analysis (Abstract 164). Testing for *IL28B* polymorphisms may help optimize HCV outcomes by identifying those who are more likely to attain SVR with treatment and potentially permit modification of treatment regimens based on *IL28B* genetic profiles.

Insulin resistance has consistently emerged as a negative predictor of SVR. Presence of insulin resistance, defined as homeostasis model of assessment of insulin resistance (HOMA-IR) value greater than 2, was the only independent negative predictor of SVR (adjusted odds ratio, 0.17; 95% CI, 0.03 – 0.55) reported by Vachon and colleagues in their study of coinfected patients undergoing retreatment for HCV with peginterferon alfa-2a and ribavirin (Abstract 655). Thirty-five percent of patients retreated for HCV achieved SVR if their HOMA-IR value was below 2, 14% with a HOMA-IR value from 2 to 4, and only 7% with a HOMA-IR value above 4. Pretreatment assessment of insulin resistance may be a powerful predictor of response, and measures to reduce insulin resistance such as weight loss or insulin sensitizers, before initiating HCV treatment, are under investigation.

Increased recognition of acute HCV infection presents an opportunity for improved treatment response and possibly an abbreviated course of therapy. Encouragingly, Vogel and colleagues found that the infection spontaneously cleared without treatment in 40% of patients with acute HCV infection (Abstract 640). For those requiring treatment, Hare and colleagues presented a kinetically guided strategy for acute HCV infection therapy (Abstract 639). Thirteen subjects with acute HCV infection and with an undetectable HCV RNA level at 4 weeks received an abbreviated 12-week course of ribavirin along with 24 weeks of interferon. All 13 achieved an end-of-treatment response (undetectable HCV RNA level), and none rebounded during treatment, despite shortened ribavirin treatment.

Hepatitis B Virus Coinfection

Tenofovir has become a mainstay of treatment for HBV infection in HIV coinfection. Several abstracts demonstrated that tenofovir appears quite effective in suppressing HBV DNA replication when taken for a sufficient length of time. After 5 years of tenofovir treatment, 88% of hepatitis B e antigen (HBeAg)-positive patients in a Dutch cohort had undetectable serum HBV DNA levels (Abstract 631), and 86.5% to 100% of patients in a Thai study had HBV DNA levels below detection after a median of up to 8.7 years of tenofovir treatment (Abstract 630). Tenofovir's efficacy was not affected by prior lamivudine or emtricitabine use in either study.

Individuals with persistent HBV viremia despite tenofovir therapy did not show evidence of tenofovir resistance in 2 studies (Abstracts 631, 636). Patients who do not achieve suppression of HBV replication with tenofovir treatment may respond to added entecavir; a pilot study found 4 of 5 patients had undetectable HBV DNA levels after 36 weeks of entecavir intensification (Abstract 636).

Persistent HBV viremia despite HBV treatment may have important public health implications by selecting for hepatitis B surface antigen (HBsAg) "vaccine escape" mutations, which have been shown to evade HBV vaccine-induced antibody protection in animal models. Lacombe and colleagues detected HBsAg mutations in up to 12% of individuals (2.1% per patient-year) with detectable HBV levels during nRTI treatment (Abstract 638). The rate of escape mutations doubled from 6% to 12% of patients over 3 years of the study, which the authors suggest may be attributed to rising use of tenofovir from 20% at baseline to 63% at the study conclusion. A cohort from Ghana exposed to lamuvidine-containing HIV treatment without tenofovir demonstrated a 9% prevalence of HBsAg mutations associated with possible vaccine escape and 6% with novel HBsAg mutations, suggesting that lamivudine monotherapy also selects for potential vaccine escape mutants (Abstract 696).

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Advances in Antiretroviral Therapy

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The 17th Conference on Retroviruses and Opportunistic Infections maintained its tradition of being 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 HIV resistance to antiretroviral drugs. Of particular note were the continued advances in antiretroviral treatment and research emanating from resource-limited settings and from large clinical trials to determine the optimal initial antiretroviral drug regimen. Several interesting smaller studies were focused on HIV-1 pathogenesis and persistent viremia.

Investigational Drugs

Inhibitors of LEDGF/p75–Integrase Interaction

Christ and colleagues presented data on inhibitors of lens epithelium-derived growth factor p75 (LEDGF/p75) interaction with integrase (Abstract 49). They used the crystal structure of integrase to rationally design molecules to inhibit this interaction. In a series of experiments, they showed that these compounds inhibit HIV-1 integration, bind at a different pocket than strand transfer inhibitors, and are active against raltegravir-resistant isolates. The existing toxicity data are supportive of further drug development.

S/GSK1349572

Johns and colleagues presented data on the discovery and development of S/GSK1349572 (Abstract 55). This investigational drug is a once-daily integrase strand transfer inhibitor (INSTI) that retains antiviral activity in clinical isolates resistant to raltegravir and elvitegravir. Prior monotherapy studies have shown that the compound has potent antiviral activity through 14 days.[1]

QNL111

QNL111 is an integrase–DNA binding inhibitor whose antiviral activity was presented at the 2009 conference.[2] Thibaut and colleagues presented further data this year confirming the mechanism of action (Abstract 492). They found that QNL111 decreased the amount of integrated DNA in cell culture, similar to raltegravir, a strand transfer inhibitor. In contrast to raltegravir, QNL111 did not lead to an increase in 2-long-terminal-repeat (LTR) circles, consistent with inhibition of HIV-1 integration before the strand transfer reaction.

CC Chemokine Receptor 5 Antagonists

Cohen presented data on TBR-652, a CC chemokine receptor 5 (CCR5) antagonist (Palleja et al, Abstract 53). The drug is dosed once daily and has a half-life of approximately 40 hours. TBR-652 is also an antagonist of CC chemokine receptor 2 (CCR2), which is found on monocytes, immature dendritic cells, and memory T cells. This receptor has been associated with the pathogenesis of atherosclerosis and the metabolic syndrome. The antiviral activity, safety, tolerability, pharmacokinetics, and CCR2 activity were investigated in a randomized, double-blinded, placebo-controlled, dose-escalating study in HIV-infected patients. Eligible subjects were treatment experienced with no HIV treatment for at least 6 weeks who had CCR5-tropic HIV, a CD4+ cell count of 250 cells/μL or more, and a plasma HIV-1 RNA level of at least 5000 copies/mL. Forty-four subjects were given 25-mg to 150-mg doses, and 10 received placebo for 10 days without other antiretroviral medications. The maximal decline in plasma HIV-1 RNA level was 1.4 $\log_{10}$ copies/mL to 1.8 $\log_{10}$ copies/mL for dose levels above 25 mg. The pharmacokinetic analysis suggested dose-proportional increases in exposure through the range of doses tested and a half-life ranging from 23 hours to 48 hours. There were no serious adverse events and no obvious safety concerns. Monocyte chemotactic protein 1 (MCP-1), the native ligand for CCR2, increased during dosing of TBR-652 relative to placebo. This suggests that TBR-652 was blocking CCR2 in these subjects. A detailed pharmacokinetic analysis was presented in Abstract 598.

Genetically Modified CD4+ T cells

There were 2 studies that evaluated genetically modified T cells as a therapeutic strategy. The first used zinc-finger nucleases to knock out the CCR5 gene in human CD34+ hematopoietic stem cells (Abstract 387). These stem cells were infused into a mouse model, and the mice were challenged with HIV-1. CCR5-deleted cells were rapidly selected, and viral replication was controlled by 12 weeks after infection.

In the second study, Tebas and colleagues reported results from an ongo-

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ing clinical trial of autologous CD4+ T cells genetically modified with a lentiviral vector to express long antisense to HIV *env* (Abstract 388). Subjects were taking suppressive antiretroviral therapy and received 3 to 6 infusions of 10^{10} modified autologous CD4+ T cells. They underwent structured treatment interruptions after the last infusion. Of the 13 patients who interrupted treatment, 8 were evaluable for the primary endpoint. Seven of 8 had a reduction in the viral load setpoint (range, decrease of 0.26 – 0.98 $\log_{10}$ copies/mL), and 1 subject had not had detectable virus at 104 days postinterruption along with an increase in CD4+ T-cell count.

Banana Lectin

Swanson and coworkers presented data on banana lectin (Abstract 487). This compound exhibited low nanomolar or picomolar inhibition of HIV-1 replication. Quantification of reverse transcriptase products suggests that banana lectin blocks HIV-1 entry similar to other mannose-specific lectins. This compound can also bind gp120, and the authors suggested that this compound may be considered for development as a microbicide.

Inhibitor of Reverse Transcriptase Dimerization

HIV reverse transcriptase is a heterodimer of p51 and p66. Agopian and colleagues presented data on peptide inhibitors of reverse transcriptase dimerization (Abstract 494). They constructed 2 peptides that exhibited low nanomolar inhibitory concentrations when delivered as nanoparticles to a cell culture system. These peptides showed activity against a broad range of HIV-1 subtypes and resistant isolates.

Immune-Based Therapies

Therapeutic HIV-1 *gag* Vaccine

Li and colleagues presented additional data from ACTG (AIDS Clinical Trials Group) A5197, a randomized, placebo-controlled trial of therapeutic vaccination with an adenovirus 5 HIV-1 *gag* vaccine for reduction of the viral load setpoint after treatment interruption (Abstract 76). Participants with stable virologic suppression with antiretroviral therapy received vaccine or placebo injections over 6 months, followed by treatment interruption for at least 16 weeks. In this analysis, investigators evaluated host and viral factors associated with viral rebound after treatment interruption. They classified participants according to HLA typing as having unfavorable, neutral, or protective alleles. There was no vaccine effect in subjects with unfavorable or protective alleles. Investigators did observe a lower plasma HIV-1 RNA level 16 weeks after treatment interruption for participants with neutral alleles who received vaccine compared with placebo (4.0 vs 4.6 $\log_{10}$ copies/mL; P = .01). Factors associated with lower plasma HIV-1 RNA levels after treatment interruption included absence of unfavorable HLA alleles, greater divergence of *gag* mutations for the vaccine sequence, lower plasma HIV RNA level before antiretroviral therapy initiation, and randomization to the vaccine arm. The authors noted that HLA determination and pre–antiretroviral therapy plasma HIV RNA levels should be considered in future therapeutic vaccine studies.

Autologous Dendritic Cell Vaccine

Plana and colleagues presented the results of a phase I, double-blind, placebo-controlled trial of a therapeutic vaccine using autologous dendritic cells pulsed with a high dose of autologous HIV-1 (Abstract 77). Eligible subjects were not receiving antiretroviral therapy and had a CD4+ cell count above 450/µL and a plasma HIV-1 RNA level above 1000 copies/mL. Subjects received dendritic cells pulsed with HIV or a placebo of dendritic cells without pulsing at entry, week 2, and week 4. The treatments appeared safe with no substantive local reactions or any evidence of autoimmunity. There was a modest difference in plasma HIV-1 RNA level between groups at weeks 24 and 48 (.20 and .31 copies/mL reductions in vaccine recipients compared with .21 and .34 copies/mL increases in placebo recipients; P = .03 and P = 0.05, respectively). There was no difference in CD4+ cell counts between groups. Vaccine recipients showed a statistically significant negative correlation between changes in plasma HIV-1 RNA level and HIV-specific T-cell responses compared with placebo recipients, in whom a positive correlation was observed.

Clinical Trials of Antiretroviral Therapy in Treatment-Naive Patients

AIDS Clinical Trials Group A5202

ACTG A5202 was a randomized equivalence study in antiretroviral-naive patients that was a double-blind, placebo-controlled comparison of abacavir/lamivudine versus tenofovir/emtricitabine and an open-label comparison of atazanavir 300 mg/ritonavir 100 mg versus efavirenz 600 mg (Abstract 59LB). The inferior antiretroviral activity of abacavir/lamivudine versus tenofovir/emtricitabine in subjects with a screening plasma HIV-1 RNA level above 100,000 copies/mL has been reported.[3]

Daar, on behalf of the ACTG A5202 study team, presented the final results of this trial. The study enrolled approximately 1800 participants aged 16 years or older with a plasma HIV-1 RNA level above 1000 copies/mL. The baseline characteristics of the study population were as follows: 83% were men, median age was 38 years, the median plasma HIV-1 RNA level was 4.7 $\log_{10}$ copies/mL, and the median CD4+ cell count was 230/µL. Only 45% had genotypic testing at some point before study entry.

The primary efficacy endpoint was time to confirmed virologic failure (a composite of plasma HIV-1 RNA level ≥ 1000 copies/mL at week 16 or ≥ 200 copies/mL at week 24 or later). In those with a screening plasma HIV-1 RNA level below 100,000 copies/mL, there was no appreciable difference in the time to virologic failure between abacavir/lamivudine and tenofovir/emtricitabine when given with efavirenz

or atazanavir/ritonavir. There was no appreciable difference in the time to virologic failure for atazanavir/ritonavir versus efavirenz when given with abacavir/lamivudine or tenofovir/emtricitabine. None of these comparisons reached prespecified equivalency bounds for the hazard ratio (HR). The number of events was much smaller than hypothesized, leading to wider confidence intervals (CIs).

Abacavir/lamivudine was associated with a shorter time to grade 3 or grade 4 signs, symptoms, or laboratory abnormalities than was tenofovir/emtricitabine when given with efavirenz. The abacavir/lamivudine groups were associated with a shorter time to regimen change. This appeared to be wholly explained by abacavir hypersensitivity reaction. Of note, testing for the HLA-B*5701 allele was not routinely performed at the time this trial was enrolling participants.

The most notable difference between efavirenz and atazanavir/ritonavir was in the rate of the emergence of genotypic evidenced resistance. Almost no protease inhibitor (PI) resistance mutations emerged at virologic failure compared with the efavirenz-receiving groups, in whom failure was associated with nonnucleoside analogue reverse transcriptase inhibitor (NNRTI)–associated mutations.

Elvitegravir/Cobicistat/Tenofovir/Emtricitabine

Cohen and colleagues presented data from 2 clinical trials involving the investigational drug cobicistat (GS-9350), an inhibitor of cytochrome P3A4 (CYP3A4) without anti-HIV activity (Abstract 58LB). Both trials enrolled antiretroviral-naive subjects, without hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, and with CD4+ cell counts above 50/μL, plasma HIV-1 RNA levels above 5000 copies/mL, and no evidence of resistance through genotypic testing. The median age of participants in the treatment groups was between 34 and 37 years; 86% to 94% were male; 55% to 78% were white; median baseline CD4+ cell count was 341/μL to 436/μL, and the mean plasma HIV-1 RNA level was 4.6 $\log_{10}$ copies/mL to 4.7 $\log_{10}$ copies/mL. Both studies were randomized, double blind, and placebo controlled.

The first study assigned 48 subjects to elvitegravir 150 mg, an investigational INSTI, in a fixed-dose, once-daily formulation with tenofovir, emtricitabine, and cobicistat 150 mg, and it assigned 23 subjects to a fixed-dose combination of tenofovir, emtricitabine and efavirenz. At 24 weeks postrandomization, 90% of the elvitegravir and 83% of the efavirenz recipients achieved a plasma HIV-1 RNA level below 50 copies/mL in the intention-to-treat (ITT), missing = failure (M = F) analysis. The observed difference was 5% (95% CI, −11% to +21%), adjusting for differences in baseline plasma HIV-1 RNA level. There were no cases of virologic failure in either group. Adverse events related to randomized treatment were observed in 35% and 57%, respectively. Serious adverse events were rare, and only 1 subject receiving efavirenz discontinued treatment because of an adverse event.

The second trial assigned 50 subjects to cobicistat 150 mg and 29 subjects to ritonavir 100 mg (Abstract 58LB). Both drugs were given once daily with atazanavir 300 mg plus fixed-dose tenofovir/emtricitabine. In the ITT, M = F analysis, 84% and 86%, respectively, achieved plasma HIV RNA levels below 50 copies/mL. Only 1 subject experienced virologic failure. Adverse events related to randomized treatment were observed in 20% and 24%, respectively. Serious adverse events were rare; 2 (4%) subjects receiving cobicistat and 1 (3%) receiving ritonavir discontinued treatment because of an adverse event.

Cobicistat was associated with a decrease in the estimated glomerular filtration rate (eGFR) by the Cockcroft-Gault equation. The investigators evaluated this further in a small safety study in HIV-uninfected volunteers. The eGFR was reduced with cobicistat but the actual GFR was not affected. This result is consistent with inhibition of tubular secretion of creatinine and not a renal toxicity per se. The results were supportive for phase III studies of the elvitegravir/cobicistat fixed-dose pill and for phase III studies of cobicistat as an alternative to ritonavir.

Nevirapine Versus Lopinavir/Ritonavir

One randomized, controlled trial of initial antiretroviral therapy in resource-limited settings (RLS) was presented at this year's conference. McIntyre and colleagues presented data from the OCTANE-2 (Optimal Combination Therapy After Nevirapine 2) trial conducted in South Africa (Abstract 153LB). The OCTANE-2 trial was an open-label, equivalence study comparing the efficacy of nevirapine to lopinavir/ritonavir (/r), both coadministered with tenofovir/emtricitabine, in antiretroviral therapy–naive women in South Africa with no history of single-dose nevirapine exposure for prevention of mother-to-child transmission (PMTCT) of HIV. (This trial is a companion trial to OCTANE-1, in which identical regimens were compared in antiretroviral therapy–naive women with a history of exposure to single-dose nevirapine for PMTCT.[4] OCTANE-1 showed a higher rate of death and virologic failure in the nevirapine group than in the lopinavir/r group).

Five hundred antiretroviral therapy–naive women with no prior history of single-dose nevirapine were enrolled, with 250 women in each treatment group. Inclusion criteria included a CD4+ cell count below 200/μL and a creatinine clearance rate greater than 60 mL/min. Women with prior exposure to zidovudine as part of PMTCT were eligible to participate if exposed to zidovudine for less than 10 weeks and if the exposure occurred more than 6 months before enrollment. The primary endpoint was time to death or virologic failure. Virologic failure was defined as a confirmed plasma HIV RNA level less than 1 $\log_{10}$ below baseline at 12 weeks or a plasma HIV RNA level above 400 copies/mL at 24 weeks. Follow-up was for at least 48 weeks after last enrollment, which was completed in August 2009. The study was powered to assess equivalence, with a CI of 95% for the HR range of 0.5 to 2.0. An ITT analysis was performed.

Baseline characteristics were as follows: median age, 34 years; median CD4+ cell count at baseline, 121/μL; plasma HIV-1 RNA level, 5.15 $\log_{10}$ copies/mL; chronic HBV infection, 7%; prior exposure to zidovudine, 1%. One subject with prior exposure to single-dose nevirapine was enrolled in error and was randomly assigned to the lopinavir/r group. Of a random sample of 199 women for whom genotypic analysis was performed, nevirapine resistance-associated mutations (RAMs) were observed in 0.6%. Seventy-one percent of participants had subtype-C HIV. Overall, 4.0% were lost to follow-up (LTFU); it was twice as high in the nevirapine recipients.

The primary endpoint was reached by 92 women: 17% in the nevirapine group and 20% in the lopinavir/r group, yielding a HR of 0.82 for the primary endpoint in the nevirapine recipients compared with the lopinavir/r group. Thus, the study met the prespecified criteria for equivalence between groups. Overall, there were 5 deaths, 2 in the nevirapine group and 3 in the lopinavir/r group. The majority of endpoints reached were driven by virologic failure. The authors also presented data on the "time to permanent discontinuation of a regimen," a composite of death, virologic failure, LTFU, or adverse events. In this analysis, 28% of subjects in the nevirapine group, compared with 9% in the lopinavir/r group, permanently discontinued treatment. These discontinuations were driven primarily by adverse events in the nevirapine recipients. Although similar rates of adverse events were observed in the 2 study groups, 14% of the nevirapine discontinuations were due to adverse events, mainly rash, whereas no discontinuations in the lopinavir/r group were due to adverse events ($P < .0001$). The authors postulated that strict protocol criteria for adverse event–mandated discontinuations may have led to the high rate of discontinuation in the nevirapine group. In sum, and in contradistinction to the results of OCTANE-1, a nevirapine-based regimen was equivalent to lopinavir/r–based therapy with respect to virologic failure and death in antiretroviral therapy–naive women with no prior exposure to single-dose nevirapine.

Clinical Trials of Antiretroviral Therapy in Treatment-Experienced Patients

Phase III Trials of Vicriviroc

Gathe and colleagues presented the results of 2 identical phase III, randomized, placebo-controlled trials of the investigational CCR5 inhibitor vicriviroc in treatment-experienced subjects (Abstract 54LB). Eligible subjects had documented resistance to 2 or more drug classes (nucleoside analogue reverse transcriptase inhibitor [nRTI], NNRTI, or PI) or at least 6 months of antiretroviral therapy experience. Originally, subjects were required to have only R5 virus as determined by tropism testing, but the analysis described here includes those subjects confirmed to have only R5 virus on retesting of screening samples using an enhanced-sensitivity tropism assay. Subjects were randomly assigned 2:1 to vicriviroc 30 mg or placebo with an optimized background regimen containing 2 or more active antiretroviral drugs predicted to have activity based on resistance testing. The primary endpoint was the proportion with plasma HIV-1 RNA levels below 50 copies/mL 48 weeks after randomization.

The 2 trials included 375 and 346 randomized subjects, respectively. In a pooled analysis, the median age of subjects was 43 years; 60% were white; and 29% were female. The mean baseline plasma HIV-1 RNA level was 4.6 $\log_{10}$ copies/mL, the mean CD4+ cell count was 257/μL, and 61% of subjects had 3 or more active drugs in their background regimens.

Pooling results from the 2 trials, investigators found no difference in the proportion with plasma HIV-1 RNA levels below 50 copies/mL at week 48: 64% of the vicriviroc group versus 62% of the placebo group. There was no difference in the CD4+ cell count gain between groups. In a prespecified subgroup analysis of subjects with 2 or fewer active drugs in the background regimen, vicriviroc led to improved virologic suppression (70% vs 55%; $P = .02$). There were 71 participants receiving vicriviroc with protocol-defined virologic failure. Emergence of CXC chemokine receptor 4 (CXCR4) use was observed in 9 (13%), and 3 (4%) had vicriviroc resistance. There was no obvious difference in observed adverse events. There were no seizures in the vicriviroc group and no evidence of increased malignancy. The antiviral activity of the background regimens may have made it more difficult to detect an additional effect of vicriviroc.

Once- Versus Twice-Daily Darunavir/Ritonavir

Daruanvir has US Food and Drug Administration approval for once-daily dosing for treatment of HIV infection in antiretroviral–naive subjects. Cahn and colleagues presented data from a clinical trial comparing darunavir/r given 800 mg/100 mg once daily and 600 mg/100 mg twice daily in HIV-1-infected patients whose prior antiretroviral regimen was failing and who had no darunavir RAMs on genotypic testing (Abstract 57). All subjects received an optimized background regimen of 2 or more nRTIs. The 590 subjects underwent randomization. The treatment groups included 33% and 39% women and had a mean plasma HIV-1 RNA level of 4.1 $\log_{10}$ copies/mL and 4.2 $\log_{10}$ copies/mL and a median CD4+ cell count of 219/μL and 236/μL, respectively. Approximately 46% of subjects had no prior PI experience, and 85% of viruses were susceptible to all available PIs at baseline. The highest fold increase in darunavir susceptibility in any subject was 1.9.

The primary endpoint was the proportion of subjects with plasma HIV RNA level below 50 copies/mL at week 48. Once-daily dosing was noninferior to twice-daily dosing (72% vs 71%; 95% CI, −6% to 9%). There was no difference in response when stratifying by baseline plasma HIV-1 RNA level ($<$ 50,000 copies/mL and $\geq$ 50,000 copies/mL). The median trough darunavir concentrations in the once- and twice-daily groups were 1896 ng/mL and

3197 ng/mL, respectively. The once-daily group had lower elevations of triglyceride levels and total cholesterol levels than the twice-daily group.

Antiretroviral Treatment Strategies

Antiretroviral Therapy During Acute or Recent HIV-1 Infection

Hogan, speaking on behalf of the ACTG A5217 study team, investigated whether antiretroviral therapy given early in HIV-1 infection would preserve HIV-specific immune responses and lead to a lower viral load setpoint after antiretroviral therapy interruption (Abstract 134). Eligible subjects had recent (but not acute) HIV-1 infection, defined as positive for HIV-1 on enzyme-linked immunosorbent assay (ELISA) and Western blot testing, with a negative result either on ELISA or detuned ELISA or an indeterminate result on Western blot testing within the 6 months prior to randomization. Subjects were excluded if they had a CD4+ cell count below 350/µL or a plasma HIV-1 RNA level below 500 copies/mL. Subjects underwent randomization to either remain without antiretroviral therapy or to receive a 36-week course of antiretroviral therapy (lopinavir/r, tenofovir/emtricitabine) followed by treatment interruption. All subjects were observed for 96 weeks.

Of a planned sample size of 150, 130 were enrolled and had the following characteristics: 90% men; median CD4+ cell count of 540/µL; and median plasma HIV-1 RNA level of 4.4 $\log_{10}$ copies/mL. The primary endpoint was a plasma HIV-1 RNA level of 1 $\log_{10}$ copies/mL at week 72. The criteria for antiretroviral therapy initiation postrandomization were consistent with treatment guidelines at the time: primarily a CD4+ cell count below 350/µL. The Data and Safety Monitoring Board recommended early stoppage of the study based on the probability that the findings regarding the primary analysis presented below would persist and that no additional study goals would be achieved by continuing the study as currently designed. Investigators found that the mean viral load at week 72 of the treated group (36 weeks after antiretroviral therapy interruption) was lower than that of the untreated group at 72 or 36 weeks postrandomization (P = .005 and P = .002, respectively).

However, the authors noted that these data are difficult to interpret because many of the plasma HIV-1 RNA values in the untreated group were imputed due to the initiation of antiretroviral therapy before week 72. Indeed, among the 79 subjects with at least 72 weeks of follow-up at the time of analysis, 50% of the patients in the untreated group initiated antiretroviral therapy before week 72 compared with 10% reinitiating antiretroviral therapy in the group randomly assigned to initial treatment. The authors estimated that initial limited antiretroviral therapy during early HIV infection had delayed the need for subsequent antiretroviral therapy by approximately 16 weeks when excluding the initial 36-week course of antiretroviral therapy. The observed disease progression in the untreated group was much higher than expected and provides support for earlier initiation of antiretroviral therapy as currently recommended by major guidelines.

Raltegravir Intensification

Buzon and colleagues conducted a randomized, placebo-controlled trial in which raltegravir or placebo was added to a suppressive antiretroviral therapy regimen (Abstract 100LB). They randomly assigned 69 subjects receiving suppressive antiretroviral therapy to add raltegravir (n = 45) or placebo (n = 24) to their regimen for 48 weeks. No difference was found between groups in the amount of total HIV-1 DNA or integrated DNA in peripheral blood mononuclear cells (PBMCs) or in the plasma HIV-1 RNA level as measured by a single-copy assay. In the raltegravir group, 2-LTR circles increased 2 weeks and 4 weeks postinitiation and decreased thereafter. Theoretically, 2-LTR circles should increase during integrase strand transfer inhibition of active HIV-1 replication. The investigators did not find similar changes in the placebo group. In a post hoc analysis, subjects in the raltegravir group who had 2-LTR circles at some point during follow-up had higher baseline CD8+ cell activation that decreased with raltegravir. The authors concluded that this was evidence of ongoing productive replication in at least a subset of participants.

Two other single-arm studies examined the addition of raltegravir to a suppressive regimen. Yukl and colleagues reported on 7 subjects whose plasma, PBMC, and gut biopsy specimens (duodenum, ileum, colon, and rectum) were sampled before and after adding raltegravir (Abstract 279). Plasma HIV-1 RNA level, as measured by a modified ultrasensitive viral load assay, was not affected. The investigators did not find any definitive changes in HIV-1 DNA or RNA levels in the gut or PBMC specimens, except for a decrease of HIV-1 RNA in the ileum from 3438 copies to 682 copies per 10^6 CD4+ T cells. Interestingly, this decrease was associated with an increase in CD4+ T cells and a decrease in percent of CD38+HLA-DR+ in CD8+ T cells in the ileum, suggesting reduced virologic replication in this site. Weigand and colleagues enrolled 8 subjects with a history of prior virologic failure (mean of 4 prior failed regimens) who added raltegravir to their regimens for 4 weeks (Abstract 280). They found no effect on plasma HIV-1 RNA level as measured by the single-copy assay.

Addition of Enfuvirtide to an Initial Antiretroviral Regimen

Joly and colleagues compared CD4+ T-cell responses in those initiating antiretroviral therapy at a very low CD4+ cell count with or without the addition of enfuvirtide to a standard antiretroviral drug regimen (Abstract 282). CD4+ cell responses did not differ between groups, but more subjects receiving enfuvirtide had a plasma HIV-1 RNA level below 50 copies/mL 24 weeks postrandomization than did control subjects (74% vs 58%, respectively; P = .03). There did not appear to be appreciable differences in this parameter at 48 weeks.

Table 1. Selected Studies of Antiretroviral Therapy Intensification

Abstract No. Authors	Intensification Drug (sample size)	Duration of Intensification	Population	Design	Virologic Outcomes	Other Outcomes
Abstract 100LB Buzon et al	Raltegravir (n = 45) or placebo (n = 24)	48 weeks	HIV-1-infected adults with virologic suppression receiving antiretroviral therapy	Randomized, placebo-controlled trial	No difference between groups by HIV-1 single-copy assay	No difference in total HIV-1 DNA or integrated DNA in peripheral blood mononuclear cells or in plasma. 2-long-terminal-repeat circles increased in the raltegravir group at 2 weeks and 4 weeks postinitiation and decreased thereafter
Abstract 279 Yukl et al	Raltegravir (n = 7)	12 weeks	HIV-1-infected adults with virologic suppression receiving antiretroviral therapy	Single-arm, open-label trial for 12 weeks	No change in HIV-1 RNA or DNA in plasma, peripheral blood mononuclear cells, or gut biopsies except for decreased HIV-1 RNA level in the ileum	Change in HIV-1 RNA in the ileum was associated with locally decreased CD8+ cell activation
Abstract 280 Wiegand et al	Raltegravir (n = 8)	30 days	HIV-1-infected adults with current virologic suppression and history of prior virologic failure	Single-arm, open-label trial	No change in HIV-1 RNA observed in patients while receiving raltegravir, compared with periods before or after adding raltegravir	No change in CD4+ cell counts
Abstract 282 Joly et al	Enfuvirtide (n = 101) or control (n = 94)	48 weeks	HIV-1-infected adults with CD4+ cell count < 100/μL initiating antiretroviral therapy with and without enfuvirtide	Randomized, controlled, open-label trial	Higher rate of virologic suppression to < 50 copies/mL at week 24 with enfuvirtide (74% vs 58%; $P = .03$)	No difference in CD4+ cell responses between groups
Abstract 284 Gutierrez et al	Maraviroc (n = 9)	12 weeks	HIV-1-infected adults with virologic suppression, CD4+ cell count > 350/μL, R5 tropism prior to treatment	Single-arm, open-label trial	Increase in HIV-1 RNA level after 12 weeks by single-copy assay	Increase in 2-long-terminal-repeat circles, decrease in HLA-DR+/CD38+ in CD8+ cells
Abstract 285 Wilkin et al	Maraviroc (n = 32)	24 weeks	HIV-1-infected adults with current virologic suppression and poor immune response	Single-arm, open-label trial	Not assessed	Decrease in immune activation as assessed by CD38+, and HLA-DR+/CD38+ in CD4+ and CD8+ T cells

Maraviroc Intensification

Two studies examined the addition of maraviroc to a suppressive regimen. Gutierrez and colleagues enrolled 9 subjects with a CD4+ cell count above 350/μL, a prior sample showing CCR5-tropic virus, and suppressed plasma HIV-1 RNA level for at least 1 year (Abstract 284). The authors suggested that a decrease in the latent reservoir was seen: 6 of 9 patients had replication-competent virus detectable on at least 1 of 2 baseline measurements compared with 1 of 9 patients at week 12. An increase was seen in plasma HIV-1 RNA level as measured by a single-copy assay at week 12: 1 of 9 subjects had detectable virus at baseline compared with 6 of 7 subjects at week 12. An increase in 2-LTR circles was also shown: 0 of 9 subjects had HIV detected at baseline compared with 5 of 9 subjects at week 12. The percent of CD38+HLA-DR+ in CD8+ T cells at week 12 was decreased, suggesting decreased immune activation (5.4% vs 2.3%, respectively; $P = .08$).

Wilkin and colleagues presented results of ACTG A5256, a single-arm pilot trial of maraviroc intensification in patients with suboptimal immune response despite sustained virologic suppression (Abstract 285). They enrolled subjects with a CD4+ cell count below 250/μL, a calculated CD4+ slope of −20 cells/μL/year to +20 cells/μL/year, and an undetectable plasma HIV-1 RNA level for longer than 48 weeks before study entry. Subjects added maraviroc to their suppressive regimen for 24 weeks. The median increase in CD4+ cell count was 11/μL (90% CI, 1 – 22/μL). The lower bound did not exclude 20/μL, and the strategy was not considered successful. A statistically significant decrease in percent CD38+ and percent CD38+HLA-DR+ expression in both CD4+ and CD8+ T cells was noted, suggesting reduced immune activation. These studies of antiretroviral therapy intensification are summarized in Table 1.

Valproic Acid to Decrease Latent Reservoir

Valproic acid is an inhibitor of histone deacetylase in vitro. Persistence of latently infected CD4+ T cells is a major challenge for HIV eradication. The histone deacetylase inhibitors are of major interest to promote HIV transcription to render these infected cells susceptible to antiretroviral therapy. Routy and colleagues presented the results of a randomized, placebo-controlled, cross-over study of valproic acid (Abstract 496). The primary endpoint was a statistically significant reduction in the proportion of memory CD4+ T cells carrying HIV proviral DNA after 16 weeks of valproic acid or placebo. Eligible subjects were taking antiretroviral therapy for at least 12 months and had a plasma HIV-1 RNA level below 50 copies/mL and a CD4+ cell count of 200/μL or more. Fifty-six subjects were enrolled: 74% were men and the median CD4+ cell count was 537/μL. Twelve subjects did not complete the protocol. There was no difference in the primary endpoint between groups: 8 of 21 (38%) subjects taking valproic acid had a statistically significant reduction versus 7 of 18 (39%) subjects receiving placebo (P = .99). Similar results were found after the cross-over was completed.

Outcome Predictors in Resource-Rich Settings

Numerous abstracts evaluated predictors of clinical and immunologic outcomes in resource-rich settings (RRS). Sighem and colleagues presented data on rates of progression to death in HIV-infected patients who have not initiated antiretroviral therapy (Abstract 526). The study included 4612 patients from the ATHENA (AIDS Therapy Evaluation in the Netherlands) cohort who received a diagnosis of HIV infection between 1998 and 2007. The investigators compared mortality in HIV-infected patients who were antiretroviral therapy–naive 24 weeks after diagnosis with mortality in age- and sex-matched control subjects in the general population. The model assumed that after 24 weeks, individuals would initiate antiretroviral therapy at CD4+ cell counts of less than 350/μL.

Baseline characteristics were as follows: 80.4% men; country of birth was Western in 64.3%, sub-Saharan African in 15.5%, and other in 20.2%. The median CD4+ cell count at baseline was 480/μL, and 90.4% were asymptomatic. The final analysis included 4174 patients without an AIDS-defining condition 24 weeks after HIV infection diagnosis, and without a history of injection drug use (IDU). There were 17,580 person-years of follow-up. The mortality rate was 6.7 per 100 person-years. There were 118 deaths in the HIV-infected patients and 35 deaths in the matched control subjects. Prognostic variables associated with death included older age (HR, 1.07/year; 95% CI, 1.05 – 1.10), nonwestern country of birth (HR, 4.9; 95% CI, 2.3 – 10.4), and Centers for Disease Control and Prevention (CDC) stage B disease at 24 weeks (HR, 4.9; 95% CI, 2.1 – 11.5).

The expected median number of remaining life-years from age 25 years was 53.1 years in the general population and 52.7 years in the HIV-infected cohort. For those receiving a diagnosis at age 25 years, HIV infection was associated with 0.4 year of life lost; when diagnosed at age 55 years, HIV infection was associated with 1.3 years of life lost compared with the general population. More years of life were lost in HIV-infected women than men. The authors concluded that asymptomatic, HIV-infected patients who remain antiretroviral therapy–naive and have CD4+ cell counts above 350/μL at 6 months after diagnosis have life expectancies similar to those of the general population.

Lewden and colleagues performed a similar analysis comparing rates of death in HIV-1–infected patients receiving antiretroviral therapy with mortality rates in the general population (Abstract 527). Utilizing data from the COHERE (Collaboration of Observational HIV Epidemiological Research Europe) network of 25 European observational cohorts, the authors compared age- and sex-specific death rates among HIV-1–infected adults who received their first antiretroviral regimen after 1998. More than 80,000 patients in the cohort (85%) were eligible for analysis.

Baseline characteristics were as follows: 30% were women; median age was 37 years; 16% were IDU; and median CD4+ cell count was 225/μL. The median duration of follow-up was 3 years. Standardized mortality ratios (observed to expected mortality) were calculated according to CD4+ cell count strata and time spent with a CD4+ cell count of 500/μL or more. The standardized mortality ratios (SMRs) were higher in HIV-1–infected patients at all CD4+ cell count strata. However, the largest differences were observed in subjects with CD4+ cell counts below 200/μL and in women. Men with CD4+ cell counts of 500/μL or more at all time points had an SMR of 1.1 (95% CI, 0.8 – 1.3). IDUs of both sexes had substantially higher SMRs than those of non-IDUs at all CD4+ cell count strata. Although death rates in the COHERE patients did not differ by sex, SMRs were higher for women. The authors postulate that this difference may stem from socioeconomic status or other unmeasured confound-

ers. Even after 5 years at a CD4+ cell count stratum above 500/μL, HIV-infected women had an SMR of close to 2; in other words, a mortality rate twice as high as that for HIV-uninfected women in the general population. The authors concluded that HIV-infected men, but not women, achieve mortality rates similar to those of the general population.

Miro and colleagues presented data on clinical progression among persons receiving concomitant diagnoses of HIV and AIDS (Abstract 529). In this retrospective multicohort study of patients from Italy, Spain, the United Kingdom, and Canada, the authors examined the effect of timing of antiretroviral therapy initiation on prognosis in patients presenting with an AIDS-defining illness (ADI) at the time of HIV diagnosis. The primary outcome was clinical progression, defined as a new ADI or death.

The analysis included patients who received a diagnosis of HIV infection between 1997 and 2004 and had an ADI within 30 days before or 14 days after the HIV diagnosis. Immediate antiretroviral therapy was defined as being administered within 30 days of an ADI, whereas deferred antiretroviral therapy was defined as beginning between 31 days and 270 days after an ADI diagnosis. Deaths between days 0 and 30 were excluded from the analysis, but deaths occurring between days 31 and 270 were included. There were 429 subjects who met the criteria for inclusion: 77% men; 10% IDU; median age at diagnosis, 39 years; and median CD4+ cell count, 36/μL. ADIs included tuberculosis (TB) in 21.7%, *Pneumocystis jiroveci* pneumonia in 40.6%, Kaposi sarcoma in 13.9%, and lymphoma in 2.3%. PI-based therapy was used in 62.9% and NNRTI-based therapy in 28.2%. The median follow-up period was 2 years. Older patients and those with Kaposi sarcoma were more likely to start antiretroviral therapy earlier than other groups.

In the multivariate analysis, deferred treatment was associated with clinical progression (HR, 1.85; $P < .002$). Other factors associated with clinical progression in the multivariate analysis were as follows: lymphoma as the ADI (HR, 2.51; $P < .05$), age (HR per 5 years older, 1.10; $P = .02$), and viral load (HR per 1 $\log_{10}$ higher, 1.30; $P < .006$). The authors did not report the number of deaths, and they acknowledged that excluding deaths in the first 30 days of treatment renders the results applicable only to those surviving beyond 30 days. These data serve as observational support to the results of ACTG A5164 and suggest that antiretroviral therapy initiation proximal to the event of an ADI is associated with reduced mortality and new clinical events.

Palella and colleagues examined the relationship between baseline CD4+ cell count at antiretroviral therapy initiation and subsequent CD4+ cell count response and mortality (Abstract 983). Data from 1378 patients enrolled in the HOPS (HIV Outpatient Study) cohort who received antiretroviral therapy between 1996 and 2007 and had more than 6 months of follow-up while on antiretroviral therapy were included. The cohort consisted of 78.3% men; 33.6% black, 49.7% white, and 12.5% Hispanic. HIV transmission risk factors included 30.1% heterosexual, 56.2% men who have sex with men (MSM), and 6.5% IDU. Sixty percent carried private health insurance.

In the multivariate analysis, lower CD4+ cell count at the start of treatment was associated with a higher risk of death: for CD4+ cell counts below 50/μL at baseline, the HR was 4.6 (95% CI, 2.68 – 7.90) and for CD4+ cell counts between 50/μL and 199/μL, the HR was 2.6 (95% CI, 1.47 – 4.81) compared with those starting antiretroviral therapy at CD4+ cell counts above 200/μL. Having public health insurance was associated with a HR of death of 1.73 (95% CI, 1.11 – 2.70).

In the CD4+ cell count strata above 200/μL at treatment initiation, 76% of deaths were non–AIDS related. The median CD4+ cell count near death was 27/μL for persons with an AIDS-related death and 193/μL for those with non–AIDS related causes ($P < .001$). At 5 years of follow-up, the median CD4+ cell count of those starting with a pretreatment CD4+ cell count below 50/μL was 350/μL, and the median CD4+ cell count of those initiating therapy at a CD4+ cell count between 350/μL and 500/μL was 650/μL. At 5 years, 70% of patients whose CD4+ cell count was below 50/μL at baseline maintained CD4+ cell counts below 500/μL, compared with 20% of those starting antiretroviral therapy at CD4+ cell counts between 200/μL and 350/μL. The authors concluded that a lower CD4+ cell count at antiretroviral therapy initiation was associated with a lower long-term CD4+ cell count rise and increased mortality.

Many poster abstracts presented data on the relationship between low-level viremia and immunologic and clinical outcomes. In addition, several studies attempted to look at viral dynamics in patients with plasma HIV-1 RNA levels below the limit of detection who were receiving effective antiretroviral therapy.

Zhang and colleagues presented data on the impact of viremic episodes on CD4+ cell counts and non–AIDS-defining events in patients receiving suppressive antiretroviral therapy (Abstract 503). The subjects were 6440 patients selected from the ATHENA cohort. Inclusion criteria were as follows: taking initial therapy, plasma HIV-1 RNA level below 50 copies/mL by 48 weeks of antiretroviral therapy, and no history of non–AIDS-defining event. Subjects were censored at 1 year of treatment interruption. The authors defined 4 levels of viral outcomes: suppressed, low-level viremia (50 – 400 copies/mL), high-level viremia (> 400 copies/mL), and treatment interruption. Baseline characteristics were as follows: 75.3% men; median age, 39 years; median CD4+ cell count at start of treatment, 200/μL, and at viral suppression, 330/μL. Eighty-five percent of follow-up time was spent in virologic suppression. The authors noted higher rates of cardiovascular disease, but not renal or liver disease, in the high-level viremia group than in the suppressed group. These associations were independent of CD4+ stratum.

A large Canadian cohort showed higher mortality in patients with persistent low-level viremia (plasma HIV-1 RNA levels, 200 – 400 copies/mL

in 25% – 75% of measurements) than in patients with transient low-level viremia (< 25% of measurements with aforementioned parameters) (Abstract 504). However, mortality data for other viral load strata were not reported. Another study looked at subsequent virologic failure in patients with plasma HIV-1 RNA levels below 50 copies/mL (Abstract 505). The authors observed that an HIV RNA level between 40 copies/mL and 49 copies/mL was associated with a greater risk of subsequent virologic failure than were levels below 40 copies/mL.

Mavigner and colleagues compared residual viremia in 23 virologically suppressed patients with good versus poor immunologic responses (Abstract 307). The subjects had plasma HIV-1 RNA levels below 50 copies/mL while receiving antiretroviral therapy. Good immunologic response was defined as increases in CD4+ cell counts by more than 500/µL with treatment, whereas poor immunologic response was defined as gains of less than 200/µL. Quantification of residual viremia was performed with an ultrasensitive real-time polymerase chain reaction (RT-PCR) assay with a detectability range of 2.5 copies/mL. A nested RT-PCR was used to amplify the V3-loop of *env* to determine coreceptor use. Low-level viremia was detected in 13 of 23 patients, with higher levels (but not higher frequency) of residual HIV-1 RNA detected in poor than in good responders ($P < .05$). Residual viremia was associated with CD4+ cell activation in poor responders only. The authors also observed viral evolution to X4-tropic virus in these virologically suppressed subjects. No data on the clinical history of the patients were presented.

Antiretroviral Treatment in Resource-Limited Settings

Treatment Scale-up in Resource-Limited Settings

Antiretroviral therapy scale-up in RLS continued to be a focus at this year's conference. A number of plenary addresses and oral presentations emphasized the achievements and the gaps in antiretroviral therapy coverage in RLS. Fauci reported that approximately 4 million people in low- and middle-income countries were receiving antiretroviral therapy in 2008 (Abstract 19). This figure represents an exponential rise in antiretroviral therapy availability in RLS, from less than 1 million people receiving antiretroviral therapy as recently as 2002. However, the 4 million people now receiving antiretroviral therapy in RLS represent only 40% of those meeting guidelines for treatment initiation (ie, at a CD4+ cell count threshold of less than 200/µL). Fauci emphasized that with evolving guidelines recommending a treatment initiation threshold of less than 350/µL, only 30% of those meeting criteria for treatment in RLS are currently receiving antiretroviral therapy.

Delay of UNAIDS (The Joint United Nations Programme on HIV/AIDS) projected that 15 million people would meet criteria for antiretroviral therapy initiation in RLS under new treatment guidelines (ie, at a CD4+ cell count of 350/µL or below), accounting for nearly half of people living with HIV (Abstract 18). In a session dedicated to a discussion of the future of PEPFAR (President's Emergency Plan for AIDS Relief), Delay noted that $16 billion (US) has been committed to provide antiretroviral therapy in low- and middle-income countries (Session 4). In a session focusing on the global response to the HIV pandemic, Sow reviewed challenges and limitations of scale-up efforts, including low CD4+ cell counts at treatment initiation, use of initial regimens that have high levels of adverse effects, presence of coinfections, absence of plasma HIV-1 RNA monitoring, and limited options for second-line treatment (SLT) (Abstract 15).

Several qualitative and quantitative evaluations of antiretroviral therapy scale-up programs were presented. In Session 28, Ingle and colleagues presented data on mortality among patients awaiting antiretroviral therapy initiation after enrollment in a provincial treatment program in South Africa (Abstract 108). The study aims were to assess the cumulative proportion of patients starting antiretroviral therapy, as well as the cumulative mortality of those awaiting treatment initiation. The setting was an antiretroviral therapy program in the Free State Province of South Africa, where the antiretroviral therapy initiation eligibility threshold is a CD4+ cell count below 200/µL.

Approximately 22,000 patients were enrolled between 2004 and 2007 and observed until 2008. Sixty-four percent of subjects were women. The disposition of patients after 2 years of follow-up was reported as follows: 26% died before antiretroviral therapy initiation, 68% started treatment, and only 6% were alive and untreated. Risk of death was much higher at lower CD4+ cell count strata. For example, among those with pretreatment CD4+ cell counts of less than 25/µL, 46% of patients had died before initiating antiretroviral therapy.

In a model adjusted for baseline characteristics, factors associated with a lower likelihood of initiating antiretroviral therapy included male sex and a CD4+ cell count below 25/µL. Higher rates of pretreatment deaths were seen at lower CD4+ cell count strata, among men, and in older patients, even after adjusting for likelihood of antiretroviral therapy initiation. The median CD4+ cell count at eligibility to initiate therapy was 101/µL, because of a median time of 183 days between CD4+ cell count measurements. Causes of death were not described in the presentation. The presentation highlighted the substantial loss of life in those awaiting antiretroviral therapy initiation; the authors suggested that guidelines raising the CD4+ cell count treatment threshold would lead to earlier access and may reduce pretreatment mortality.

Serenata and colleagues evaluated progress toward meeting the September 2009 PEPFAR-South Africa target of providing antiretroviral therapy to 456,571 patients (Abstract 828). The authors also looked at rates of antiretroviral therapy continuation within the program. In June 2005, 120,904 patients were receiving antiretroviral therapy under the program. The authors report that by September 2009, 646,972 patients were receiving treatment, representing a 435% increase in

coverage, exceeding the set target by 42%. Sixty-seven percent of patients were women. Of those who initiated treatment, 4.4% died, 8.0% were LTFU, 1.4% stopped treatment, and 1.1% had an unknown status. The overall rate of antiretroviral therapy continuation was 77%. Government-run treatment sites showed a slightly higher rate of continuation than did private clinics or those managed by nongovernment organizations. Overall, rates of coverage and continuation were excellent and exceeded set targets.

Primary Treatment Outcomes in Resource-Limited Settings

Five-year follow-up data from the DART (Development of Antiretroviral Therapy) trial in Africa trial were presented by Munderi and colleagues (Abstract 110). DART is a randomized trial of 2 strategic approaches to antiretroviral therapy management—a clinically driven approach and a laboratory-enhanced monitoring strategy. The data presented in this session pertained to treatment outcomes in 3316 adults enrolled in the study in Uganda and Zimbabwe. Patients were included if they were antiretroviral therapy–naive with advanced immune deficiency by clinical staging and had a CD4+ cell count below 200/μL. Median pretreatment CD4+ cell count was 86/μL, with one-third of subjects having a CD4+ cell count below 50/μL. All subjects received zidovudine/lamivudine with the following distribution of the third drug: tenofovir in 74%, nevirapine in 16%, and abacavir in 9%.

The authors presented data on immune restoration and the estimated time to attainment of prespecified CD4+ cell count stratum change in subjects remaining on the initial regimen. The median follow-up time was 4.7 years. At follow-up, 301 patients had died, 108 were LTFU, and 697 switched to a second regimen. Of those patients remaining on initial therapy at 5 years, 69% ever achieved a CD4+ cell count above 250/μL, 46% ever achieved a CD4+ cell count above 350/μL, and only 19% ever achieved a CD4+ cell count above 500/μL. The authors note that, even in subjects with the highest baseline CD4+ cell counts (150 – 200/μL), less than 75% achieved CD4+ cell counts above 350/μL.

Using receiver operating characteristic analysis, the authors sought to determine a CD4+ cell count threshold at 1 year of treatment that would predict failure to attain a CD4+ cell count above 250/μL at 5 years. This analysis identified a CD4+ cell count cut-off of less than 125/μL as having the best operating characteristics for predicting failure to attain the prespecified threshold. The operating characteristics were as follows: specificity, 93%; sensitivity, 42%; positive predictive value, 74%; and negative predictive value, 78%. The rate of CD4+ cell count increase did not identify those who would attain a CD4+ cell count above 250/μL. Once again, these data suggest that treatment at higher CD4+ cell count thresholds would be associated with more robust restoration of immunologic parameters.

Renaud-Thery and colleagues presented a systematic review of the literature on antiretroviral therapy outcomes in cohort studies in RLS (Abstract 827). Inclusion criteria were publications reporting on antiretroviral therapy–naive subjects prescribed WHO-defined initial regimens. Outcomes of interest included treatment failure and attrition rates. Failure was defined using WHO criteria for clinical, immunologic, and virologic failure (for definitions, see Evaluation of World Health Organization Clinical and Immunologic Criteria for Treatment Failure of Antiretroviral Therapy below). Attrition was defined as death, LTFU, transfer, or discontinuation. Retention was defined as alive and taking any antiretroviral therapy. A total of 804 citations were identified, representing 124,491 patients. Five studies were cross-sectional, with the remainder being observational cohorts. Sixty-six percent of studies reported data from Africa. Overall the clinical and immunologic failure rate was 1.9 per 100 person-years, and the virologic failure rate was 6.08 per 100 person-years. Attrition rate was 19.6 per 100 person-years. Failure and attrition rates were higher in Africa than in Latin America and Asia. The authors urged cautious interpretation of the results because of the heterogeneity of the studies included.

Cortes and colleagues presented national data on 3045 patients receiving initial antiretroviral therapy since 2001 in Chile's expanded access antiretroviral therapy program (Abstract 523). In this cohort, 84.7% of patients were men, and the median age was 36.9 at enrollment. Outcome measures included mortality, LTFU, switch of initial regimen, viral suppression, and immune recovery over the first 4 years of treatment. At 48 months, 84.2% remained enrolled in the program. Of those, 86% achieved a plasma HIV-1 RNA level below 400 copies/mL, and 81% achieved a level below 80 copies/mL. Eleven percent had died, and 4.3% were LTFU. NNRTI-based regimens were used by 64% of patients, and indinavir-based regimens by 15%. At 48 months, 60% of patients remained with their initial regimen. The most common cause for regimen switch was an adverse event. At 48 months, the median CD4+ cell count was 350/μL.

Chinh and colleagues looked at mortality and treatment durability in 889 patients starting an initial antiretroviral regimen at a hospital-based site in Vietnam (Abstract 517). Seventy-seven percent of patients were men, 80% were IDUs, and 51% had WHO stage 3 or 4 disease at baseline. The baseline median CD4+ cell count was 122/μL, and 77% had prior antiretroviral therapy exposure (although the authors do not characterize past regimens). Median duration of treatment was 10 months, with all patients receiving NNRTI-based therapy.

The following outcomes were observed: 5% of patients died, 4% were LTFU, 2.1% had treatment failures and 1.2% transferred care. At 1 year, 88% of participants were still in follow-up and on initial antiretroviral therapy. Not surprisingly, advanced disease at baseline was predictive of subsequent death. No difference in the probability of regimen switch was observed between the antiretroviral–naive and –experienced groups. In this mostly pretreated cohort with a majority re-

porting IDU, high rates of retention in care and low rates of treatment failure were reported.

Outcome Predictors in Resource-Limited Settings

Many poster presentations examined predictors of treatment outcomes in RLS. Fox and colleagues presented data on outcomes in patients initiating antiretroviral treatment at different CD4+ cell count strata in a prospective cohort of 812 patients in the CIPRA-SA (Comprehensive International Programme for Research on AIDS – South Africa) trial (Abstract 521). This randomized, controlled trial compared physician-monitored with nurse-monitored HIV care in South Africa. The trial enrolled antiretroviral treatment–naive adults with a CD4+ cell count below 350/μL or a previous ADI. Ninety-two percent of subjects received NNRTI-based therapy for a maximum follow-up period of 252 weeks. No differences were found between the physician- and nurse-monitored groups.[5]

The authors now presented data on treatment outcomes in 2 nonrandomized groups of patients: those who started treatment at CD4+ cell counts below 200/μL, and those who started treatment at CD4+ cell counts between 200/μL and 350/μL. Outcome measures included treatment failure (defined as death or virologic failure), incident TB, and program failure (defined as patients with more than 3 missed visits). At baseline, and by definition, patients in the low CD4+ cell count group had more advanced disease, but no other differences were noted in age, sex, or treating practitioner. Adjusted HR for death or virologic failure was 2.13 (95% CI, 1.3 – 3.6) in the CD4+ cell count group below 200/μL compared with those in the group above 200/μL. The HR for death was 5.39 (95% CI, 1.26 – 22) between the low- and high-CD4+ cell-count groups (the authors did not report on adjustments made). The adjusted HR for incident TB was 2.59 (95% CI, 1.28 – 5.26) in the lower compared with the higher CD4+ cell count strata (although data presented in the Kaplan-Meier analysis showed less follow-up time in the higher CD4+ cell-count stratum). In total, these data provide observational support to current WHO guidelines for initiation of antiretroviral therapy.

Takuva and colleagues explored the relationship between initial CD4+ cell count response and subsequent survival in adults receiving initial antiretroviral therapy in a public sector clinic in South Africa (Abstract 520). Patients treated with an initial regimen between 2004 and 2009 and who achieved a plasma HIV-1 RNA level below 400 copies/mL by 6 months of treatment were included in the analysis. The authors defined 2 response groups: those with and those without an increase in CD4+ cell count of more than 50/μL at 6 months of treatment. Outcome measures included death, ADI, and a composite outcome of death and ADI. More than 6000 patients were included in the analysis. An increased risk of death, ADI, and composite death and ADI was observed in the group with a CD4+ cell count gain of less than 50/μL at 6 months, despite virologic suppression. The HR for death was 1.95 (95% CI, 1.25 – 3.04) between the group without and the group with gains of at least 50/μL. The analysis controlled for age, sex, baseline CD4+ cell count, hemoglobin (hgb) level, and TB treatment status.

May and colleagues created a prognostic model for predicting mortality during the first year of antiretroviral therapy in sub-Saharan Africa (Abstract 815). Using data from more than 10,000 patients enrolled in antiretroviral therapy scale-up programs in Cote d'Ivoire, Malawi, and South Africa, the authors created 2 models predictive of mortality: a CD4+ cell-count inclusive model, and a model based on hgb level and total lymphocyte count (TLC). Both models also incorporated the variables of age, sex, WHO stage 3 or 4 disease at baseline, and body weight. The baseline characteristics of the cohort were 68% women; median age, 34 years; 85% with advanced disease, and median pretreatment CD4+ cell count, 111/μL. During the first year of follow-up, 8.2% of patients died. Observed and predicted mortality tracked closely with one another. Both models predicted mortality accurately, and the hgb-TLC model predicted mortality as accurately as did the CD4+ cell-count–based model. The authors plan to make the model available as a Web-based calculator at www.iedea-sa.org.

Another approach to outcome prediction was presented by Koethe and colleagues, who looked at pretreatment body mass index (BMI) and subsequent mortality and CD4+ cell count gains (Abstract 819). More than 33,000 adults in Zambia who initiated antiretroviral therapy between 2004 and 2009 were included in the analysis if they had received antiretroviral therapy for at least 6 months and had a CD4+ cell count measurement at 6 months of treatment. The cohort was stratified according to WHO categories for malnutrition based on pretreatment BMI.

Sixty-two percent of patients were women, median age was 35 years, and median BMI was 20.1 kg/m^2. At baseline, median CD4+ cell count was 142/μL, 13% of patients had active TB, and 37.2% had WHO stage 1 or 2 disease. No statistically significant difference was found in CD4+ cell count gains at 6 months among the different BMI strata. However, the risk of death was statistically significantly higher in malnourished individuals unable to achieve a gain in CD4+ cell count of at least 100/μL. The highest risk of death by BMI stratum was in subjects with a baseline BMI below 16 kg/m^2 (severely malnourished) and a decline in CD4+ cell count at 6 months, with an HR of death of 6.08 (95% CI, 3.59 – 10.3). All analyses were adjusted for age, sex, baseline hgb level, WHO clinical stage, TB infection, initial antiretroviral therapy regimen, and adherence. The synergistic relationship between nutritional status (BMI), low CD4+ cell count gain, and mortality underscores the importance of integrating nutritional support and food security into health systems providing antiretroviral therapy.

Two studies found a relationship between clinic attendance and mortality. Brennan and colleagues conducted a retrospective analysis of 7788 adults initiating antiretroviral therapy in South Africa (Abstract 821). All pa-

tients were antiretroviral therapy–naive at baseline and attended clinic for at least 6 months after antiretroviral therapy initiation. A 2-fold increase in mortality was observed in patients missing more than 1 visit in the first 6 months of treatment. A similar but much larger study in a RRS looked at the relationship between early missed visits and mortality in China (Abstract 822). Twenty-seven thousand antiretroviral treatment–naive adults initiating antiretroviral therapy were included: 61% were men, median age was 38.6 years, and baseline CD4+ cell count was 126/μL. After adjustments for numerous variables, any missed visit in the first 6 months was associated with an increase in mortality over 60 months of observation. Missing 3 or more visits was associated with a HR of death of 1.72 (95% CI, 1.36 – 2.16).

Two posters compared treatment outcomes in RLS and RRS. Geng and colleagues compared the immunologic efficacy of antiretroviral therapy in a North American setting with that of an African treatment setting (Abstract 518). A total of 8457 patients contributed a median of 2.2 years of observation. Patients included in the analysis had a baseline CD4+ cell count below 350/μL and had achieved a plasma HIV-1 RNA level below 1000 copies/mL within 1 year of treatment. Baseline characteristics differed between African and North American sites in sex (68% and 19% women, respectively) and baseline CD4+ cell count (122/μL and 161/μL, respectively). At 36 months, African patients showed slight but statistically significantly greater gains in CD4+ cell counts than those of their North American counterparts. The authors commented, however, that an opposite trend was seen in the first year of treatment and postulate that comorbid infections in the African setting may have contributed to the slower gains. There was no mention of the impact of baseline characteristics on the findings.

Wester and colleagues compared rates of non–AIDS-defining events in patients receiving antiretroviral therapy in Botswana and the United States (Abstract 726). Baseline characteristics differed between the Botswana and US groups with respect to sex (69% and 26% women, respectively), ethnicity (100% and 36% black, respectively), BMI (21.3 and 24.5 kg/m^2, respectively), and median CD4+ cell count (199/μL and 243/μL, respectively). Non–AIDS-defining events were adjudicated by an endpoints committee in Botswana and by *International Classification of Diseases, Ninth Revision (ICD-9)* code extraction in the United States. Crude incidence of non–AIDS-defining events was 9.99 per 100 person-years in Botswana and 12.2 per 100 person-years in the United States. Higher rates of hepatic and renal disease were observed in the United States whereas higher rates of malignancies were observed in Botswana. There was higher mortality in African patients.

A number of abstracts looked at HIV treatment outcomes in patients coinfected with the viral hepatidites. Chadwick and colleagues examined HIV treatment outcomes in HIV monoinfected and HIV-HBV coinfected patients receiving antiretroviral therapy in Ghana (Abstract 690). Prevalence of HBV coinfection at the treatment site was 17%. No differences were observed in clinical, immunologic, or virologic HIV treatment outcomes between the mono- and coinfected groups. Because most patients were receiving de facto HBV monotherapy with lamivudine as part of their antiretroviral regimen, the authors performed HBV genotypic analysis in a subset of coinfected patients. They found 18% of their HBV sample to have lamivudine RAMs.

On the other hand, Christian and colleagues showed slower rates of immune recovery in nearly 5000 HIV-infected patients coinfected with either HBV or HCV and receiving antiretroviral therapy through PEPFAR-supported sites in Tanzania (Abstract 694). Nguyen and colleagues conducted a retrospective review comparing mortality in HIV monoinfected and HIV-HCV coinfected patients receiving antiretroviral therapy in Vietnam (Abstract 817). Almost 2000 patients treated between 2005 and 2008 were included in the analysis. Twenty-seven percent were coinfected. Coinfected individuals were more likely than HIV-monoinfected patients to be men, have a history of IDU (76% and 33%, respectively), and have higher baseline CD4+ cell counts (79/μL and 71/μL, respectively) and alanine aminotransferase levels. At a median follow-up of 15.7 months, 14% of the sample had died, and 5.2% were LTFU. LTFU was more frequent in coinfected patients, even after controlling for IDU status. There were no differences in mortality between the groups. CD4+ cell counts at follow-up did not differ between the groups, but monoinfected individuals had larger CD4+ cell count gains. The duration of follow-up in this study was likely too short to observe differences in mortality.

Outcomes of Second-Line Therapy in Resource-Limited Settings

There was a paucity of data on second-line treatment outcomes in RLS. Pujades-Rodriguez and colleagues presented mortality and virologic outcome data in patients receiving SLT at 27 Medecins sans Frontieres–supported sites (Abstract 524). Adults (n = 632) who were antiretroviral therapy–naive at treatment initiation, received NNRTI-based initial treatment, were subsequently switched to PI-containing SLT, and had at least 6 months of follow-up while receiving SLT were included in the analysis. All programs had routine CD4+ cell-count monitoring, and 4 sites tested for plasma HIV-1 RNA level. SLT failure was defined using 2006 WHO criteria for clinical, immunologic, and virologic failure. The primary outcome was SLT failure and mortality after 6 months of treatment. Median follow-up time with SLT was 35 months.

Nineteen percent of subjects met any criteria for treatment failure, 5% had died, and 4% were LTFU. Factors associated with SLT failure included lower CD4+ cell count at start of SLT; factors inversely associated with failure included hospital-based setting (compared with health care center), changing more than 1 nRTI at time of switch to SLT (compared with a switch of 1 nRTI), and use of lopinavir/r (com-

Table **2.** Selected Studies on Antiretroviral Treatment Outcomes in Resource-Limited Settings

Abstract No. Study Title	Research Question or Aim	Study Design (no. participants) Participating Locations	Findings
Abstract 153LB. Efficacy of ART with NVP + TDF/FTC vs LPV/r + TDF/FTC Among Antiretroviral-Naive Women in Africa: OCTANE Trial 2/ACTG A5208	Is there equivalence in efficacy between nevirapine + tenofovir/emtricitabine and lopinavir/r + tenofovir/emtricitabine in ART-naive women without exposure to sdNVP as part of PMTCT?	Randomized, controlled, open-label equivalence study (n = 500) South Africa	For primary endpoint of death or virologic failure, HR was 0.82 comparing nevirapine to lopinavir/r both in combination with tenofovir/emtricitabine; this finding met prespecified criteria for equivalence
Abstract 110. Immune Restoration Over 5 Years on ART Among Patients Initiating Treatment With Advanced Immune Deficiency in the DART Trial in Uganda and Zimbabwe	What are the CD4+ cell count attainments in persons with a pretreatment CD4+ count < 200/µL who initiate ART in Africa?	Parent study (DART) is a randomized, controlled trial comparing clinical versus laboratory-driven monitoring of HIV-infected patients initiating ART. Current analysis presents observational data on CD4+ cell count stratum attainment (n = 3316) Uganda, Zimbabwe	At median follow-up of 4.7 years, 66% of subjects remained on initial regimen 69% ever achieved a CD4+ cell count > 250/µL 19% ever achieved a CD4+ cell count > 500/µL A pretreatment CD4+ cell count threshold < 125/µL was most predictive of failure to achieve CD4+ cell count > 250/µL
Abstract 827. Adult ART in Resource-Limited Settings: A Systematic Review of First-Line Treatment Failure and Attrition Rates	To perform a systematic review of the literature on initial ART outcomes in resource-limited settings	Meta-analysis of published data on outcomes in ART-naive subjects receiving initial therapy in resource-limited settings (n = 804 citations reflecting 124,491 subjects) Africa, Latin America, Asia	Primary outcome was treatment failure as defined by WHO criteria Clinical and immunologic failure rate: 1.9/100 person-years Virologic failure rate: 6.08/100 person-years Attrition rate (including death, loss to follow-up, transfer, or discontinuation): 19.6/100 person-years
Abstract 521. Effect of Initiating Patients on HAART at CD4 Counts Above 200 on Virologic Failure and Death in South Africa: Evidence from the CIPRA-SA Trial	Are there differences in treatment outcomes in ART-naive adults initiating therapy at CD4+ cell counts < 200/µL vs < 350/µL?	Parent study (CIPRA-SA) was a randomized, controlled trial comparing nurse- versus physician-monitored care; current analysis compared 2 nonrandomized groups of patients: those who initiated ART at a CD4+ cell count < 200/µL and those who initiated at a CD4+ cell count between 200/µL and 350/µL (n = 812) South Africa	Primary outcome measures included treatment failure, incident TB, and loss to follow-up Comparing the CD4+ cell count < 200/µL group with the < 350/µL group, HRs were: Death or virologic failure, adjusted HR = 2.13 Death, unadjusted HR = 5.39 Incident TB, adjusted HR = 2.59
Abstract 524. Failure to Second-Line Therapy and Associated Mortality in 27 MSF-Supported African and Asian ART Programs	To determine treatment outcomes in HIV-infected patients receiving second-line ART in resource-limited settings	Retrospective analysis of patients receiving second-line ART in Médecins sans Frontières–supported clinical sites (n = 632) Africa, Asia	Primary outcome was treatment failure as defined by WHO criteria. At median follow-up of 35 months, 19% met any criteria for failure, including 5% who had died Treatment failure was associated with lower CD4+ cell count, use of nelfinavir (compared with lopinavir/r), and switch of 1 nRTI (compared with switch of 2 nRTIs) at time of switch to second-line therapy

ACTG indicates AIDS Clinical Trials Group; ART, antiretroviral therapy; CIPRA-SA, Comprehensive International Programme for Research on AIDS–South Africa; DART, Development of Antiretroviral Therapy; FTC, emtricitabine; HAART, highly active antiretroviral therapy; HR, hazard ratio; LPV, lopinavir; MSF, Médecins sans Frontières; nRTI, nucleoside analogue reverse transcriptase inhibitor; NVP, nevirapine; OCTANE, Optimal Combination Therapy After Nevirapine Exposure; PMTCT, prevention of mother-to-child transmission; /r, ritonavir-boosted; sdNVP, single-dose nevirapine; TB, tuberculosis; TDF, tenofovir; WHO, World Health Organization

pared with nelfinavir). Mortality was strongly associated with immunovirologic failure, but all types of WHO failure criteria were associated with an increased risk of death. The authors commented that rates of failure of SLT were 46% higher than those of initial antiretroviral therapy, but did not present these data. This study and others presented on treatment outcomes in RLS are summarized in Table 2.

Evaluation of WHO Clinical and Immunologic Criteria for Treatment Failure of Antiretroviral Therapy

The 2006 WHO definition of treatment failure includes clinical, immunologic, and virologic criteria. Clinical treatment failure is defined as new stage 3 or 4 events after 6 months of treatment. Immunologic failure is defined as any of the following: CD4+ cell count decrease to pretherapy baseline level, a CD4+ cell count consistently below 100/μL, or a 50% fall from pretreatment peak after 1 year of treatment. Virologic failure is defined as a plasma HIV RNA level above 10,000 copies/mL after 6 months of treatment.

A number of presentations evaluated the accuracy of the clinical and immunologic WHO failure criteria in predicting virologic failure. Rawizza and colleagues presented data assessing the performance of immunologic criteria in predicting virologic failure in the Harvard–PEPFAR treatment program (Abstract 111). All patients undergo CD4+ cell count and plasma HIV-1 RNA measurements at baseline, at 3 months and 6 months, and every 6 months thereafter. In this study, virologic failure was defined as 2 consecutive plasma HIV-1 RNA measurements above 1000 copies/mL after at least 6 months of antiretroviral therapy. The analysis included 9690 antiretroviral therapy–naive adults. The median follow-up time was 33 months. Virologic failure was observed in 25.9% and immunologic failure in 32.2%. WHO CD4+ cell count failure criteria had a sensitivity of 54.9% and specificity of 75.7%, a positive predictive value of 44.2%, and a negative predictive value of 82.7% for virologic failure. In other words, CD4+ cell count criteria missed 45.1% of virologic failures and misclassified 44.2% as failures that were in fact virologically suppressed. Furthermore, plasma HIV-1 RNA level monitoring identified failure earlier than immunologic criteria by a mean of 4.2 months ($P < .001$).

Further data on the poor predictive value of immunologic criteria for predicting virologic failure were presented by Eisenberg in a cross-sectional study from a Medecins sans Frontieres–supported treatment site in Kenya (Ferreyra et al, Abstract 816). Included in the analysis were 926 antiretroviral therapy–naive adults who were initiated on treatment with NNRTI-based therapy and had a follow-up period of at least 12 months. The cohort consisted of 67.3% men, with a median age at treatment initiation of 38 years and baseline CD4+ cell count of 133/μL. At 12 months, 83.9% of participants had a plasma HIV-1 RNA level below 400 copies/mL. At a median follow-up time of 38 months, 13.3% of patients experienced clinical failure, 5.7% immunologic failure, and 4.7% virologic failure. The sensitivity of immunologic and clinical criteria for diagnosing virologic failure was 23.6% and 18.2%, respectively; the specificity was 95.4% and 87%, respectively; and the positive predictive value was 24.5% and 8.1%, respectively. The use of the 2006 WHO definition of virologic failure (plasma HIV-1 RNA level > 10,000 copies/mL) would have led to an underestimation of more strictly defined criteria for virologic failure and may have falsely lowered the positive predictive value.

Laboratory Monitoring in Resource-Limited Settings

Chaiwarith and colleagues compared antiretroviral therapy outcomes in Thai patients undergoing once–versus twice–yearly monitoring of plasma HIV-1 RNA level as part of routine care (Abstract 500). The retrospective cohort analysis included 578 patients receiving antiretroviral therapy at a single hospital center in Thailand. Outcome measures included the incidence of virologic failure, time to virologic failure, and reverse transcriptase resistance mutations at failure. Virologic failure was defined as a plasma HIV-1 RNA level above 1000 copies/mL. In this cohort, 46.2% were men, the median age at baseline was 40 years, and baseline CD4+ cell count was 60/μL. Ninety-seven percent were receiving NNRTI-based therapy. Once-yearly plasma HIV-1 RNA level monitoring was performed in 73.4%, whereas twice-yearly monitoring was performed in 26.6%. There were no baseline differences in the monitoring groups with respect to age, sex, or first antiretroviral regimen.

At 7 years of follow-up, the incidence of virologic failure was 4.32 per 100,000 person-days in the once-yearly HIV-1 RNA monitoring group and 3.08 per 100,000 person-days in the twice-yearly group, ($P = .43$). Mutation rates between the groups did not differ. Virologic failure was highly associated with adherence rates of less than 95% (actual adherence rates were not reported). The authors concluded that in settings with high adherence rates, frequency of plasma HIV-1 RNA level monitoring does not affect rates of virologic failure. The authors did not comment on the timing of HIV-1 RNA measurements in the course of treatment.

Walker and colleagues presented additional data on the impact of laboratory monitoring and treatment outcomes in the DART trial (Abstract 56) (see "Primary Treatment Outcomes in Resource-Limited Settings" above). Briefly, antiretroviral therapy–naive adults with advanced disease underwent randomization to 1 of 2 monitoring approaches: a laboratory and clinical monitoring (LCM) group, which included routine monitoring of biochemistry parameters and CD4+ cell count, and a clinically driven monitoring (CDM) group, for which CD4+ cell counts were not available in real time and biochemistry analysis for toxicity was performed only when clinically indicated.

There was no difference in mortality between the 2 monitoring approaches in the first 2 years of follow-up, but after 2 years, the LCM group showed lower rates of death.

The current analysis tried to explain the difference in mortality. After 2 years of treatment, subjects in the CDM group spent more time with CD4+ cell counts below 200/μL than did those in the LCM group (39% versus 33% of follow-up time, respectively). No difference in risk of death at a given CD4+ cell count was observed between groups. However, more WHO-defined stage 4 events were observed in the CDM subjects but only at *higher* CD4+ cell counts.

Why was this counterintuitive relationship observed? The authors argue that the different rates of WHO stage 4 events between the CDM and LCM groups at higher CD4+ cell counts was due to an underestimation of events in the LCM subjects. In other words, the authors hypothesize that knowledge of a high CD4+ count in the LCM subjects led to a CD4+-dependent underreporting bias of WHO stage 4 events. They argue that this bias may have important implications for the measurement of outcomes in open-label randomized and observation studies.

Resistance in Resource-Limited Settings

Dlamini and colleagues investigated the prevalence and type of RAMs in patients in South Africa receiving initial antiretroviral therapy and who achieved virologic suppression and had a subsequent viral load rebound (Abstract 589). The authors also looked at virologic and immunologic responses of patients after viral rebound. The data were obtained from a subgroup of the South African Phidisa II trial subjects, which compared 4 different antiretroviral drug regimens in treatment-naive individuals with advanced HIV disease. In the parent Phidisa II study, 1771 subjects were enrolled and underwent randomization to receive efavirenz or lopinavir/r and zidovudine plus didanosine or lamivudine plus stavudine.

Included in this resistance substudy are 73 patients who met virologic failure criteria (plasma HIV-1 RNA level > 1000 copies/mL on 2 consecutive visits) after achieving viral suppression at 6 months of treatment. Of the 73 patients, 68 had genotypes available. At the time of virologic failure, 30 patients were receiving efavirenz-based regimens, and 31 were receiving lopinavir/r-based regimens (the remainder were not receiving antiretroviral therapy). In patients taking an efavirenz-based regimen at treatment failure, 56.7% had any reverse transcriptase mutations, and 36.7% had both NNRTI and nRTI RAM. In the lopinavir/r group, 16.1% had any reverse transcriptase mutations, but no PI RAMs were observed. The most common RAMs observed were K103N and M184V. Thirty-three percent of patients had no RAMs at failure.

Saravanan and colleagues looked at resistance mutations among patients in India for whom SLT was failing (Abstract 592). The study was a cross-sectional analysis of 107 patients receiving PI/r-based SLT in a setting the authors describe as having limited virologic monitoring. All patients with a plasma HIV-1 RNA level above 1000 copies/mL underwent genotypic analysis. The group consisted of 75% men, the mean age was 35 years, and 97% reported heterosexual risk factors. The median CD4+ cell count at failure was 146/μL, and the mean duration of PI exposure was 13 months. Fifty-one percent were receiving atazanavir/r, 46% indinavir/r, and 3% lopinavir/r. The nRTI backbone was tenofovir/emtricitabine in 55%, didanosine plus lamivudine in 24%, and zidovudine or stavudine with lamivudine in 21%.

Of the 107 patients, 45 (42%) experienced virologic failure, and 100% of those had any RAM at failure. Seventy-three percent had PI resistance mutations, 91% had nRTI resistance mutations, 73% had NNRTI resistance mutations, and 53% showed triple-class resistance. The rates of failure and RAMs reported in this analysis were far higher than described in the literature, especially with ritonavir-boosted, PI-based regimens. No data were provided regarding the treatment history of the patients included in the analysis. At failure, most patients were sensitive by phenotype to darunavir/r, but less than 50% were sensitive to lopinavir/r, suggesting the possibility of unreported PI exposure before current SLT.

Rosen and colleagues presented a Markov model comparing the cost-effectiveness of 2 initial therapy switch strategies: a viral load–based strategy, and a strategy incorporating viral load and resistance testing (Abstract 823). The models utilized clinical and cost data derived from a large clinical cohort in South Africa. In the viral load–based model, all patients with confirmed virologic failure are switched to SLT. In the model incorporating resistance testing, patients with virologic failure undergo genotypic analysis, but only patients with RAMs at failure are switched to SLT. The model assumed low failure rates and a 16% rate of RAMs at initial treatment failure. Modeling predicted that at 5 years, 20% of subjects experienced virologic failure. At this rate, resistance testing was found to be cost-saving, with approximately $33 (US) saved per patient. Interestingly, there was no statistically significant difference in switch rates to SLT between the strategies, with 20% and 17% switching in the viral load–versus the resistance-based strategy, respectively. In the sensitivity analysis, decreasing the rates of resistance at failure increased cost-savings, presumably because of lower rates of switch to SLT. The authors conclude that incorporating resistance testing into treatment algorithms in Africa will be either cost-saving or cost-neutral.

Mother-to-Child Transmission of HIV Infection

Incident HIV Infection During Pregnancy

Kinuthia and colleagues determined factors associated with incident HIV-1 infections during pregnancy and the postpartum period among women who brought their infants for 6-week routine vaccinations at maternal-child health clinics in Nairobi and Kenya (Abstract 155). Women who had tested HIV-seronegative during the antenatal period were evaluated. These women completed a questionnaire and received HIV testing. Acceptability of HIV testing was high (95.3%). Fifty-three (2.6%) of 2035 women who ac-

cepted HIV testing were HIV-seropositive, with a relatively high HIV-infection incidence of 6.8 per 100 person-years. On multivariate analysis, HIV seroconversion was statistically significantly associated with employment and residence in a high-HIV-prevalence region. Other factors such as age, marital status, education level, and economic well-being were not associated with seroconversion.

Six-Week Extended Nevirapine Studies

Twelve-month follow-up data from the SWEN (Six-Week Extended Nevirapine) Studies were presented by Bedri and colleagues (Abstract 157). The SWEN trials consisted of 3 randomized controlled studies in Ethiopia, India, and Uganda comparing extended-dose nevirapine through 6 weeks of age with single-dose nevirapine to prevent HIV transmission from HIV-infected mothers to their infants through breastfeeding. Six-week and 6-month data from these trials have been presented previously.[6,7] A total of 1890 infants were included: 903 in the SWEN (extended-dose) group and 987 in the single-dose group. Three 12-month endpoints were analyzed: HIV transmission, cumulative mortality, and a combined outcome of HIV transmission or mortality. No statistically significant difference in HIV transmission at 12 months was observed between the 2 groups (8.9% in the extended-dose group vs 10.4% in the single-dose group). Infants in the extended-dose group had a 47% lower cumulative mortality at 12 months than did those in the single-dose group. When stratified by maternal CD4+ cell count, mortality and the combined outcome of HIV transmission or mortality were lower among infants whose mothers had a CD4+ cell count of at least 350/μL.

Nevirapine Resistance Study

Moorthy and colleagues examined the effect of nevirapine resistance frequencies on virologic outcomes among HIV-infected children enrolled in the NEVEREST (Nevirapine Resistance Study) trial (Abstract 159). The NEVEREST trial involved HIV-infected children who had been exposed to single-dose nevirapine and received lopinavir/r–based antiretroviral therapy as their initial regimen. Children with virologic suppression for at least 3 months underwent randomization to starting nevirapine-based antiretroviral therapy or continuing lopinavir/r–based antiretroviral therapy. In this analysis, the authors focused on children who were switched to the nevirapine-based antiretroviral therapy at study randomization. The authors used ultra-deep pyrosequencing in plasma and long-lived cells to determine nevirapine resistance frequencies. High-frequency nevirapine resistance (defined as ≥ 20% present), but not low-frequency resistance (defined as 1% – 19% present) in plasma, was found to be statistically significantly associated with virologic failure at 24 weeks and 52 weeks. Cellular nevirapine resistance was not associated with virologic failure at either time point.

Persistence of Resistance and Treatment Outcomes in Women After Single-Dose Nevirapine

Boltz and colleagues used allele-specific polymerase chain reaction to detect low-frequency NNRTI-resistant variants at baseline among HIV-infected women who received prior single-dose nevirapine and initiated antiretroviral therapy in the OCTANE (Optimal Combination Therapy After Nevirapine Exposure) trial 1/A5208 (Abstract 154). This randomized study showed higher rates of virologic failure or death in women with prior nevirapine exposure than in those receiving lopinavir/r (26% vs 8%, respectively; $P = .0004$). The authors identified NNRTI-resistant variants in 70 (35%) women who had no mutations detected by standard genotype. Among these 70 women, a higher proportion in the nevirapine-treated group experienced virologic failure or death than in the lopinavir/r group (32% vs 9%; $P = .04$), and this difference was seen across the range of mutants detected (0.3% to > 30%).

Single-dose nevirapine continues to be used widely for PMTCT in RLS despite the high frequency of emergence of antiretroviral drug resistance mutations in women shortly after drug exposure. Yang and colleagues studied the effect of HIV-1 subtypes on persistence of NNRTI resistance mutations in 330 women exposed to single-dose nevirapine in Kenya, Thailand, and Zambia (Abstract 912). None of these women received any additional antiretroviral therapy after the single-dose nevirapine treatment.

Conventional sequencing analysis involving the reverse transcriptase codons 1 to 251 was used to detect NNRTI resistance mutations, whereas allele-specific RT-PCR was employed to identify minor strains of NNRTI resistance mutations, including K103N, V106M/I, Y181C, and G190A. Phylogenetic analysis identified HIV-1 subtype-C infection in 181 women, subtype CRF01_AE infection in 80 women, subtype-A infection in 46 women, and other subtype infections in 23 women. No statistically significant difference in the prevalence of NNRTI resistance mutations using conventional sequencing analysis was seen by HIV-1 subtype. However, resistance mutations as determined by allele-specific RT-PCR were more prevalent in women with subtype-C infection than in those with nonsubtype-C infection, particularly among women exposed to single-dose nevirapine more than 12 months earlier (21% vs 1%; $P < .01$). The authors suggested that NNRTI drug resistance mutations might endure for a longer period of time in subtype-C infections than in nonsubtype-C infections.

Hudelson and colleagues investigated risk factors associated with the emergence and persistence of nevirapine-resistant HIV in breast milk in 51 HIV-infected Ugandan women who had been exposed to single-dose nevirapine for PMTCT (Abstract 913). None of the women received any other antiretroviral therapy. Breast milk and plasma samples were collected and tested at 4 weeks postpartum, with follow-up specimens available for a subset of women. Standard genotyping was successful for 10 breast milk samples with plasma HIV RNA levels above 500 copies/mL and for 21 of 41 samples

with levels below 500 copies/mL; 1 woman was excluded from the analysis. Phylogenetic analysis showed a predominance of subtype-A and -D HIV. Twelve (40%) of 30 breast milk samples had at least 1 nevirapine resistance mutation. The most common mutations were K103N and Y181C. Nevirapine resistance was present by 10 weeks postpartum in 4 of 10 breast milk samples that were available at this time point. The study was limited by a small sample size.

A limited number of studies to date have evaluated the long-term clinical outcomes of antiretroviral therapy among women with previous intrapartum exposure to nevirapine for PMTCT. Chintu and colleagues compared post–12-month clinical outcomes among 5172 Zambian women starting a NNRTI-based regimen: 596 (12%) had prior nevirapine exposure for PMTCT, and 4576 (88%) had no prior exposure (Abstract 914). The following outcome variables were assessed after 12 months of follow-up using Kaplan-Meier analysis: mortality, clinical treatment failure (defined as worsening WHO clinical staging after 3 months of antiretroviral therapy initiation, CD4+ cell count decrease below 95% of pre–antiretroviral therapy initiation level after at least 3 months of antiretroviral therapy [with or without a switch to second-line antiretroviral regimen]), and a composite of the first 2 outcomes.

Baseline characteristics at time of antiretroviral therapy initiation differed between the 2 groups: women with prior nevirapine exposure were younger, had higher baseline CD4+ cell counts, were more likely to have WHO clinical stage 1 or 2 HIV disease, and had higher hemoglobin levels than did women with no previous exposure. Median follow-up was 29 months. A trend toward increased risk of clinical treatment failure did not reach statistical significance (adjusted HR, 1.18; 95% CI, 0.95 – 1.47), and surprisingly, decreased mortality (adjusted HR, 0.53; 95% CI, 0.27 – 1.06) was noted among women with previous nevirapine exposure. The authors cautioned that the finding of a statistically nonsignificant association between prior nevirapine exposure and increased survival might be related to residual confounding.

Virologic failure among HIV-infected South African women exposed to single-dose nevirapine was compared with that among those with no prior exposure in the CIPRA-SA study (Abstract 915). CIPRA-SA was a randomized comparative trial evaluating treatment outcomes of doctor-initiated and -monitored antiretroviral therapy versus doctor-initiated and nurse-monitored antiretroviral therapy in 573 HIV-infected women with baseline CD4+ cell counts below 350/μL. Of 573 women, 165 (29%) previously received single-dose nevirapine, and 29 (5%) received single-dose nevirapine in combination with zidovudine. A majority of the women (89%) received a NNRTI-based regimen. The only baseline characteristic that differed statistically significantly between nevirapine-exposed and -unexposed women was age, with women in the nevirapine-exposure group being younger.

Overall, virologic failure was seen in 9.8% (50 of 511) of the women, with no statistically significant difference between nevirapine-exposed and -unexposed women (12.9% vs 8.2%, respectively). A 2.3-fold higher risk of early virologic failure was seen in nevirapine-exposed women compared with -unexposed women. No statistically significant difference in late virologic failure was observed between the 2 groups of women. Resistance mutations were absent in 32 of 50 resistance tests (64%). Among those with resistance mutations, the following mutations were detected: K103N, K103R, E138A, and M46L.

Weidle and colleagues examined the prevalence of mutations associated with nevirapine resistance among women exposed to single-dose nevirapine more than 1 year before initiating NNRTI-based antiretroviral therapy and assessed whether baseline resistance mutations were associated with treatment failure (Abstract 916). A total of 878 women in Zambia, Thailand, and Kenya were enrolled in the parent study; 355 women had previous nevirapine exposure and 523 did not. A subset of 172 women who started treatment with a NNRTI-based regimen more than 1 year after single-dose nevirapine exposure was included in the analysis. A majority of these women (95%) received nevirapine-based antiretroviral therapy, with the remainder receiving efavirenz-based antiretroviral therapy. Infections with HIV-1 subtypes C and CRF01_AE were common. Median time from single-dose nevirapine exposure to commencement of antiretroviral therapy was 25 months. To screen for specific mutations, investigators used both conventional sequencing involving reverse transcriptase codons 1 to 251 and allele-specific RT-PCR. At baseline, NNRTI resistance mutations were detected in 13% (19 of 152 subjects) of available samples by RT-PCR and in 2% (4 of 163) of available samples by conventional sequencing analysis.

The authors did not find any statistically significant association between detection of nevirapine resistance mutations by RT-PCR and virologic failure (defined as plasma HIV-1 RNA level > 400 copies/mL at 24 or 48 weeks after antiretroviral therapy initiation). Similarly, in subgroup analysis restricted to women with subtype-C HIV infection, no association between these 2 factors was observed. The study did not evaluate the relationship between nevirapine resistance mutations and long-term clinical outcomes such as mortality.

HIV Drug Resistance in Breastfeeding Infants Exposed to Antiretroviral Therapy

Dross and colleagues evaluated the incidence of nevirapine resistance in Mozambique in infants infected with HIV through breastfeeding (Abstract 917). The prospective observational study involved 740 infants who received single-dose nevirapine for PMTCT. Nevirapine resistance was found in 7 (47%) of 15 infants who acquired HIV. The majority of the infants with nevirapine resistance (86%) had 100% mutant HIV populations in their first positive DNA PCR test specimen, which persisted through 3 months to 12 months of age. One

infant with nevirapine resistance had 20% mutant populations at Y181C, and none had the V106M mutant detected.

Lidstrom and colleagues compared nevirapine resistance in infants who were HIV infected by 14 weeks of age and received extended nevirapine treatment either with or without zidovudine prophylaxis in the PEPI–Malawi (Post-Exposure Prophylaxis for Infants–Malawi) study (Abstract 918). The PEPI–Malawi study was a randomized controlled trial in which infants received 1 of the following regimens at birth for PMTCT: a control regimen consisting of single-dose nevirapine plus 1 week of daily zidovudine; 1 week of daily zidovudine plus extended nevirapine daily to age 14 weeks; or extended nevirapine plus zidovudine to age 14 weeks. The study showed that the risk of HIV transmission at 9 months of age was lower in both extended-prophylaxis groups than in the control group; HIV transmission risk in the 2 extended-prophylaxis groups showed no statistically significant difference.

In the current analysis, the authors compared nevirapine resistance in 150 HIV-infected infants receiving extended nevirapine with those receiving extended nevirapine plus zidovudine using HIV genotyping assays from plasma specimens collected at 14 weeks of age. Nevirapine resistance was lower in the extended-nevirapine plus zidovudine group than in the extended-nevirapine group (65.6% vs 86.0%; $P = .01$). In subgroup analyses, this difference was observed only in a subset of infants with in utero HIV infection who stopped prophylaxis by 6 weeks of age. None of the samples had any detectable zidovudine resistance mutations.

A shift in nevirapine resistance from low to high frequencies was found in Ethiopian infants for whom extended nevirapine prophylaxis was failing for the prevention of breast-milk transmission of HIV in the SWEN trial (Abstract 919). HIV genotyping was performed on dried blood spots collected at 6 months in 53 HIV-infected infants, most of whom (81%) had their HIV infection diagnosed at or before 14 weeks of age, with the remainder of infections diagnosed by 6 months of age. High-frequency nevirapine resistance was defined as nevirapine resistance detected by population genotyping, whereas low-frequency resistance was defined as nevirapine resistance detected only through cloning.

The authors observed that infants receiving extended nevirapine who became HIV infected by 14 weeks of age had a greater prevalence of high-frequency nevirapine resistance at 6 months than did infants receiving single-dose nevirapine (62% vs 18%, respectively; $P = .05$). However, when both high- and low-frequency nevirapine resistance were included in the analysis, there was no statistically significant difference in the prevalence of nevirapine resistance between the 2 groups. Among infants who received diagnoses of HIV infection after 14 weeks of age, the prevalence of high- and low-frequency nevirapine resistance was similar in the 2 groups.

Antiretroviral Regimens, Viral Response, and Mother-to-Child Transmission Outcomes

Tariq and colleagues investigated the impact of non–zidovudine-containing antiretroviral therapy on pregnancy and clinical outcomes using data from a population-based surveillance study and a multicenter cohort study in 10 European countries (Abstract 895). HIV-infected women who had at least 14 days of antiretroviral therapy in pregnancy and had live, singleton births were included in the analysis. Sixteen percent of the women received non–zidovudine-containing antiretroviral therapy, with tenofovir and abacavir the most common alternate nRTIs. There was no statistically significant difference in the following outcome variables between women who received zidovudine-containing antiretroviral therapy and those who received non–zidovudine-containing antiretroviral therapy in multivariate models: detectable maternal viral load at delivery, risk of congenital abnormality among infants born to all women, risk of congenital abnormality among infants born to women exposed to antiretroviral therapy during the first trimester, and risk of mother-to-child transmission of HIV.

Briand and colleagues found no negative impact of prior short-term antiretroviral prophylaxis for PMTCT on virologic response to PI-based antiretroviral therapy in subsequent pregnancies among HIV-infected women (Abstract 898). Data from the French Perinatal Cohort, a multicenter prospective cohort study in France, were analyzed. At onset of last pregnancy, 714 women were naive to antiretroviral therapy, and 193 previously received antiretroviral therapy for PMTCT. Among women who received antiretroviral therapy during their most recent pregnancy, 43% had a PI-based regimen, 5% a non–PI-based regimen, 19% dual-nRTI therapy, and 33% zidovudine monotherapy. A majority of the women (89%) were started on a PI-based regimen during their subsequent pregnancy. Among these women who received PI-based antiretroviral therapy during their subsequent pregnancy, there was no statistically significant difference in the proportion achieving virologic suppression (plasma HIV RNA level < 50 copies/mL) at delivery between those who were naive to antiretroviral therapy and those who previously received antiretroviral therapy.

Tuberculosis Impact on Prevention of Mother-to-Child Transmission of HIV

Gupta and colleagues noted an association between maternal active TB and MTCT of HIV among 783 mother-infant pairs enrolled in the India SWEN study (Abstract 899). The SWEN study was a comparative trial of extended nevirapine treatment versus single-dose nevirapine for PMTCT of HIV in breastfeeding infants. Median follow-up was 1 year. Three mothers had active TB diagnosed in pregnancy (prevalent TB), and 30 mothers had active TB by 12 months postpartum (incident TB). In multivariate analysis, mothers with prevalent or incident TB were 2.53 times more likely to transmit HIV to their infants than were mothers without active TB, after adjusting for maternal and child factors such as

maternal HIV viral load, maternal antiretroviral therapy, infant nevirapine prophylaxis, and duration of breastfeeding. The study findings were limited by lack of culture confirmation in all TB cases and lack of ascertainment of potential confounders like HCV coinfection and nutritional status.

Breast-Milk Shedding of HIV and Antiretroviral Therapy Impact

Exclusive breastfeeding in the first 6 months of life poses a risk of 4% for MTCT of HIV, followed by a risk of 1% per month after 6 months.[8] Neveu and colleagues conducted a nested, case-control study among HIV-infected women and their infants in KwaZulu-Natal, South Africa, to examine the relationship between HIV RNA shedding in breast milk, cumulative HIV exposure through breast milk, and postnatal HIV transmission (Abstract 901). Infants who acquired HIV from their HIV-infected mothers between 6 weeks and 200 days of age were considered cases, and HIV-uninfected infants born to HIV-infected mothers served as control subjects. A total of 36 mother-infant pairs with complete data were included. Breast milk and blood specimens were collected monthly. The authors observed that the cases were more likely to shed HIV-1 RNA in breast milk than were the control subjects. In addition, cumulative breast milk HIV-1 RNA exposure (calculated between 6 weeks and time of HIV acquisition) was 15-fold higher in cases than in control subjects. The association between cumulative breast milk HIV RNA exposure and postnatal HIV transmission remained statistically significant after controlling for maternal antenatal CD4+ T-cell count and plasma viral load.

Treatment of HIV Infection in Children

Response to Initial Antiretroviral Therapy in Children

Violari and colleagues studied early virologic and immunologic outcomes in 386 HIV-infected infants initiating antiretroviral therapy as part of the CHER (Children With HIV Early Antiretroviral Therapy) study in South Africa (Abstract 843). The children were started on a lopinavir/r-based regimen at a median age of 8.4 weeks. Virologic and immunologic responses were assessed at 24 weeks and 40 (or 48) weeks after initiating antiretroviral therapy. Virologic suppression was defined as plasma HIV RNA level below 400 copies/mL. An increase in CD4+ percentage to a level that was at least 10% above the baseline pre–antiretroviral-therapy level constituted an immunologic response.

At 24 weeks, virologic suppression was seen in 71% of children and in 77% at 40 or 48 weeks after antiretroviral therapy initiation, with a minority (8%) experiencing virologic rebound to plasma HIV RNA levels above 400 copies/mL at 40 or 48 weeks after having achieved virologic suppression at 24 weeks. Virologic suppression was not associated with age at antiretroviral therapy commencement, weight-for-age *z* score, viral load, or sex. However, children with active TB diagnosed before or within 1 month of starting antiretroviral therapy and receiving concurrent TB treatment had poorer virologic response at 24 weeks than did children without TB coinfections. The median increase in CD4+ percentage from baseline level at the time of antiretroviral therapy initiation was 7% at 24 weeks and 40 or 48 weeks. Immunologic response was associated with lower baseline CD4+ percentage.

Raltegravir in Children

Nachman and colleagues presented interim pharmacokinetics, 12-week efficacy, and safety results from IMPAACT P1066 (International Maternal Pediatric Adolescent AIDS Clinical Trials P1066), an open-label study of raltegravir in HIV-infected, treatment-experienced children (Abstract 161LB). This analysis included only 10 children between the ages of 6 years and 11 years from the cohort in which an oral chewable tablet formulation of raltegravir was administered. All children had plasma HIV RNA levels above 1000 copies/mL at baseline and were naive to raltegravir. Median baseline CD4+ cell count was 456/μL and plasma HIV RNA level was 4.2 $\log_{10}$ copies/mL. The authors found lower pharmacokinetic variability and lower drug clearance among children receiving the oral chewable tablet formulation than in children in the other cohort, who received an adult formulation of raltegravir. Seven of the 10 children receiving oral chewable tablets had plasma HIV RNA levels suppressed below 400 copies/mL at 12 weeks.

HIV Drug Resistance after Treatment Failure in Children

Three studies evaluated antiretroviral drug resistance after treatment failure in children. Limited access to virologic testing in RLS has led to an increased risk of unrecognized virologic failure and emergence of drug resistance. Achan and colleagues investigated the incidence of early virologic failure and evolution of drug resistance mutations in 126 Ugandan children starting antiretroviral therapy as part of the CHAMP (Children with HIV and Malaria Project) (Abstract 849). The authors defined virologic failure as plasma HIV RNA level above 1000 copies/mL in the 6-month to 9-month period following antiretroviral therapy initiation, and they excluded data from children with antiretroviral therapy nonadherence. Initial antiretroviral therapy consisted of nevirapine plus either zidovudine/lamivudine or stavudine plus lamivudine. Median follow-up was 746 days beyond 6 months of antiretroviral therapy. Eighteen children (14%) developed early virologic failure. All of these children had persistent, detectable viremia during the follow-up period. Only 2 of these children had mothers who used nevirapine for PMTCT. Within the first 6 months, M184V and NNRTI RAMs emerged in most children, thymidine analogue–associated mutations (TAMs) emerged after 12 months, and 2 etravirine-associated mutations emerged by 30 months.

Another study on drug resistance in HIV-infected children in Uganda showed higher rates of virologic failure

in children exposed to single-dose nevirapine for PMTCT than in unexposed children (Abstract 850). At 24 weeks after antiretroviral therapy initiation, 65.4% (17 of 26) of children exposed to single-dose nevirapine experienced virologic failure (defined as plasma HIV RNA level > 400 copies/mL) compared with 36.5% (19 of 52) of unexposed children (P = .0127). Similar rates of virologic failure were seen at 48 weeks: 62.1% (18 of 29) of exposed children compared with 32.1% (17 of 53) of unexposed children (P = .0086). NNRTI- and nRTI-associated resistance mutations were analyzed in a subset of 20 children (15 exposed and 5 unexposed). Among children exposed to single-dose nevirapine, the most common NNRTI resistance mutations were Y181C, G190A/G, K103N, and V108I/V, and the most frequent nRTI resistance mutations were M184V, D67N, and K70R. Unexposed children had fewer drug resistance mutations than exposed children did; the predominant mutations were K103N and M184V. It is important to note that only subtype-A and subtype-D HIV-1 strains were represented in this drug resistance analysis.

Darunavir-associated resistance mutations in PI-naive and -experienced HIV-infected children in the United Kingdom were examined using combined data from the CHIPS (Collaborative HIV Paediatric Study) and the UK HIV Drug Resistance Database (Abstract 851). Darunavir resistance mutations were derived from the 2008 IAS–USA mutations list[9] and the Stanford University Drug Resistance Database.[10] Among 344 PI-naive children, 14 (3%) were found to have a single mutation, and no children had more than 1 mutation. A majority of the PI-naive children with a single mutation (83%) had nonsubtype-B HIV-1 infection. A total of 156 PI-experienced children were studied. Median time on PI-based antiretroviral therapy was 2.6 years, with approximately one-third of the children receiving lopinavir/r as their only PI. Of the PI-experienced children, 21 (13%) had a single mutation, 5 (3%) had 2 mutations, and 3 (2%) had 3 mutations. Intermediate-level resistance to darunavir, as determined by the Stanford University database, was observed in only 3 (2%) PI-experienced children.

On multivariate analysis, the following factors were associated with increased number of darunavir resistance mutations: longer time taking PI-based antiretroviral therapy, prior exposure to PIs other than lopinavir/r, and larger area under the viremia curve from PI initiation. The authors suggested that given the low prevalence of darunavir-associated resistance mutations in PI-naive and PI-experienced children in the study, darunavir/r could be used as an initial or a second-line PI-based regimen.

Survival of HIV-Infected Children in Africa

Becquet and colleagues from the UNAIDS Child Survival Working Group conducted a pooled analysis of 12 trials and cohort studies in sub-Saharan Africa to estimate survival of children infected with HIV perinatally or through breastfeeding (Abstract 840). Estimations of mortality were based on the HIV serostatus of the child, with timing of HIV acquisition incorporated into the mortality calculations for HIV-infected children. Random-effects Weibull regression models were used, with adjustments for sub-Saharan African region, maternal vital status, maternal CD4+ cell count, any breastfeeding, and HIV serostatus and sex of the child. Non–HIV-related causes of mortality were excluded from the models. A total of 2509 HIV-infected and 8964 uninfected children were analyzed. Overall estimated 24-month mortality was higher among HIV-infected children than among uninfected children, regardless of timing of HIV acquisition. Kaplan-Meier survival analysis showed that among HIV-infected children, those with HIV acquired during breastfeeding had statistically significantly lower estimated 18-month mortality than did children infected with HIV perinatally (36% vs 60%, respectively).

Venkatesh and colleagues examined correlates of infant morbidity and mortality within the first 100 days of life in a South African multicenter prospective study of infants who were born to HIV-infected women and received antiretroviral drugs for postexposure prophylaxis (Abstract 841). A total of 848 HIV-infected mother and infant pairs were included in the analysis. Overall, the 100-day cumulative probability of not having a serious adverse event (defined as infant hospitalization) was .89 (95% CI, 0.85 – 0.92), and the cumulative probability of survival was .98 (95% CI, 0.97 – 0.99). Gastrointestinal and respiratory infections were the most frequent causes of infant morbidity. Hospitalization occurred more frequently among HIV-infected than -uninfected infants and among those with maternal plasma HIV RNA level above 100,000 copies/mL; maternal age below 20 years was associated with less frequent hospitalization. Not surprisingly, statistically significant predictors of mortality were infant HIV infection (HR, 4.10; 95% CI, 1.18 – 14.31) and maternal plasma HIV RNA level above 100,000 copies/mL (HR, 6.93; 95% CI, 1.64 – 29.26). The authors did not find infant feeding route (ie, breastfeeding vs formula feeding) to be associated with infant morbidity or mortality. The authors recommended prompt initiation of antiretroviral therapy in HIV-infected women of childbearing age, given the increased risk of hospitalization and mortality among infants whose mothers had plasma HIV RNA levels above 100,000 copies/mL.

Infant Outcome after Prenatal Antiretroviral Therapy Exposure

Conway and colleagues examined the prevalence of congenital abnormalities among 1112 infants with in utero exposure to antiretroviral therapy using data from IMPAACT P1025, a large prospective cohort study in the United States (Abstract 923). Sixty-one children were found to have congenital anomalies (as defined by The Antiretroviral Pregnancy Registry, www.apregistry.com), yielding an anomaly rate of 5.49 per 100 live births (compared with 2.8/100 live births among the general population and 3.56/100 live births among HIV-infected women and their children). Exposure to efavi-

renz during the first trimester had a 2.89-fold increased risk of congenital anomalies, whereas exposure to nonefavirenz antiretroviral therapy in any trimester during pregnancy was not associated with increased anomaly risk. Other factors such as race or ethnicity, maternal age, folate supplementation, and in utero exposure to alcohol, tobacco, heroin, and other illicit drugs were not associated with increased anomaly risk.

In another study, no increased risk of congenital, renal, or growth abnormalities was found with in utero exposure to tenofovir among infants born to HIV-infected mothers in a subset of the DART study in Uganda and Zimbabwe (Abstract 924). A smaller comparative study among 40 children with and without in utero exposure to tenofovir did not show any elevation in cystatin C or urea levels in either group during the 2-year follow-up period (Abstract 925). The effects of in utero exposure to tenofovir, particularly during the second and third trimesters, on bone development and metabolism of HIV-uninfected children born to HIV-infected mothers were examined by Vigano and colleagues (Abstract 926). No statistically significant differences in anthropometric parameters, tibial speed of sound *z* score (as measured by quantitative ultrasound), and levels of serum bone alkaline phosphatase and C-terminal telopeptide of type I collagen were noted between children with in utero tenofovir exposure and those without such drug exposure.

Antiretroviral Therapy During Treatment for Tuberculosis

Lopinavir/r is superior to an NNRTI-based regimen as initial therapy in HIV-infected infants and young children previously exposed to nevirapine for PMTCT of HIV.[11] However, modifications to the antiretroviral regimen are necessary in HIV and TB coinfections because of drug interactions between lopinavir/r and rifampin. Moodley and colleagues conducted a retrospective case-control study evaluating virologic outcomes in South African HIV-infected children who started PI-based antiretroviral therapy (Abstract 160). A total of 526 children were included in the study: 294 children who were treated concurrently with TB drugs (cases) and 232 children who did not receive TB treatment (control subjects). All control subjects were treated with a standard lopinavir/r-based regimen. The cases were stratified according to their PI combinations: (1) super-boosted lopinavir/r (ritonavir concentrations were increased up to 1:1 concentration with lopinavir by the addition of ritonavir), (2) double-dose lopinavir/r (standard doses of lopinavir/r were doubled), and (3) ritonavir alone. All children received stavudine plus lamivudine.

The authors found that a lower proportion of children treated with double-dose lopinavir/r or ritonavir had viral suppression at 6 months than that of control subjects. At 12 months the proportion of children receiving double-dose lopinavir/r or super-boosted lopinavir/r who had suppressed HIV viral loads was similar to that of the control subjects (76.9% and 82.9% vs 83.3%, respectively). However, children taking ritonavir alone were less likely to have viral suppression than were control subjects at 12 months (63.9% vs 83.3%, respectively). Not surprisingly, severe elevations of alanine transaminase levels were most common in children who received super-boosted lopinavir/r, occurring in nearly 30% of the children. The authors cautioned against use of ritonavir alone with concurrent rifampin-based TB treatment and suggested that super-boosted lopinavir/r was best. The authors did not explore the reason for the worse 6-month outcome in children taking double-dose lopinavir/r than in children taking super-boosted lopinavir/r.

Resistance

Prevalence and Consequences of Transmitted Drug Resistance

Two studies examined the prevalence of transmitted drug resistance associated mutations (TDRM) in newly diagnosed HIV-infected persons from the US HIV surveillance system. The surveillance system collects population-based drug resistance data on all new HIV diagnoses from 10 states and 1 county in the United States. Kim and colleagues analyzed the prevalence of TDRM among new HIV diagnoses in 2007 using the WHO mutation list (Abstract 580).[12] A total of 10,496 new HIV diagnoses occurred in 2007, one-fourth of whom had genomic sequences reported to the national surveillance list. Sixteen percent of the new HIV diagnoses with available genomic sequences had at least 1 TDRM. Eight percent had NNRTI-associated resistance mutations, 6% had nRTI resistance mutations, and 4% had PI resistance mutations. Prevalence of multiclass resistance was low: 2% for 2 drug classes and less than 1% for 3 drug classes. The presence of TDRM was not associated with age, sex, race, or transmission mode.

Prejean and colleagues compared the prevalence of TDRM between recent and longstanding HIV infections using data from the US HIV surveillance system (Abstract 581). The surveillance system utilizes a serologic testing algorithm and the BED HIV-1 capture enzyme immunoassay to distinguish recent from longstanding HIV infections among persons with newly diagnosed HIV infection. A total of 1626 antiretroviral-naive persons with newly diagnosed HIV infection in 2006 were included in the analysis. A majority (73.1%) had longstanding HIV infections or AIDS within 6 months of HIV diagnosis. The remainder (26.9%) had recent HIV infections. Prevalence of TDRM was higher in recently infected persons than in those with longstanding infections (18.3% vs 13.8%; $P = .02$). TDRM related to NNRTIs and nRTIs were seen more frequently in persons with recent infections than in those with longstanding infections. No differences in the prevalence of PI-associated resistance mutations were seen between the 2 groups. This study confirmed findings from previous studies noting a higher prevalence of TDRM in recent infections than in longstanding infections, reflecting either increasing transmission of drug-resistant HIV or a propensity of HIV strains to revert to wild type over time

with archiving of low-frequency mutant viral populations.

Changing Prevalence of Multidrug Resistance

Abraham and colleagues applied novel multiple imputation methodology to estimate the cumulative prevalence of multiclass drug resistance from 2000 to 2005 among 9786 HIV-infected persons from 9 HIV cohorts within the NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) consortium (Abstract 584). HIV-infected persons receiving antiretroviral therapy who had no known drug resistance before antiretroviral therapy initiation and who had at least 1 study visit that included a viral load result were included in the analysis. Genotypic test results were available for nearly one-third of the sample. The Stanford University HIV Drug Resistance Database[9] was used to determine drug resistance. A steady decline was observed in the prevalence of multiclass resistance among those with available genotypic test results from 2000 to 2005, from 57.9% in 2000 to 38.5% in 2005 for resistance to at least 2 drug classes and from 22.9% in 2000 to 19.0% in 2005 for resistance to 3 drug classes. Using imputation methodology to estimate accumulated drug resistance among those without genotypic testing results, the authors noted an increase in the prevalence of multiclass resistance during the study period, from 13.9% in 2000 to 18.8% in 2005 for accumulated resistance to at least 2 classes and from 5.8% in 2000 to 8.6% in 2005 for accumulated resistance to 3 classes.

Aldous and colleagues noted a decline in the prevalence of drug resistance mutations from 2002 to 2008 in the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems Cohort from 6 sites in the United States (Abstract 585). A subset of persons taking antiretroviral therapy who had available genotypic testing results was analyzed. The 2008 IAS–USA criteria[8] were used to screen for major and minor drug resistance mutations. A steady decrease in the prevalence of at least 1 major PI resistance mutation, at least 1 thymidine analogue resistance mutation, and the M184V mutation was observed over the 7-year period. The pattern for the prevalence of at least 1 major NNRTI resistance mutation was slightly different over time: it was 45% in 2002, increased to 52% in 2004, and gradually dropped to 36% by 2008. A steady decline in multiclass resistance was also noted.

Sequencing Technologies

New sequencing technologies were a major focus of this year's conference. An oral presentation by Henn and colleagues provided an overview and evaluation of deep-sequencing technologies (Abstract 9). New platforms for deep sequencing (also known as ultra-deep sequencing and pyrosequencing) have reduced costs and enabled high-throughput, high-sensitivity analyses. In the presentation, different proprietary deep-sequencing assays were compared in terms of read-length and throughput. As opposed to "bulk-sequencing" assays that produce a genotypic analysis of the majority population in a sample, deep sequencing was described as analogous to single-genome amplification. The assays utilize capture technologies, such as beads or wells, to allow the amplification of single DNA molecules by PCR. The advantages of deep sequencing include its ability to sequence unknown viral elements, characterize quasi species within an individual, and evaluate diversity across the entire viral genome. Another excellent overview of deep-sequencing technology was presented by Brumme, the moderator of Session 15.

Resistance to Nucleotide Analogue Reverse Transcriptase Inhibitors

Coutsinos and colleagues examined the mechanisms responsible for the emergence of the K65R mutation in subtype-B and subtype-C HIV (Abstract 548). Referring to prior work, the authors note that subtype-C HIV-1 is more prone to the emergence of the K65R mutational pathway than is subtype-B HIV. Nucleotide extension assays of the *pol* gene were performed utilizing recombinant subtype-B and subtype-C HIV-1 reverse transcriptase (RT). An enzymatic pause at the K65R substitution site was observed in subtype-C virus. Incorrect nucleotide incorporation via dislocation mutagenesis was the postulated mechanism. This observation has implications for the introduction of tenofovir for initial antiretroviral therapy in regions where subtype-C virus is endemic.

A related study by Varghese examined the frequency of minority K65R variants in subtype-B and subtype-C virus using ultra-deep sequencing (Abstract 547). Antiretroviral therapy–naive subjects with subtype-B and subtype-C HIV were compared for the presence of K65R minority populations. K65R was detected in 0.85% of subtype-C and 0.25% of subtype-B samples (P = .01). However, the authors noted that these minority variants may be spurious in subtype-C HIV and that ultra-deep sequencing may overestimate the clinical relevance of this mutation.

Resistance to Nonnucleoside Analogue Reverse Transcriptase Inhibitors

The data on NNRTI resistance presented at the conference focused primarily on etravirine RAMs. Asahchop and colleagues conducted in vitro etravirine RAM selection assays in different HIV-1 subtypes (Abstract 552). Subtype-B, subtype-C, and CRF02_AG clones underwent serial passage through increasing concentrations of etravirine and efavirenz. After 18 weeks of etravirine selective drug pressure, the E138K substitution was the first to emerge in the 3 subtypes tested. No differences in RAMs selected were observed between the different subtypes. The CRF02_AG clone that harbored only the E138K mutation showed a 5.3-fold increase in the 50% inhibitory concentration (IC_{50}) to etravirine. Efavirenz did not select for this mutation.

Maiga and colleagues examined the susceptibility to etravirine in isolates from nonsubtype-B HIV-1-infected patients (Abstract 553). Isolates from 726

antiretroviral therapy–naive individuals from France and Mali underwent genotypic and phenotypic evaluation. The most common etravirine RAMs in this treatment-naive population were V90I, E138A, V106I, and V179E. Overall, 10.3% of patients had virus with at least 1 etravirine RAM: 9.8% had 1 etravirine RAM, 0.5% had 2 etravirine RAMs, and none had 3 or more RAMs. Only the CRF02_AG strain harbored more than 1 etravirine RAM ($P = .004$ compared with all other subtypes). The following mutational combinations were associated with an increased IC_{50} fold increase to etravirine: E138A plus V179I (fold change, 5.2), Y181C plus H221Y (fold change, 11.1), V90I plus Y181C (fold change, 3.3).

Resistance to Protease Inhibitors

Koh and colleagues presented mechanistic data on darunavir and tipranavir resistance mechanisms (Abstract 559). Both darunavir and tipranavir block protease activity by inhibition of protease subunit dimerization, which is required for protease's catalytic activity. The authors looked at the ability of wild-type and mutant protease to dimerize in the presence or absence of these drugs. Fluorescence resonance energy transfer, a florescent-tag–based system used to detect dimerization on the basis of color change, was used. Only the combined presence of the major darunavir resistance mutations V32I, L33F, I54M, and I84V was associated with an inability of darunavir to block protease dimerization in vitro. In contrast, tipranavir failed to block dimerization in the presence of any of the major mutations L24M, L33I, or L33F. This study confirms the high genetic barrier to darunavir resistance and provides a mechanistic explanation for this barrier.

Parry and colleagues presented data on the compensatory mechanisms of HIV-1 in maintaining replication fitness despite the accumulation of protease mutations (Abstract 561). The authors describe mutational pathways in the *gag* sequence encoding for matrix protein. These mutations were able to restore normal replication capacity in highly replication-capacity-deficient (replication capacity, 5%) protease-resistant clones. The following compensatory mutations in *gag* matrix domain were associated with the restoration of viral replication capacity: R76K, Y79F, and T81A.

CC Chemokine Receptor Tropism and CCR5 Antagonists

A substantial amount of information was presented at the conference on the ability to predict HIV-1 coreceptor tropism and CCR5 antagonist antiviral activity using novel technologies. These new technologies include deep sequencing of the V3 loop of the *env* gene and the amplification of viral genomic sequences from nonplasma sources such as proviral and episomal DNA. An entire session was dedicated to the use of new technologies in the prediction of HIV-1 coreceptor use (Session 15). The following section is divided into thematic subsections, reflecting the volume of data presented on this topic.

Comparisons of tropism assays. Several presentations compared the predictive capacity of different tropism assays. These included comparisons of the 2 commercially available phenotypic tropism assays, the enhanced-sensitivity and the older tropism assay (both Monogram Biosciences, Inc, South San Francisco, CA), as well as evaluation of genotypic predictions of tropism.

Wilkin and colleagues reexamined tropism data from cohorts and clinical trials using the enhanced-sensitivity tropism assay rather than the original tropism assay (Abstract 538). The enhanced-sensitivity tropism assay and the original tropism assay are described as having a sensitivity of 100% to detect non–R5-tropic virus at a population prevalence of 0.3% and 5%, respectively. Samples from participants in the CPCRA (Community Program for Clinical Research on AIDS) cohort, and the New Works Concept Sheet 261, MERIT (Maraviroc versus Efavirenz Regimens as Initial Therapy), and ACTG 5211 clinical trials were included in the analysis. The outcome of interest was the proportion of patients with virus reclassified from having R5 tropism to having dual-mixed, X4 (DM/X4) tropism. Of 2407 patients included in the analysis, 84% were treatment naive. On average, the enhanced-sensitivity assay detected between 8% and 13% more DM/X4 tropic virus than did the original tropism assay. One-fourth of treatment-experienced patients with R5-tropic virus as determined by the original assay were found to have virus with DM/X4-tropism by the enhanced-sensitivity assay. In a multivariate analysis, lower CD4+ cell count was the only factor statistically significantly associated with reclassification to DM/X4 tropism.

Use of genotypic analysis in the prediction of coreceptor tropism was the main focus of presentations on this topic. McGovern and colleagues retrospectively used V3-loop sequencing to evaluate maraviroc response in the MERIT trial (Abstract 92). MERIT was a randomized clinical trial comparing the safety and efficacy of maraviroc with those of efavirenz, both coadministered with zidovudine/lamivudine, in treatment-naive patients. R5 tropism as determined by the original tropism assay was an inclusion criterion for the study. In this analysis, the HIV-1 V3 loop was genotyped using population-based sequencing. The analysis was performed with investigators blinded to treatment response and to reanalysis of baseline tropism with the enhanced-sensitivity assay. Utilizing the geno2pheno coreceptor tropism predictor algorithm (http://www.geno2pheno.org/), V3-loop sequencing was highly predictive of response to maraviroc. Patients with virus screened as non–R5-tropic by genotypic testing had virus with a more rapid change in tropism. The authors argue that the enhanced-sensitivity assay and V3-loop genotyping showed equivalence in predicting response to maraviroc. They also commented that population sequencing had a good predictive value of virologic response and that deep sequencing may not be required in clinical practice.

Swenson and colleagues looked at the use of V3-loop deep sequenc-

ing in predicting coreceptor tropism (Abstract 545). The authors retrospectively sequenced samples obtained from participants in 4 maraviroc clinical trials: MERIT, MOTIVATE-1 and -2 (Maraviroc Versus Optimized Therapy in Viremic Antiretroviral Treatment–Experienced Patients 1 and 2), and A4001029 (the MERIT trial is described above; MOTIVATE-1 and -2 were randomized controlled trials of maraviroc in treatment-experienced patients; and A4001029 was a trial of maraviroc in non–R5-tropic infections). All trials originally used the older tropism assay to determine tropism for the inclusion or exclusion criterion.

In this analysis, deep-sequencing results were compared with results from the original phenotypic assay. In the deep-sequence analysis, tropism was designated R5 if less than 2% of viral sequences were determined to be X4 tropic by the geno2pheno algorithm. There was good correlation between results of the V3 loop deep-sequencing assay and phenotypic prediction by the original tropism assay. In addition, baseline samples from the MERIT trial were also reanalyzed using the enhanced-sensitivity tropism assay, and these results showed equivalent correlation with V3-loop sequencing. Finally, in the combined analysis of the treatment–experienced trials, samples initially screened as R5 tropic by the original assay were more likely to be reclassified as non-R5 tropic at baseline by deep-sequencing analysis. The authors did not report the proportion of subjects with virus reclassified to DM/X4 tropism in the genotypic analysis.

Pou and colleagues compared deep sequencing analysis to analysis using the enhanced-sensitivity tropism assay and found close correlation between the 2 technologies (Abstract 544). However, deep sequencing had the highest sensitivity for detection of X4-tropic virus in PBMCs compared with plasma. Van't Wout and colleagues compared deep sequencing with phenotypic assay in predicting tropism in a subgroup of subjects in the Amsterdam cohort (Abstract 276). They also found earlier detection of X4-tropic virus using sequencing analysis. Sanchez and colleagues presented a predictive model of X4 tropism in treatment-experienced patients based on clinical and deep-sequencing criteria (Abstract 543).

Tropism prediction using viral DNA sequencing. Soulie and colleagues examined proviral DNA sequences in 140 HIV-1-infected patients taking maximally suppressive antiretroviral therapy (Abstract 537). All patients had plasma HIV-1 RNA levels below 40 copies/mL and all were CCR5-antagonist naive. Coreceptor use was determined with the geno2pheno algorithm. Thirty-one percent of subjects harbored X4-tropic virus. The following predictors of X4 tropism were investigated in a multivariate analysis: time since HIV diagnosis, duration of treatment, length of time with undetectable viral load, HIV subtype, current treatment regimen, number of prior regimens, age, sex, phenotypic sensitivity score, and nadir and current CD4+ cell counts.

Nadir CD4+ cell count was the only variable associated with X4 tropism; the median CD4+ cell count nadir for DM/X4-tropic virus was 108/μL and was 193/μL for R5-tropic virus. However, X4-tropic virus was found in patients at all CD4+ cell count nadir strata. Among patients with the R5-tropic strains, 4.1% harbored maraviroc-associated resistance mutations despite being naive to CCR5 antagonists. The authors cautioned that tropism analysis should be performed in patients taking suppressive antiretroviral therapy before they undergo a switch to CCR5-antagonist-containing regimens, even in patients with high CD4+ cell count nadirs. It is unclear when this technology will become commercially available to clinicians.

Babic and colleagues reported on the use of episomal DNA for V3-loop sequencing (Abstract 540). The authors stated that episomal DNA has the advantage of being dynamic and nonarchival, representing recent infection events. The sample included 14 patients who experienced virologic failure in the vicriviroc trial ACTG A5211. All study participants had virus that was classified R5 tropic by the original tropism assay. PBMCs were collected at various time points, and the full length of *env* was amplified from episomal DNA. V3-loop sequencing from episomal DNA was concordant with the phenotypic tropism assay in 10 of 14 subjects. In 2 subjects there was discordance at all time points, and in 2 subjects DNA sequencing predicted subsequent tropism shift from R5 to DM/X4 at earlier time points than predicted by phenotypic tropism analysis. The authors concluded that episomal DNA sequencing is a useful method that has high concordance with tropism analysis and may be applicable to aviremic patients as well.

Mechanisms of CCR5-antagonist resistance and prevalence of CCR5 coreceptor tropism. Svitcher and colleagues provided data on the genetic determinants of HIV-1 coreceptor use (Abstract 542). Tropism was assessed using the enhanced-sensitivity tropism assay and V3-loop sequencing in samples from 279 patients. The presence of wild-type S11S and the substitutions T22A and E25D of the V3 loop were highly correlated with R5 tropism. Several novel V3-loop genetic mutations were associated with X4 tropism. The authors also show that differential binding affinities of the V3 loop to the CCR5 N-terminus are implicated in the determination of viral coreceptor preference. Yoshimura and colleagues describe a 2-step escape pathway induced by in vitro exposure to maraviroc (Abstract 535). Henrich and colleagues presented data on vicriviroc resistance in subtype-C HIV-1-infected patients (Abstract 534). The authors constructed a series of recombinant viruses and illustrate that several RAMs at the V3 loop are required to produce vicriviroc resistance.

Craig and colleagues presented 96-week data on mechanisms of virologic failure in the MERIT trial (Abstract 536). All patients with DM-tropic virus at baseline by enhanced-sensitivity tropism assay reanalysis were excluded from the current study. Subjects with a HIV-1 RNA level above 500 copies/mL while receiving study therapy were in-

cluded. There were 73 of 311 subjects in the maraviroc group and 43 of 304 subjects in the efavirenz group. In the maraviroc group, 53% had virus that exhibited lamivudine resistance, 26% had maraviroc resistance, and 3% had zidovudine resistance. There were 19 subjects in the maraviroc group experiencing treatment failure without nRTI resistance mutations or maraviroc resistance mutations; of these, 12 had X4-tropic virus and 7 had R5-tropic virus at failure. The specific mutations identified at failure are not described. In the efavirenz group, efavirenz mutations were found in virus of 53% of subjects and lamivudine mutations in 30%. Rates of virologic suppression were similar between the 2 treatment groups.

Lin and colleagues estimated the prevalence of X4-tropic virus among treatment-naive subtype-C HIV-1-infected women in the Mashi study (Abstract 278). The Mashi study examined different strategies for PMTCT in Botswana. Women who reached the CD4+ cell count criterion for starting antiretroviral therapy (< 200/µL) were offered antiretroviral therapy and also underwent tropism analysis. An in-house genotypic tropism assay was performed that was validated to detect minority X4-tropic virus at a population prevalence of 1%. A total of 206 women met criteria for treatment. The median age at enrollment was 29 years, the baseline CD4+ cell count was 132/µL, and the plasma HIV-1 RNA level was 4.95 $\log_{10}$ copies/mL; 51% had previously received single-dose nevirapine for PMTCT. Samples were obtained for 137 women, of which 97% could be genotyped.

Of treatment-naive women in this study, 74% had R5-tropic virus and 26% showed DM virus. No subject had pure X4-tropic virus. The probability of having DM virus was similar across study sites and by original study group. There were no statistically significant differences observed in clinical outcomes between women with R5 virus versus DM virus, although the authors observed a trend toward earlier initiation of antiretroviral therapy and higher mortality in DM- versus R5-tropic subjects.

Jacobson and colleagues evaluated viral resistance and coreceptor tropism in subjects exposed to the investigational drug PRO 140, a humanized anti-CCR5 monoclonal antibody with potent antiviral activity in vitro (Abstract 531). Subjects receiving PRO 140 monotherapy as part of pharmacokinetics and antiviral activity studies were included in the analysis. PRO 140 was administered as either a single dose or in 3 weekly doses. All 84 subjects had R5-tropic virus at baseline as determined by the original tropism assay. Six subjects experienced a tropism shift while taking PRO 140, 4 of whom had pretreatment DM virus when baseline samples were reanalyzed using the enhanced-sensitivity tropism assay. The mechanism of tropism switch in the 2 other subjects remains under investigation. There was no statistically significant change in IC_{50} or maximal percent inhibition to PRO 140 at the end of the study and at viral rebound.

Resistance to Integrase Strand Transfer Inhibitors

Miller and colleagues examined the impact of a short course of raltegravir monotherapy on the emergence of raltegravir RAMs and the durability of subsequent raltegravir treatment (Abstract 557). The analysis was conducted in subjects participating in Protocol 004, a 2-part randomized controlled trial comparing raltegravir with efavirenz, coadministered with tenofovir/emtricitabine, in treatment-naive patients. In part 1, 35 participants received raltegravir monotherapy or placebo for 10 days as part of a raltegravir dose-ranging investigation. The authors compared subsequent raltegravir outcomes in patients who received raltegravir versus placebo in part 1 and were later treated with raltegravir in part 2. Additional inclusion criteria for this analysis were a reduction in plasma HIV-1 RNA level by 0.5 to 3 $\log_{10}$ copies/mL in part 1 and availability of a part 2 baseline genotype sample. Deep sequencing was performed and the following mutations examined: Y143C/H/R, Q148H/K/R, N155H, L74M, E92Q, T97A, E138K, G140A, V151U, and S230R. Seventeen patients were included in the analysis.

Prior to raltegravir monotherapy exposure, the RAMs Y143C, E138K, and S230R were each detected in a single subject. These mutations were seen in less than 4% of sequences obtained per subject. In 1 subject, G140S was detected in 3.04% of sequences while the subject was receiving raltegravir monotherapy. At the end of raltegravir monotherapy, 5 subjects had the following RAMs detected: Y142H, V151I, and E138K. These RAMs were seen in less than 1.5% of sequences. The detection of these RAMs had no impact on subsequent raltegravir virologic activity as measured by viral suppression at 96 weeks in part 2. The authors concluded that low levels of raltegravir RAMs, either at baseline or during raltegravir monotherapy, did not result in increased rates of virologic failure during subsequent raltegravir therapy.

Roquebert and colleagues described raltegravir-associated mutations in HIV-2-infected patients for whom a raltegravir-containing regimen was failing (Abstract 558). Seven heavily pretreated HIV-2-infected patients with incomplete viral suppression (defined as plasma HIV-2 RNA level > 100 copies/mL while receiving raltegravir and optimized background therapy) were identified through the ANRS (French National Agency for Research on AIDS and Viral Hepatitis) HIV-2 cohort. At failure, the genetic pathways associated with raltegravir resistance in HIV-2 included Y143C, Q148R/K, and N155H. In 6 of 7 samples these mutations, which mirror the primary positions for raltegravir resistance observed in HIV-1, were accompanied by the additional mutations T97A, G140S, and E92Q.

Marcelin and colleagues examined the prevalence of baseline mutations to the investigational INSTI S/GSK1349572 in INSTI-naive and raltegravir-treated patients (Abstract 554). Samples from 650 INSTI-naive patients and 84 patients experiencing raltegravir failure were sequenced for the presence of T124A, T124A/S153F,

S153Y, T124A/S153Y, and L101I, T124A/S153Y. All patients were infected with subtype-B HIV-1. INSTI-naive subjects included both antiretroviral therapy–naive and antiretroviral therapy–experienced individuals. In INSTI-naive patients, the mutations L101I and T124A were found in frequencies of 45.8% and 24.5%, respectively, and were described as polymorphisms. The S153Y/F substitutions were not observed in INSTI-naive subjects, either alone or in combination with other mutations. However, the mutations T124A and L101I/T124A were statistically significantly more frequent in subjects for whom raltegravir was failing than in INSTI-naive subjects.

Pharmacokinetic Considerations

Cervicovaginal Raltegravir Concentrations

Clavel and colleagues evaluated the concentrations of raltegravir in cervicovaginal fluid in 14 HIV-infected women receiving raltegravir-containing antiretroviral therapy (Abstract 608). They found that raltegravir concentrations were 2.3-fold higher in cervicovaginal fluids than in plasma. This confirms similar findings from HIV-uninfected women.

Effect of Etravirine on Darunavir and Raltegravir

Investigators Barrail-Tran and colleagues enrolled 12 participants from the ANRS TRIO trial in an intensive pharmacokinetic substudy to examine the interaction of etravirine with raltegravir and darunavir/r (Abstract 606). Participants in this substudy received darunavir, ritonavir, and raltegravir plus an investigator-selected background regimen of nRTIs with or without enfuvirtide. Participants added etravirine after 2 weeks. Investigators found that darunavir concentrations were increased in the presence of etravirine. Raltegravir concentrations were highly variable between participants and increased in the presence of etravirine. The observed levels of etravirine were lower than that reported in healthy volunteers. The overall safety and efficacy of this combination suggests that these interactions are not clinically important.

Nevirapine and Rifampicin

Lamorde and colleagues investigated the pharmacokinetics of nevirapine in 18 HIV-infected adults receiving rifampicin for TB (Abstract 602). Subjects were randomly assigned to start nevirapine at full dose (400 mg daily) or at lead-in dosing (200 mg once daily for 14 days followed by 400 mg daily). They found that subjects with the lead-in dosing had 40% lower exposure to nevirapine at treatment initiation. They also noted that the majority of subjects had 12-hour nevirapine concentrations that were below the minimum effective concentration. Further studies are needed on alternative dosing strategies.

Nevirapine and Antimalarial Medications

Kredo and colleagues investigated the interaction between nevirapine and lumefantrine concentrations in HIV-infected adults (Abstract 603). They enrolled 18 HIV-infected adults not receiving antiretroviral therapy and 18 stable on nevirapine-containing treatment. All participants received 6 doses of artemether/lumefantrine and underwent intensive pharmacokinetic sampling for 72 hours, with additional samples taken through 21 days. Subjects taking nevirapine had higher exposure to lumefantrine and were more likely to have therapeutic lumefantrine concentrations at day 7 (6 of 18 subjects not taking antiretroviral drugs had suboptimal concentrations compared with 1 of 18 taking nevirapine; $P = .06$). No differences were found between groups in observed adverse events or corrected QT intervals. The results were surprising, as the authors predicted that lumefantrine exposure would be decreased by nevirapine. Further study is clearly needed given the frequent clinical use of this drug combination in many parts of the world.

Atazanavir Exposure in HIV-Infected Women

Gandhi and colleagues performed intensive pharmacokinetic sampling in 122 women receiving atazanavir in the WIHS (Womens Interagency HIV Study) to identify factors associated with atazanavir exposure (Abstract 617). As expected, ritonavir coadministration resulted in a statistically significantly higher atazanavir exposure. The 24-hour area under the curve was reduced by 47% in women receiving hormonal contraception. Atazanavir concentrations were increased in those with renal insufficiency and in patients with higher bilirubin levels.

Buprenorphine/Naloxone and Once-Daily Lopinavir/Ritonavir

Bruce and colleagues examined the pharmacokinetics of buprenorphine/naloxone with and without once-daily lopinavir/r in HIV-uninfected subjects stabilized with 3 or more weeks of buprenorphine/naloxone therapy (Abstract 620). They did not find any statistically significant changes in buprenorphine/naloxone concentrations after 10 days of once-daily lopinavir/r except for increased clearance of a buprenorphine metabolite. No subjects exhibited opioid withdrawal. The authors concluded that no dose modification of buprenorphine/naloxone was needed when coadministering with lopinavir/r.

Antiretroviral Therapy and Emergency Hormonal Contraception

Carten and colleagues examined the effect of efavirenz on levonorgestrel given at doses standard for emergency contraception in 24 HIV-uninfected women (Abstract 934). Subjects were given a single dose of levonorgestrel before and after 14 days of efavirenz. The exposure to levonorgestrel was statistically significantly reduced with efavirenz. The 12-hour area under the curve and maximal concentration were reduced by 58% and 45%, respectively. The concentrations of levonorgestrel needed for efficacy are unknown, and the authors suggest that further stud-

ies should investigate alternative dosing strategies.

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13. Put Your Money Where Your Model Is: ART for the Prevention and Treatment of HIV/AIDS. Brian Williams and C Dye.

14. HIV in Couples. Rebecca Bunnell.

15. Evolving Realities of HIV Treatment in Resource-limited Settings. Papa Salif Sow.

18. The Future of PEPFAR: Discussion. Paul De Lay. (Presentation not available in abstract book. Available within webcast of The Future of PEPFAR: Moving Forward from Lessons Learned. Eric Goosby; at http://www.retroconference.org/2010/data/files/webcast_2010.htm)

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33. Decreases in Community Viral Load Are Associated with a Reduction in New HIV Diagnoses in San Francisco. Moupali Das-Douglas, P Chu, G-M Santos, S Scheer, W McFarland, E Vittinghoff, and G Colfax.

34. Monitoring the Impact of Expanded HIV Testing in the District of Columbia Using Population-based HIV/AIDS Surveillance Data. Amanda Castel, R Samala, A Griffin, T West-Ojo, A Greenberg, N Rocha, and S Hader.

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150LB. Organ and Cell Lineage Dissemination of XMRV in Rhesus Macaques during Acute and Chronic Infection. Prachi Sharma, S Suppiah, R Molinaro, K Rogers, J Das Gupta, R Silverman, J Hackett, Jr, S Devare, G Schochetman, and F Villinger.

151. XMRV: Examination of Viral Kinetics, Tissue Tropism, and Serological Markers of Infection. X Qiu, P Swanson, K-C Luk, J Das Gupta, N Onlamoon, R Silverman, F Villinger, S Devare, G Schochetman, and John Hackett, Jr.

153LB. Efficacy of ART with NVP + TDF/FTC vs LPV/r + TDF/FTC among Antiretroviral-naïve Women in Africa: OCTANE Trial 2/ACTG A5208. James McIntyre, M Hughes, J Mellors, Y Zheng, J Hakim, A Asmelash, F Conradie, R Schooley, J Currier, S Lockman, and A5208/OCTANE Study Team.

154. NNRTI-resistant Variants Detected by Allele-specific PCR Predict Outcome of NVP-containing ART in Women with Prior Exposure to sdNVP: Results from the OCTANE/A5208 Study. Valerie Boltz, Y Zheng, S Lockman, F Hong, E Halvas, J McIntyre, J Currier, M Hughes, J Coffin, J Mellors, and A5208 OCTANE Study Team.

155. Co-factors for HIV Incidence during Pregnancy and the Postpartum Period. John Kinuthia, J Kiarie, C Farquhar, B Richardson, R Nduati, D Mbori-Ngacha, and G John-Stewart.

157. 12-Month Follow-up of the SWEN Randomized Controlled Trials: Differential Impact of Infant Extended-dose NVP by CD4 Count on Prevention of HIV Transmission via Breastfeeding, and Infant Mortality. Abubaker Bedri and SWEN Study Team.

159. Plasma Frequencies of Nevirapine Resistance Influence Virologic Responses to Nevirapine Maintenance Therapy in Single-dose Exposed HIV-infected Children Initially Treated with Lopinavir HAART. Anitha Moorthy, L Kuhn, A Coovadia, T Meyers, G Sherman, W-Y Tsai, R Strehlau, Y Chen, E Abrams, D Persaud, and NEVEREST-2 Study Team.

160. Treatment Outcomes among HIV-infected Infants and Young Children following Modifications to Protease Inhibitor-based Therapy Due to TB Treatment. M Moodley, C Reitz, Lee Fairlie, H Moultrie, A Coovadia, L Kuhn, and T Meyers.

161LB. Interim Results from IMPAACT P1066: Raltegravir Oral Chewable Tablet Formulation in Children 6 to 11 Years. Sharon Nachman, E Acosta, P Samson, H Teppler, B Homony, T Fenton, E Handelsman, C Worrell, B Graham, A Wiznia, and the 1066 Group.

163. Association of *IL28B* Haplotypes with Chronic HCV Infection in HIV/HCV Co-infected Individuals. Julia di Iulio, P-Y Bochud, M Rotger, H Furrer, F Negro, A Telenti, A Rauch, and Swiss HIV and HCV Cohort Studies.

164. Genetic Variation in IL28B and Treatment-induced Clearance of HCV in HCV/HIV Co-infected Patients. Jacob Nattermann, M Vogel, A Baumgarten, U Naumann, H-J Stellbrink, M Danta, C Tural, R Bruno, U Spengler, and J Rockstroh.

165LB. Strong Association of a Single Nucleotide Polymorphism Located Near the Interleukin-28b Gene with Response to Hepatitis C Therapy in HIV/HCV Co-infected Patients. Norma Rallon, S Naggie, J Benito, J Medrano, C Restrepo, D Goldstein, K Shianna, J McHutchison, and V Soriano.

166. Baseline Liver Disease Is Independently Associated with Risk of Death among 631 HIV/HCV Co-infected Adults with Histologic Staging. Mark Sulkowski, S Mehta, C Sutcliffe, M Torbenson, Y Higgins, B Limketkai, R Moore, and D Thomas.

167. Sustained Virological Response to Interferon plus Ribavirin Reduces HIV Progression and Non-liver-related Mortality in Patients Co-infected with HIV and HCV. Juan Berenguer, M Crespo, M Galindo, M Téllez, C Barros, J Guardiola, R Rubio, E Barquilla, J Bellón, J González-García, and Gesida 3603 Study Group.

171. HIV Treatment Modulates Global Resting Cerebral Blood Flow in HIV+ Subjects. J Thomas, H Peng, T Benzinger, M Mintun, D Clifford, and Beau Ances.

172. Correlates of CSF Viral Loads in 1221 Volunteers of the CHARTER Cohort. Scott Letendre, C FitzSimons, R Ellis, D Clifford, A Collier, B Gelman, J McArthur, F Vaida, R Heaton, I Grant, and the CHARTER Group.

173. Correlates of Epidermal Nerve Fiber Density in HIV-infected Individuals without Neuropathy prior to Initiation of Potent ART. Cecilia Shikuma, J Ananworanich, V Valcour, A Thomas, V DeGruttola, J McArthur, P Praihirunkit, P Hongchookiat, P Mathajittiphun, N Phanuphak, and SEARCH 003 Protocol Team.

174. An SIV Macaque Model of HIV-induced Peripheral Neuropathy. Joseph Mankowski, V Laast, J Dorsey, C Pardo, P Hauer, R Adams, J McArthur, and M Ringkamp.

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177. *Treponema pallidum* Strain Type Is Associated with Neurosyphilis. Christina Marra, S Sahi, L Tantalo, T Reid, S Lukehart, and A Centurion.

178. NK Cell Function. Galit Alter.

179. Chasing Immunity—The Ongoing Search for Correlates of Protection Induced by SIVΔ*nef*. Paul Johnson. (Presentation added late and not available in abstract book. Available as webcast at http://www.retroconference.org/2010/data/files/webcast_2010.htm)

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213. HIV-1 Vpu Internalizes Cell-surface BST-2/Tetherin and Leads It to Lysosomes. Y Iwabu, H Fujita, M Kinomoto, K Kaneko, Y Ishizaka, Y Tanaka, T Sata, and Kenzo Tokunaga.

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253. Influence of Host Gene Transcriptional Level and Orientation on HIV-1 Latency in Primary Cells. Liang Shan, H-C Yang, S Rabi, H Bravo, J Siliciano, R Irizarry, and R Siliciano.

257. Establishment of Latency in Naïve and Central Memory T Cells in a Primary CD4 Cell Model. Maile Young, D Richman, and C Spina.

258. Myeloid DC Induce HIV-1 Latency in Resting CD4+ T Cells *in vitro*. V Evans, S Saleh, P Cameron, and Sharon Lewin.

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403. 2 Patterns of Cerebral Metabolite Abnormalities Are Detected on Proton Magnetic Resonance Spectroscopy in HIV+ Subjects Electively Commencing ART. A Winston, C Duncombe, P Li, J Gill, S Kerr, Rebekah Puls, S Taylor-Robinson, S Emery, D Cooper, for the Altair Study Group.

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412. Mitochondrial Dysfunction in HIV and SIV-associated Sensory Neuropathy. H Lehman, J Mankowski, and Ahmet Hoke.

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543. A Highly Sensitive and Specific Model for Predicting HIV-1 Tropism in Treatment-experienced Patients Combining V3 Loop Sequences Interpretation and Clinical Parameters. Victoria Sánchez, C Robledano, B Lumbreras, S Padilla, E Poveda, V Soriano, C De Mendoza, M Masiá, and F Gutiérrez.

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