

Topics in HIV Medicine®

A publication of the International AIDS Society–USA

Highlights of the 15th Conference on Retroviruses and Opportunistic Infections

| | |
|--|----|
| Basic Science Summary | 1 |
| <i>Mario Stevenson, PhD</i> | |
| <i>Cellular Restrictions and Viral Defenses • Cellular Cofactors in the Viral Replication Cycle • Viral Navigation Through the Cell • Viral Dissemination Between Cells • Inhibitors and Enhancers of Viral Infectivity • Underlying Mechanisms of Viral Pathogenicity</i> | |
| Basic HIV Vaccine Development | 7 |
| <i>David I. Watkins, PhD</i> | |
| <i>Vaccine Development: The Problems • Pathogenesis Studies • Vaccines in Phase I and II Studies and Therapeutic Vaccines • Frontiers in Vaccine Research • A New Attenuated SIV for Understanding the Correlates of Protection</i> | |
| HIV Testing and Prevention Strategies | 9 |
| <i>Susan Buchbinder, MD</i> | |
| <i>HIV Testing Programs • HIV Vaccines • Herpes Suppression • Male Circumcision • Preexposure Prophylaxis and Microbicides • Prevention of HIV Transmission Through Breastfeeding • Factors Driving the US HIV Epidemic</i> | |
| Neurologic Complications of HIV Disease and Their Treatment | 15 |
| <i>Scott Letendre, MD, J. Allen McCutchan, MD, MSc, and Ronald J. Ellis, MD, PhD</i> | |
| <i>Neuroeffectiveness of Antiretroviral Drugs • Susceptibility to NeuroAIDS: HIV Correlates, Host Correlates, and Comorbidities • Peripheral Neuropathy • Other Neurologic Infections</i> | |
| Complications of HIV Disease and Therapy | 23 |
| <i>Judith S. Currier, MD, and Diane V. Havlir, MD</i> | |
| <i>Morbidity and Mortality in the Potent Antiretroviral Therapy Era • Cardiovascular Disease • Lipoatrophy and Lipohypertrophy • Bone Density • Renal Disease • Toxicity in Resource-limited Settings • Aging • Tuberculosis Coinfection • Hepatitis C Virus • Opportunistic Infections and Timing of Therapy • Immune Reconstitution</i> | |
| Advances in Antiretroviral Therapy | 31 |
| <i>Timothy J. Wilkin, MD, MPH, Barbara Taylor, MD, Susan Olender, MD, and Scott M. Hammer, MD</i> | |
| <i>Investigational Agents • Clinical Trials in Treatment-naïve and in Treatment-experienced Subjects • Treatment Strategies • Antiretroviral Therapy in Resource-limited Settings • Mother-to-Child Transmission • Resistance • Acute Infection • GB Virus C • Race, Ethnicity, and Sex as Predictors of Virologic Outcomes and Mortality • Outcome Data • Predictors of Response to Second-line Antiretroviral Therapy • Pharmacokinetic Considerations</i> | |

Special Contribution

| | |
|---|----|
| Update of the Drug Resistance Mutations in HIV-1: Spring 2008 | 62 |
| <i>International AIDS Society–USA Drug Resistance Mutations Group</i> | |



About This Issue

This issue features highlights of the 15th annual *Conference on Retroviruses and Opportunistic Infections*, held in Boston, Massachusetts, from February 3 to 6, 2008, and an update of drug resistance mutations in HIV from the IAS-USA Drug Resistance Mutations Group. Mario Stevenson, PhD, reviews recent advances in basic HIV science and pathogenesis, including factors that influence virus-host cell interplay and mechanisms of viral pathogenesis. David I. Watkins, PhD, reviews the current state of HIV vaccine development and the need to refocus efforts toward basic research such as on antibody responses and on understanding the first infecting viruses and the correlates of protection. Susan Buchbinder, MD, reviews testing and prevention strategies, including the failure of a candidate HIV vaccine, and provides updates on male circumcision, HIV testing programs, and the larger factors driving the US and global HIV epidemic. Neurologic complications of HIV disease are reviewed by Scott Letendre, MD, J. Allen McCutchan, MD, MSc, and Ronald J. Ellis, MD, PhD, who discuss advances in understanding neuroeffectiveness of antiretroviral drugs, factors influencing susceptibility to neuroAIDS, and neurologic coinfections. Judith S. Currier, MD, and Diane Havlir, MD, review the complications of HIV disease and therapy such as coinfections, cardiovascular disease, renal disease, toxicity in resource-limited settings, and others. Timothy J. Wilkin, MD, MPH, Barbara Taylor, MD, Susan Olender, MD, and Scott M. Hammer, MD, address advances in antiretroviral therapy, including recently approved and investigational drugs, management of treatment-naïve and -experienced patients, prevention of mother-to-child transmission, and drug resistance.

Topics in HIV Medicine®

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Basic Science Summary 1
Mario Stevenson, PhD

Basic HIV Vaccine Development 7
David I. Watkins, PhD

HIV Testing and Prevention Strategies 9
Susan Buchbinder, MD

Neurologic Complications of HIV Disease and Their Treatment 15
Scott Letendre, MD, J. Allen McCutchan, MD, MSc, and Ronald J. Ellis, MD, PhD

Complications of HIV Disease and Therapy 23
Judith S. Currier, MD, and Diane V. Havlir, MD

Advances in Antiretroviral Therapy 31
Timothy J. Wilkin, MD, MPH, Barbara Taylor, MD, Susan Olender, MD, and Scott M. Hammer, MD

Abstracts Cited 69

Special Contribution

Update of the Drug Resistance Mutations in HIV-1: Spring 2008 62
International AIDS Society–USA Drug Resistance Mutations Group

Announcements

Guidelines for Authors and Contributors 78
Educational Programs of the International AIDS Society–USA 61
Subscription Request/Address Change Form 80

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Basic Science Summary

Mario Stevenson, PhD

The scientific advances made in the year leading up to the 15th Conference on Retroviruses and Opportunistic Infections were overshadowed, to some extent, by setbacks in the AIDS vaccine research arena and in particular, the failure of the Merck STEP trial. Arguably, these disappointments were offset by strong advances that were being made in basic science and pathogenesis. In particular, recent discoveries into cellular factors that influence virus–host cell interplay and new insights into the mechanisms of viral pathogenesis were highlighted at the meeting. These research discoveries paint an optimistic picture regarding the development of new strategies to combat HIV and AIDS.

Cellular Restrictions and Viral Defenses

One of the most exciting areas of AIDS research in the past several years has been in cellular restrictions. This area of research was initiated with independent demonstrations by Malim's and Kabat's groups^{1,2} that cells retained an activity that dominantly suppressed HIV-1 infection and that the HIV-1 accessory protein Vif counteracted the dominant restriction. Four years later, Malim and colleagues identified the nature of the restriction itself.³ The restriction, called APOBEC 3G, is a cytidine deaminase that, when packaged into virions, causes extensive G-to-A hypermutation during reverse transcription of viral complementary DNA (cDNA). This compromises the stability of the viral cDNA as well as the functionality of the resulting provirus. To avoid this cellular restriction, primate lentiviruses have evolved a *vif* gene whose function is to target APOBEC 3 proteins for proteasomal destruction.

In 2004 the Sodroski laboratory identified a second cellular restriction termed TRIM 5 α .⁴ This protein targets the viral Gag polyprotein to exert a species-specific inhibitory effect on early events in virus infection. For example, the targeting of HIV-1 Gag by monkey TRIM 5 α explains the resistance of cer-

tain monkey cells to HIV-1 infection. Subtle amino acid changes can render Gag insensitive to TRIM 5 α restriction.

Presentations by Guatelli (Abstract 104A) and Bieniasz (Abstract 114) described a third antiviral restriction that is counteracted by the accessory protein Vpu of primate lentiviruses. Research from a number of groups has revealed that in primary cells and in some cell lines, Vpu-defective viruses are unable to detach from the surface of the infected cell. Spearman's group⁵ provided evidence that these cells contain a dominant restriction and that the Vpu protein counteracts the restriction.

At the conference, the Bieniasz and Guatelli groups independently revealed the nature of the cellular restriction that is counteracted by Vpu. In his plenary presentation, Bieniasz summarized recently published findings⁶ that Vpu counters a cellular protein called CD317, or BST-2. Bieniasz's group has coined this protein a tetherin because it tethers fully formed virions to the surface of the infected cell. Their research has revealed that tetherin is an interferon- α inducible protein that causes retention of viral particles on the cell surface. These viral particles are subsequently endocytosed into CD317-positive cytoplasmic compartments. When tetherin was depleted by RNA interference, virus particle release was no longer Vpu-dependent. Bieniasz also demonstrated that Vpu colocalized with tetherin in infected cells. Guatelli, in his presentation, extended these findings and demonstrated that Vpu directly interacts with BST-2 and in the presence of Vpu,

surface levels of BST-2 are diminished. The BST-2 protein is a glycosylphosphatidylinositol (GPI)-anchored membrane protein of unknown function; BST-2 most likely, crosslinks cholesterol-rich virion membranes with the plasma membrane of the cell. Furthermore, the cellular expression of BST-2 appears to mimic the cells in which virus release is Vpu-dependent. Therefore, BST-2 expression is high in HeLa cells, in which virus production is Vpu-dependent, but low in HEK293 cells, in which Vpu is not required for efficient virus release. These presentations summarize exciting advances in understanding cellular restrictions against primate lentiviruses. That 2 of the 4 viral accessory proteins (Vif, Vpu) have evolved as counterdefenses to cellular restrictions illustrates how primate lentiviruses have responded to evolutionary pressure to evolve defense mechanisms to counter these cellular restrictions. Small-molecule inhibitors of these viral accessory proteins would be predicted to block the viral defense against the cellular restrictions, thereby rendering cells resistant to virus infection.

Cellular Cofactors in the Viral Replication Cycle

Presentations describing new cellular cofactors of HIV-1 replication were also highlights of the conference. Primate lentiviruses have a limited genetic repertoire comprising only 9 genes. Therefore, primate lentiviruses commandeer cellular proteins to complete certain aspects of their replication cycle. For example, these viruses use cell-surface proteins such as CD4, CCR5, and CXCR4 to gain entry to the host cell. An exciting presentation by Brass (Abstract 104bLB) summarized his group's recent published study,⁷ which identified numerous host proteins required for HIV-1 infection. Brass and colleagues employed a functional genomic screen to survey proteins of the cell that were necessary for early and late events in

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HIV-1 replication. In their screen, they transfected HIV-1-susceptible indicator cells with short interfering RNA (siRNA) pools. These cells were then infected with HIV-1. Supernatants of the transfected cells were recovered and used to initiate fresh infections of indicator cells. This 2-step process was used to reveal genes that were important for early events in viral replication as well as late events in the viral life cycle.

The approach identified over 250 host factors (referred to by the group as HIV-dependency factors, HDFs). Thirty-six host factors identified in the screen were previously implicated in HIV-1 biology (genes such as *CD4*, *CXCR4*, nuclear factor [*NF*]- κ B). The remaining 237 genes were novel, and more than 100 of these revealed a phenotype when silenced by 2 or more individual siRNAs. The validity of the observations was increased by the fact that some HDFs found to be important for HIV replication were part of the same macromolecular complex. For example, 4 of 6 subunits of the nuclear pore complex *nup160* sub-complex were identified as HDFs. The involvement of the nuclear pore complex in HIV-1 infection is not surprising because a long-recognized feature of primate lentivirus infection is the ability to translocate through the nuclear pore envelope. This is a property that has been considered necessary for the ability of primate lentiviruses to infect nondividing cells. Therefore, silencing of nuclear pore complex components likely prevented efficient translocation of viral reverse transcription complexes from the cytoplasm to the nucleus.

Three late-acting HDFs were found to encode enzymes involved in the glycosylation of cellular proteins. Again, this is not surprising because the viral envelope protein is heavily glycosylated, and this modification is necessary for envelope function. However, the screen by Brass and colleagues revealed some unexpected HDFs. For example, several factors involved in autophagy, which is essential for the degradation and recycling of cellular components, were required for HIV-1 infection. This finding is surprising because no published scientific data link the HIV-1 rep-

lication cycle with autophagy. Similarly, RAB6 and VPS53, which are important for retrograde vesicular transport, were necessary for HIV-1 infection but were dispensable for murine leukemia virus (MLV) infection and for HIV-1 infection by the endocytic route.

Further insight into fundamental steps in HIV-1 replication were also revealed by the demonstration by Brass and colleagues that the karyophenin transportin3 and RAN BP2 were required for HIV-1 infection. The RAN BP2 protein is large and lies on the cytoplasmic side of the nuclear pore. This protein contains phenylalanine-glycine (FG)-domains. Current models of nuclear import suggest that nuclear pore filaments capture proteins to be imported, and these proteins "slide" down the FG domains toward the nuclear pore itself. Nuclear pore proteins also contain FG domains, which then capture the importing cargo. Transportin is a nuclear importer shown to be important for recruiting serine arginine splice factors to the nucleus. It was required for HIV-1 entry and for HIV-1 entry by the endocytic route but was dispensable for MLV infection. This information fits current models of lentivirus biology, in which lentiviruses have the capacity to translocate across the nuclear envelope, whereas simple retroviruses such as MLV cannot.

These observations underscore a model in which HIV-1 usurps transportin3 and proteins of the nuclear pore complex to shuttle into the nucleus of the nondividing cell. Future research will seek to determine which HIV-1 proteins interact with these nuclear pore constituents. More importantly, the identification of more than 200 novel cellular cofactors is an important advancement because each cellular cofactor represents a potential point of intersection with which to truncate HIV-1 replication. For example, small-molecule inhibitors of HIV-1 envelope-CCR5 interaction are being exploited clinically for the treatment of HIV-1 infection. The challenge will be to use this information to accelerate the development of novel HIV-1 inhibitors.

In session 31, several presentations focused on cellular proteins that influ-

ence HIV-host cell interactions. For example, Hakata (Abstract 100) described the role of the cellular proteins DCAF1 and DDB1 in the activity of the HIV-1 accessory protein Vpr. Several activities have been described for the HIV-1 Vpr protein, including enhancement of macrophage infection, cell cycle arrest, and association with DNA repair enzymes. Hakata presented evidence that the interaction of Vpr with proteins such as DDB1 is species-specific in that the Vpr of simian immunodeficiency virus of African green monkeys (SIV_{agm}) was unable to bind human DDB1. As a consequence, Vpr of SIV_{agm} was unable to induce cell-cycle arrest in human cells. This underscores many recent studies implicating DDB1 as a cellular cofactor necessary for induction of cell-cycle arrest by Vpr.

In another presentation (Abstract 150), de Noronha described the identification of proteins that interact with HIV-1 Vpr to mediate its ability to induce cell-cycle arrest. His group's studies also revealed an association between HIV-1 Vpr and a previously described Vpr binding protein (originally Vpr BP, now called DCAF1) that forms part of a ubiquitin-ligase complex. This suggests that Vpr commandeers the ubiquitin-ligase complex perhaps to degrade other cellular proteins; however, the identities of cellular proteins that may be targeted for degradation by Vpr are not known. The ability of Vpr to induce cell-cycle arrest was inhibited when DDB1 was depleted, suggesting that the protein targeted for degradation by Vpr is required for normal cell-cycle progression.

The presenter also raised the possibility that Vpr may target DNA repair enzymes for degradation. Previous studies have suggested that Vpr associates with and promotes degradation of the DNA repair enzyme uracil DNA glycosylase to prevent destruction of APOBEC-3-edited cDNA. He presented evidence that overexpression of DDB1, a protein that binds Vpr, impaired turnover of uracil DNA glycosylase and promoted its redistribution to the cell nucleus. With his colleagues, de Noronha suggests a model in which uracil DNA glycosylase associates normally with the DCAF1, DDB1, CUL4A ubiquitin-li-

gase complex and is targeted for proteasomal destruction upon ubiquitylation by this complex. In the presence of Vpr, however, association of uracil DNA glycosylase with the ubiquitin-ligase complex is enhanced, thereby augmenting degradation or nuclear shuttling of the glycosylase.

Viral Navigation Through the Cell

New insight was provided in session 15 into how HIV-1 navigates through the cell and between cells. After infection of cells by HIV-1, reverse transcription of viral cDNA is initiated in the cytoplasm. Nascent viral cDNA then translocates to the nucleus in the context of a high-molecular-weight nucleoprotein complex (commonly referred to as the reverse transcription complex). In the nucleus, a derivative of the reverse transcription complex (commonly referred to as the preintegration complex) binds to chromatin and catalyzes integration of viral cDNA with host cell DNA.

The diameter of the reverse transcription complex has been estimated to be approximately 30 nm, whereas the diameter of the cell is nearer 20 μm to 30 μm . Therefore, the voyage that the viral reverse transcription complex takes from the point of virus entry at the cell membrane to the host cell nucleus can be compared to the movement of a soccer ball across a soccer field. Thus, the virus likely uses a road map to navigate through the cell in an orderly fashion.

In her presentation (Abstract 49), Arhel provided a summary of current knowledge about the road map used by viruses such as HIV-1 to navigate from the plasma membrane to the nuclear envelope. She presented a model in which reverse transcription complexes deposited in the cytoplasm upon infection of the cell rapidly contact microtubules and then transit to actin filaments. These reverse transcription complexes then move along actin filaments at a speed of approximately 1 $\mu\text{m}/\text{s}$ toward the nuclear membrane. At the nuclear membrane, a moiety on viral cDNA, referred to as the central

DNA flap, promotes the maturation of reverse transcription complexes to the preintegration complexes by prompting dissociation of the capsid shell. These events are prerequisites for the ability of the reverse transcription complex to translocate through the nuclear pore complex. Arhel and colleague Chameau have used electron microscopy to provide images of reverse transcription complexes docked at a nuclear pore complex.

Viral Dissemination Between Cells

Hope, in his introductory comments to the session, summarized current models of how HIV-1 virions are transmitted between cells. Previously, it was assumed that in HIV-1-infected individuals, viral particles produced by infected cells entered body fluids, where they randomly encountered new target cells. However, studies from the research groups of Martin and Ho demonstrated that cell-free simian immunodeficiency virus (SIV) particles, when injected into monkeys, were rapidly cleared from body fluids to the extent that cell-free virions had a half-life of minutes. For this reason, many investigators have favored the model in which viruses spread in the tissues between cells that are in close contact. Hope presented microscopic evidence for the transmission of viruses between cells through a virologic or infectious synapse.⁸ These synapses comprise existing cellular pathways involved in antigen presentation and T-cell communication (for review see Jolly and Sattentau⁹).

It is now apparent that a variety of retroviruses and lentiviruses exploit receptor-containing adhesive junctions formed between cells in order to pass directly from infected to uninfected immune cells. Mothes (Abstract 50) presented live images of retroviruses transmitting between cells and summarized exciting new published information on the role of nanotubes in the transmission of HIV-1 between cells.¹⁰ He and his group have been investigating why the infectivity of HIV-1 is 2 to 3 \log_{10} higher when cells are in

contact and whether movement between cells is through diffusion or a direct process. For example, in the case of human T-lymphotrophic virus 1, there is an almost complete lack of virus-particle release into cultured fluids, yet the virus is able to spread efficiently between cells. Using fluid fluorescently labeled MLV as a model system, Mothes and colleagues obtained evidence that viruses move from infected to uninfected cells through filopodia. These filopodia are thin membrane projections along which viral particles “surf” unidirectionally toward the uninfected cell. Filopodia are normally short-lived structures; however, during the transmission of viral particles, they appear to form stable bridges between infected and uninfected cells. Virus particles can take in the order of 20 minutes to move along filopodia that connect the infected and uninfected cells. These filopodia can extend 10 μm to 20 μm from the surface of the infected cell.

The presence of filopodial bridges between infected and uninfected cells is dependent upon the presence of the viral envelope in the infected cell and the transmembrane receptor on the target cell. Although filopodia appear as rodlike membrane protrusions, virus particles surf on the outside of the filopodia during cell-to-cell transmission. The HIV-1 transmits across filopodia formed between T cells.¹⁰ Also, nanotubes physically connect T cells over long distances and offer a route of transmission for HIV-1. Nanotubes have been shown to connect many cell types and allow transmission of calcium signals. They are formed when T cells make contact and subsequently part, and they can extend several cell diameters (100 μm). As with the distribution of MLV through filopodia, HIV dissemination through nanotubes is receptor dependent and occurs at a rate of approximately 0.08 $\mu\text{m}/\text{s}$. Therefore, membrane nanotubes provide a novel route for cell-to-cell dissemination of HIV-1. Nanotubes most likely avoid the rate-limiting diffusion step of cell-free virus spread, and further, may help minimize exposure of the virus particle to neutralizing antibody.

Inhibitors and Enhancers of Viral Infectivity

Kirchhoff, in his plenary presentation (Abstract 66), described the presence of natural enhancers and inhibitors of HIV-1 infectivity. He and his colleagues undertook a systematic analysis of compounds present in human body fluids that could influence HIV-1 infectivity. The investigators obtained a peptide library from large volumes of hemofiltrate obtained from individuals with renal failure. This hemofiltrate contains toxins as well as substances with a molecular rate less than 30 kDa. The peptide library obtained from the hemofiltrate was then screened for anti-HIV-1 infectivity.

A 20-amino-acid fragment of α_1 -antitrypsin, termed VIRIP, was identified as a potent inhibitor of HIV-1 replication. The protein α_1 -antitrypsin is present in large quantities in individuals with infection and inflammation. Its main function is to inhibit neutrophil elastase in the lung and the liver. The peptide VIRIP was active against all HIV-1 and SIV isolates and inhibited viral entry.¹¹ Although the inhibitory concentration of the initial VIRIP was in the micromolar range, structure-activity-relationship analysis led to the development of analogues with greatly increased antiviral potency. Importantly, VIRIP was active against HIV-1 variants resistant to other types of entry inhibitors such as T20. These studies suggest that VIRIP may target a novel step in HIV-1 entry before or shortly after insertion of the fusion peptide of HIV-1 envelope into the target cell membrane.

Kirchhoff and colleagues then used a similar approach to screen a semen-derived peptide library for novel inhibitors of HIV-1 infection. Although the goal was to identify an inhibitor of HIV-1 infection in semen, all of the peptide pools analyzed failed to significantly inhibit HIV-1 infection. In contrast, 1 of the peptide fractions markedly enhanced HIV-1 infection. This fraction contained a 34- to 40-amino-acid fragment of prostatic acid phosphatase (PAP). Although freshly diluted synthetic PAP fragments were inactive against HIV-1 infection, these

became active after overnight incubation. Electron microscopy of the active form revealed the presence of amyloid fibrils of PAP. These fibrils were coined semen enhancer of virus infection (SEVI) and were found to capture virus particles and mediate their attachment to the surface of target cells. The SEVI enhanced both R5 and X4 HIV-1 infection of lymphocytes and macrophages. The enhancing effect of SEVI was greatly manifested during infection with low amounts of input virus. Remarkably, SEVI enhanced HIV-1 infection of lymphocytes and cells of the CEM cell line by up to 400,000-fold. This meant that in the presence of SEVI, 1 to 3 HIV-1 particles was sufficient for productive infection.¹² This study has important implications for the understanding of HIV-1 transmission at mucosal surfaces and for the development of microbicide. It will be important to identify the protease that clears PAP to generate the active peptide because interfering with peptide formation as well as amyloid fibril formation could represent a strategy for prevention of HIV-1 transmission across mucosal surfaces.

Underlying Mechanisms of Viral Pathogenicity

Exciting research aimed at understanding the underlying mechanism of pathogenic lentiviral infections was represented at the meeting in sessions 11 and 36. Pathogenic lentivirus infection (eg, HIV-1 infection of humans, SIV infection of rhesus macaques) is reflected by high-level viremia, accelerated CD4 + lymphocyte turnover, and increased immune activation. In contrast, nonpathogenic lentivirus infections (eg, SIV infection of sooty mangabeys) is reflected by high-level viremia and accelerated CD4 + lymphocyte turnover but normal levels of immune activation. Therefore, the extent of immune activation appears to be a distinguishing feature between pathogenic and nonpathogenic lentivirus infection.

For this reason, mechanisms driving immune activation have been of intense interest to AIDS investigators because this area may hold the key

to how HIV-1 causes disease. At this year's conference, research was presented to suggest that immune activation is driven by translocation of bacterial products across mucosal surfaces. At last year's conference (2007), several presentations revealed the rapid destruction of gut lymphoid tissue during acute HIV-1 infection. Those studies showed that CD4 +, CCR5 + memory T cells were rapidly depleted as a consequence of HIV-1 infection.

This year, 4 presentations (Abstracts 115, 116, 117LB, 374) provided evidence that a subset of these cells (T_H17 -CD4 + T cells) are preferentially depleted in the gastrointestinal (GI) tract of HIV-1-infected humans but not SIV-infected sooty mangabeys. The significance of this finding is that T_H17 cells produce interleukin 17 (IL-17), which is thought to be important for antibacterial immunity. This cytokine is responsible for recruiting neutrophils, inducing the proliferation of GI enterocytes, and inducing the production of antibacterial defensins. The T_H17 cells were found to be preferentially located in the GI tract but present at very low frequencies in blood. Therefore, the destruction of T_H17 cells may undermine the ability of the immune system to control microbial agents. Furthermore, if IL-17 plays an important role in the proliferation of GI enterocytes, loss of the T_H17 -CD4 + subset may compromise the integrity of mucosal surfaces and permit translocation of bacterial products from the gut lumen into mucosal tissue.

This hypothesis was supported by 2 presentations (Abstracts 119, 377) that demonstrated a direct correlation between the extent of immune activation and the presence of bacterial products such as lipopolysaccharide or bacterial DNA. Because activated lymphocytes are preferred targets for HIV-1 infection, the increased immune activation driven by microbial translocation would serve to enhance conditions for viral replication and spread. These observations have very important implications for HIV-1 pathogenesis and the treatment of HIV-1 infection. If damage to the mucosal barrier and microbial translocation are triggering events in pathogenic in-

fection, strategies aimed at preserving mucosal activity and neutralizing microbial products would be predicted to limit the extent of pathogenicity. Next year's conference is likely to provide a forum for the presentation of research findings based on these therapeutic strategies.

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A list of all cited abstracts appears on pages 69-77.

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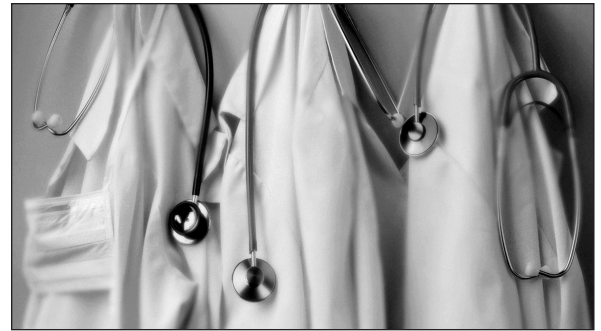
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Cases on the Web – www.iasusa.org/cow

Cases on the Web (COW) is an ongoing series of case-based, advanced online continuing medical education activities sponsored by the International AIDS Society—USA that offers physicians access to convenient, top-quality education about HIV and AIDS care.

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Our latest *COW* activities feature an enhanced and dynamic case-based format. Participants start making clinical and case-management decisions from the outset of the activity, and each clinical decision point in the unfolding case is supported by a succinct discussion of related medical findings, research-based evidence, and related practice-management recommendations.



NEW

Strategic Use of Antiretroviral Drugs in the Patient with Numerous Treatment Failures and Multidrug Resistance

by Harry W. Lampiris, MD, and Elvin H. Geng, MD

Managing HIV treatment-experienced patients has become more complicated than ever owing to the arrival of 2 new classes of antiretroviral agents and half-a-dozen new antiretroviral drugs. In this state-of-the-art activity, learners will identify key mutations associated with antiretroviral drug resistance and strategic approaches to using new antiretroviral drugs in preexisting classes and those in new classes in designing antiretroviral salvage regimens.

Syphilis in the HIV-infected Patient

by Jeanne M. Marrazzo, MD, MPH

The incidence of syphilis has increased dramatically among HIV-infected persons in the United States. This well-received new *COW* activity introduces learners to routine screening for sexually transmitted diseases in the HIV-infected patient, interpreting the significance of a reactive nontreponemal serologic test for syphilis, and determining the management of latent syphilis in the HIV-infected patient.

Severe Mycobacterial Infection in a Patient with Advanced AIDS

by William J. Burman, MD

HIV health care practitioners need expertise in diagnosing and managing HIV-related mycobacterial infections because of the atypical presentation, severity, and high likelihood for person-to-person spread of such infections. This activity discusses radiographic features that distinguish HIV-related mycobacterial infections from *Pneumocystis jirovecii* pneumonia, antiretroviral drugs that cannot be given with rifampin-based tuberculosis treatment, and the differential diagnosis of immune reconstitution inflammatory syndrome (IRIS).

Using Biomedical Prevention as Part of HIV Prevention

by Raphael J. Landovitz, MD

The use of postexposure prophylaxis (PEP) after sexual exposure to HIV has been recommended by the Centers for Disease Control and Prevention. This engaging *COW* activity introduces crucial considerations about initiating PEP after sexual exposure to HIV and about creating a strategy to avoid HIV infection for high-risk, HIV-seronegative patients, as well as what is known about preexposure prophylaxis for HIV (PrEP).

Selected Endocrine Problems in HIV-infected Patients

by Todd T. Brown, MD, PhD

Because current antiretroviral drug regimens have dramatically reduced morbidity and mortality among HIV-infected patients, HIV health care practitioners are increasingly managing chronic complications of therapy and conditions related to aging. This new *COW* activity focuses on diabetes mellitus and adrenal insufficiency, summarizes current evidence about the optimal evaluation of these disorders, and highlights their causes, presentation, and treatment in HIV-infected patients.

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- **Managing Oral Health Concerns for People with HIV Infection**
- **HIV and Hepatitis C Virus Coinfection**
- **HIV and Travel Medicine**

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

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Basic HIV Vaccine Development

David I. Watkins, PhD

The highlight of the 2008 Conference on Retroviruses and Opportunistic Infections was a sober assessment of the HIV vaccine field by one of its pioneers. Desrosiers delivered a plenary session in which he called for refocusing our HIV vaccine effort. He suggested that none of the current vaccine candidates in human clinical trials stands a chance against HIV. Thus, we need to redirect our efforts to basic vaccine research. This call for a sea change in how we carry out HIV vaccine research has already had an impact, prompting a recent HIV vaccine summit in Bethesda, MD. This will likely herald a new era in HIV vaccine research, resulting in a redoubling of effort to uncover innovative new ways of making an HIV vaccine.

Desrosiers delivered a candid, and to some a controversial, assessment of the HIV vaccine field, providing the sobering highlight of the recent 15th Conference on Retroviruses and Opportunistic Infections in Boston. He suggested that we do not have a viable HIV vaccine candidate in development currently and that we need to return to basic research. Only a creative idea would solve the enormous barriers to an effective vaccine.

HIV Vaccine Development: The Problems

The enormity of the problems posed by this virus to the vaccine field was delineated by Desrosiers (Abstract 91). He began by posing 3 questions: where are we, where are going, and where should we be going? He then discussed whether a vaccine for HIV was feasible at this time. He pointed out that the natural response to HIV neither controls viral replication nor prevents superinfection. The enormous sequence diversity and the fact that we do not know what a protective immune response is against this virus make it unlikely that we have the necessary information to make a vaccine at this stage. Furthermore, our best vaccine results to date in monkeys afford only a 1.0- to 1.5- \log_{10} copies/mL reduction in viral replication—and these trials were conducted under

highly idealized conditions with homologous viral challenges. We are 0 for 3 in clinical vaccine trials, and we have no idea how to elicit a broadly reactive neutralizing antibody response.

Desrosiers asked whether we should be surprised by the failure of the STEP trial vaccine. He referred to monkey studies using a trivalent adenovirus type 5 (Ad5) vaccine (Merck & Co, Inc) that afforded little or no reduction in viral load after challenge with a monkey virus that was exactly matched in sequence to the vaccine. He went further to ask whether any of the products in the vaccine pipeline had a reasonable chance of showing efficacy, especially against nonhomologous challenges, and again was pessimistic about the likelihood of success with these products.

Finally, Desrosiers suggested that we rethink the way in which the National Institutes of Health (NIH) spends its HIV vaccine budget. Given the paucity of good vaccine candidates currently, we should probably refocus our research efforts on basic discovery.

Desrosiers suggested several topics that should be high priority for discovery research. How do we elicit broadly reactive neutralizing antibodies? We need novel vaccine and preventive concepts. We need to understand what is responsible in those rare cases in which virus replication is controlled: in elite controller humans and in macaques vaccinated with attenuated simian immunodeficiency viruses (SIVs) that subsequently control replication of highly pathogenic challenge viruses. We also need to understand why sooty

mangabys and African green monkeys have high levels of viral replication but show no signs of disease. Desrosiers also called for comparative testing of vaccines in macaques and humans.

Nathanson (Abstract 92) then gave the second plenary presentation of the session and discussed vaccine approaches and animal models. Many of his points supported and expanded those of Desrosiers. Nathanson emphasized the need to get honest answers from the nonhuman primate challenge models and wondered if a refocusing of the vaccine field is necessary.

Pathogenesis Studies with Relevance to Basic Vaccine Research

In the conference session titled “Viral Pathogenesis and Immune Surveillance,” several oral presentations addressed T-cell responses to SIV and HIV that might be relevant to vaccine development. Loffredo (Abstract 18) suggested that broad CD8+ T-cell responses might play a role in control of SIV replication in macaques that expressed protective major histocompatibility complex types. Streeck (Abstract 22) presented interesting data from the Altfeld group suggesting that “polyfunctional” CD8+ T-cell responses were a result of antigen load and sequence diversification. Should this prove to be correct, it will have implications for assessing CD8+ T-cell responses in vaccines.

Vaccines in Phase I and II Studies and Therapeutic Vaccines

Robinson (Abstract 85) presented her group’s safety and immunogenicity data for the clade-B DNA-priming and modified vaccinia virus Ankara (MVA) product (GeoVax Labs, Inc). Volunteers were vaccinated with low and high

Note: The STEP vaccine trial results are summarized in the accompanying report by Susan Buchbinder, MD.

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doses of DNA and MVA expressing the Gag, Pol, and Env proteins. The vaccine was well tolerated, and the majority of volunteers responded to the vaccine in the CD4+ (82%) and CD8+ (67%) T-cell compartments when given the highest dose. Although it was not clear whether this vaccine induced T-cell responses that were significantly different from those induced by the Ad5 Gag, Pol, and Nef product (Merck), planning for a phase II trial is underway.

Similarly, Schuetz (Abstract 86) presented immunogenicity data from 20 volunteers vaccinated with the Vaccine Research Center (VRC) DNA prime/Ad5 boost expressing Env proteins from clades A, B, and C along with clade B expressing Gag, Pol, and Nef proteins. T-cell responses were predominantly against Env (16/20 responders), whereas weaker responses were generated against Nef (5/20) and Pol (3/20). Unfortunately Gag-specific responses were not assessed. Again, it was difficult to assess whether this VRC vaccine induced better immune responses than those induced by the failed Ad5-only Gag, Pol, and Nef vaccine (Merck).

Data from a therapeutic trial of an Ad5 vaccine expressing Gag were presented by Schooley (Abstract 87). Even though the vaccine was generally safe and well tolerated, no significant reductions in viral replication were seen in vaccines compared with placebo after analytical treatment interruption.

Finally, efficacy results from the STEP trial (Abstracts 88LB and 89LB) of the Ad5 vaccine (Merck) were presented. These are covered in greater detail in Buchbinder's article, "HIV Testing and Prevention Strategies," on pages 9–14.

Frontiers in Vaccine Research

Antibody Responses

Inducing a broadly reactive antibody response to the envelope glycoprotein (Env) is probably the most important goal of HIV vaccine research. This has been difficult to achieve for a variety of reasons, including the fact that the conserved sites are difficult to access by antibody and Env is covered by

sugars and is highly variable. In the final session on vaccine research, Wyatt (Abstract 152) discussed the biophysical and antigenic properties of the Env. He showed that stabilization of the CD4-induced coreceptor binding site enhances elicited immune responses to this region. He also analyzed antibody responses generated in animal models to the soluble trimers.

The First Infecting Viruses

Understanding the nature of the first infecting virus is central to vaccine development. Are people infected by a diverse swarm or by a single virus? Are these viruses sensitive to immune responses? Shaw (Abstract 153) presented evidence of infection by 1 to 2 viruses by sampling very early after infection. By making a few assumptions, he and his colleagues could predict the nature of the starting virus from the diversity of the viral sequence at sampling. They found that in 78 of 102 patients infected with HIV-1, clade B had evidence of infection by only a single virus. The others were infected by a minimum of 3 to 5 viruses. The virus population seemed to evolve randomly until CD8+ T cells exerted pressure and antibodies subsequently also exerted selective pressure. Interestingly, there was no evidence for adaptation to cell-specific replication. Thus, most (80%) of the infections examined appeared to have been caused by a single virus that then diversifies. It is thus likely that the majority of HIV-1 clade-B infection is not caused by a swarm of several viruses, one of which is then selected. Interestingly, all viruses used CCR5, and transmitted Envs were typical of primary isolates, that is, not easily neutralizable.

A New Attenuated SIV for Understanding the Correlates of Protection

Currently, only 1 vaccine confers complete protection from homologous challenge of nonhuman primates. Delineating the immune responses that account for this control in macaques vaccinated with attenuated SIV will be

very important in vaccine design. Hoxie (Abstract 154) presented his group's data describing a new attenuated SIV termed Δ GY, which contains a mutation in the cytoplasmic tail of Env. This mutant in the Env trafficking signal had no effect on peak viral replication, but in the chronic phase, virus replication was undetectable. It offered complete protection from challenge with the homologous SIV isolate SIVmac239 and afforded some measure of protection from disease after heterologous E660 challenge. Indeed, 2 out of 3 pigtailed macaques controlled E660 viral replication. After depletion of CD8+ T cells in vivo, the challenge virus replicated, suggesting that CD8+ T cells were involved in control of replication. The animals were then challenged with SIVmac239, and nothing happened.

After a subsequent E660 challenge, 1 animal had a blip of viral replication and the other had 1000 copies/mL of E660, and later, low levels (100 copies/mL) of E660. Three more animals were vaccinated with Δ GY, and 2 of 3 completely controlled the vaccine strain in the chronic phase, the other to less than 1000 copies/mL. Anti-CD16 antibody was administered with no viral replication. The animals were then challenged with additional E660. Two of 3 had a peak of viral replication and then controlled viral replication to less than 1000 copies/mL. After anti-CD8 antibody administration in vivo, SIVmac239 replicated in 1 animal. In the second animal, E660 returned. In the third animal, E660 replicated to 10 million copies/mL, and the animal subsequently died. Thus, this model of attenuated virus vaccination may prove informative in our understanding of how attenuated live vaccines might provide protection against heterologous challenge.

Financial Disclosure: Dr Watkins has no relevant financial affiliations to disclose.

A list of all cited abstracts appears on pages 69-77.

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HIV Testing and Prevention Strategies

Susan Buchbinder, MD

A number of presentations at the 15th Conference on Retroviruses and Opportunistic Infections focused on approaches to identify HIV-infected persons for early referral to treatment and prevention. This year's conference also highlighted the challenges we face in developing effective biomedical preventions, with reports on the failure of a candidate HIV vaccine and chronic herpes simplex virus type 2 suppression to prevent HIV acquisition, and the failure of male circumcision for HIV-seropositive men to prevent HIV transmission to their uninfected female partners. On the other hand, there were presentations on progress being made in animal models of microbicides and preexposure prophylaxis and on prevention of HIV transmission through breastfeeding. Several interesting presentations addressed the need to move beyond individual-level interventions into those that target sexual partnerships, communities, and policy changes, as these larger factors are driving the HIV epidemic in the United States and globally.

HIV Testing Programs

Testing programs for HIV are useful in identifying the estimated 25% of persons in the United States who are unaware of their HIV infection and the larger number of persons unaware of their status globally. Testing programs also provide insight into HIV infection rates and risk factors for infection on a population level.

It has been challenging to increase rates of HIV testing in clinical settings in the United States. Heffelfinger (Abstract 533) presented data on 3 programs in emergency departments (EDs) to offer point-of-care rapid HIV testing to medically stable patients 13 years of age or older on an opt-out basis. Each program was developed locally, tested fewer than 10% of patients seen in their EDs, and identified approximately 1% of those tested to be newly diagnosed with HIV infection. Linkage to care was excellent in 2 programs (93% and 100%) and lower in the third (63%). The estimated cost per newly diagnosed patient linked to care was approximately \$11,000. Such enhanced testing programs will have to be tailored to the specific needs of the health care setting, but more

must be done to improve testing rates and ensure linkage to care for infected persons in all programs.

Greater success in roll-out of testing was reported in a Ugandan antenatal clinic (Abstract 537). During the opt-in period, an average of 549 clinic attendees (82%) were counseled each month and 270 (40%) were tested, of whom 20 (7.3%) per month were HIV-seropositive. In the year after implementation of opt-out testing, 688 (98%) were counseled each month, and 612 (88%) received HIV testing. An average of 36 women per month (5.8%) were found to be HIV-seropositive. This result represented a more than doubling in the proportion of women agreeing to be tested, with a nearly comparable increase in the absolute number of infections detected through this program. The presenters also spoke to the need to maintain a stable supply of test kits.

Cohan and colleagues (Abstract 535a) addressed the impact of switching from standard to abbreviated pretest counseling in an antenatal setting in San Francisco. She presented data from a randomized control trial of 278 women assigned to standard versus abbreviated pretest counseling. Women in the abbreviated counseling arm had slightly lower knowledge scores than those in the standard pretest counseling arm (78.4% vs 83.7% correct, respectively) but similar satisfaction and decision-making scores. These data

support efforts to streamline pretest counseling in antenatal settings.

Other presentations focused on implementing testing in hard-to-reach populations. Several focused on HIV testing in Washington, DC, one of the most heavily affected cities in the United States. Castel and colleagues (Abstract 543) reported on the very high rates of late presenters for care. From 1997 to 2006, 66% of AIDS patients in Washington, DC, had received a diagnosis of HIV within 1 year of their AIDS diagnosis, and 53% had been HIV-tested within 1 month of their AIDS diagnosis. Blacks, Hispanics, persons older than 60 years, heterosexuals, uninsured persons, and those born outside of the United States were all more likely than other groups to receive their HIV diagnosis late. Over that 10-year period, there was no substantial improvement in the rates of late testing, pointing to an urgent need to implement new HIV-testing strategies.

In a separate abstract, Castel and colleagues (Abstract 541) presented data on rapid testing of more than 32,000 Washington, DC, residents from June 2006 onward. Approximately 2% (638) of the clients had a positive initial screening result, one-fourth of whom stated they had never been tested before and nearly one-third of whom stated they would not have been tested if it had not been offered.

Malave and colleagues (Abstract 538) presented data on testing in homeless shelters in New York City. Overall, approximately one-half of those offered testing accepted, 1.8% of whom had a preliminary positive test result. Of these, approximately one-half were confirmed seropositive, and an additional 13% were already known to be seropositive. The remainder were largely lost to follow-up or refused confirmatory testing, suggesting that other strategies are needed to help those who screen positive to access care.

Walensky (Abstract 534) sounded a cautionary note about rates of false-positive test results using a particular rapid

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test (OraQuick ADVANCE HIV 1/2 Antibody Test, Abbott Diagnostics). In an ED setting, they found 31 patients to have initially reactive test results, only 5 of whom were confirmed to be HIV-seropositive (positive predictive value [PPV], 16.1%; expected PPV, 75%, based on the manufacturer's specifications). The specificity of the test in this setting (96.9%; 95% confidence interval [CI], 95.7%-98.1%) was significantly lower than published values (99.8%; 95% CI, 99.6%-99.9%). Of the 19 patients with faint lines appearing on the test result, all were ultimately determined to be HIV-seronegative, suggesting that training focus on correct interpretation of faint lines. Western blot results were indeterminate in 50% of those with false-positive responses.

Delaney and colleagues (Abstract 535b) addressed challenges with rapid-testing algorithms requiring that patients return for results of laboratory-based confirmatory tests. He presented data from 3043 clients tested at 8 counseling and testing sites and 8570 patients screened in 2 EDs; each site used its own algorithm using results of multiple rapid tests to identify and confirm HIV infection at point of care. Overall, 101 clients (0.9%) tested initially seropositive, 78 of whom were seropositive on all confirmatory tests and were referred immediately for care. This approach limits the need for confirmatory laboratory-based tests to those with discordant test results on rapid tests, and allows for rapid referral of most newly identified HIV-infected persons into care.

HIV Vaccines

Data were presented at this year's conference on the STEP Trial, a test-of-concept vaccine trial conducted by the HIV Vaccine Trials Network, the National Institute of Allergy and Infectious Diseases, and Merck & Co, Inc. (Abstracts 88LB and 89LB). This trial enrolled 3000 HIV-seronegative volunteers from 34 sites in the Americas and Australia to evaluate the efficacy of a trivalent adenovirus type 5 (Ad5) vaccine (Merck) to prevent HIV acquisition, lower early viral load setpoint, or both.

Abstract 88LB focused on efficacy results from an interim analysis of the 1500 volunteers with low preexisting Ad5 neutralizing antibody (NAb) as well as post hoc analyses on the entire group. Vaccinations in the trial were halted when data from the first interim analysis crossed prespecified futility boundaries for both the infection and viral load endpoints. In those participants with baseline Ad5 NAb titers at or below 200 units, HIV infection rates were 2.92 per 100 person-years in vaccine recipients and 2.51 per 100 person-years in placebo recipients. Mean plasma HIV RNA levels at approximately 3 months postdiagnosis of infection were 4.61 \log_{10} copies/mL in vaccinees and 4.41 \log_{10} copies/mL in placebo recipients. Only 1 infection was seen in a woman, so post hoc analyses were limited to male study participants regardless of baseline Ad5 titer.

Post hoc analyses revealed an increased number of HIV infections in vaccine versus placebo participants (49 vs 33 infections, respectively). The increased infection rate in vaccinees appeared to be concentrated in male participants who were both uncircumcised and Ad5-seropositive (Ad5 NAb > 18 units). In various multivariate models, the estimated increased risk associated with receiving the vaccine (relative hazard) for men who were both uncircumcised and Ad5-seropositive ranged from 4.2 to 4.8, fairly consistent along a spectrum of multivariate models.

On the other hand, there was no evidence of increased risk to vaccinees in the subpopulation who were both circumcised and Ad5-seronegative, with relative hazards ranging from 0.6 to 0.8 in multivariate models. Hazard rates for the subgroups of men who were either uncircumcised or Ad5-seropositive (but not both) were intermediate between these 2 groups. The vaccine did not cause infection itself but may have made study participants more susceptible to infection if later exposed. Additional analyses are being conducted to rule out other potential confounders, such as herpes simplex virus (HSV)-2 status, human leukocyte antigen type, and sexual network clusters.

Robertson (Abstract 89LB) presented the initial laboratory data exploring reasons for lack of protection from the vaccine as well as potential mechanisms for increased risk of HIV acquisition among vaccinees. The vaccine was immunogenic, generating positive interferon gamma (IFN- γ) enzyme-linked immunospot assay responses in more than three-fourths of study participants with low preexisting Ad5 immunity (NAb < 200 units) and more than one-half of study participants with high preexisting immunity (NAb > 200 units). Similarly, results of intracellular cytokine staining confirmed that the vaccine generated both CD8+ and CD4+ cell responses, and those with preexisting Ad5 immunity had lower levels of response. There was no substantial difference between immune response in those who later became HIV-infected and those who remained HIV-uninfected, suggesting that the quantity, quality, breadth, or homing of the immune responses generated by this vaccine were insufficient to confer protection.

In exploring potential mechanisms for increased HIV-acquisition risk, there appeared to be no difference between vaccinees and placebo recipients in the level of activated CD4+ T cells in peripheral blood. The CD4+ and CD8+ T-cell responses to an empty Ad5 vector were lower in participants with preexisting Ad5 NAb titers over 200 units, failing to provide an explanation for increased HIV-infection rates in this group. Additional studies are underway or being planned to explore both the vaccine's failure to protect and the potential for increased HIV-acquisition rates. A process for soliciting the input and engagement of the broad scientific community was also described.

Two plenary lectures described the challenges posed in developing an HIV vaccine and urged 2 related, but somewhat different paths forward. Desrosiers (Abstract 91) summarized the obstacles facing development of a successful HIV vaccine and argued that efforts should focus on basic discovery, particularly efforts to create broadly neutralizing antibodies. He also argued that efficacy trials that produce

negative results could have a negative impact on the research field, and that a high threshold of protection in stringent simian immunodeficiency virus (SIV) challenge models be attained before moving new candidates into efficacy trials.

Nathanson (Abstract 92) also argued for the need to devote additional thought and resources into basic discovery. He urged that new, innovative mechanisms be developed to stimulate and fund high-risk research of novel ideas, and he used as an example strategies that focus on development of broadly neutralizing antibody. In contrast to Desrosiers, Nathanson pointed out that the predictive value of nonhuman primate challenge models is still unknown. He recommended that a hierarchy of nonhuman challenge models be built and validated through data generated from human efficacy trials. He also urged that non-vaccine prevention efforts be moved forward aggressively, as the global epidemic needs efforts now to stem the tide of new infections.

Herpes Suppression

Celum and colleagues presented final data from a randomized, placebo-controlled trial of HSV suppression in HSV-2-seropositive, HIV-seronegative men and women in Peru, the United States, Zambia, Zimbabwe, and South Africa (Abstract 32LB). The HIV Prevention Trials Network 039 study evaluated the use of 400 mg of acyclovir, given twice daily, to prevent HIV acquisition in 1871 men who have sex with men (MSM) and 1380 heterosexual women. Seroincidence rates of HIV were 3.9 per 100 person-years in the acyclovir arm and 3.3 per 100 person-years in the placebo arm (relative risk [RR], 1.16; 95% CI, 0.83-1.62).

There were no significant differences in vaccine efficacy by sex, adherence measures, or history of clinical genital ulcer disease. The rate of clinical genital ulcers decreased by 37% in the acyclovir arm. Surprisingly, the amount of viral shedding from these ulcers was reduced by acyclovir only in the United States but not in the

Peruvian or African cohorts. Although adherence appeared to be excellent as measured by pill count and self-report, additional efforts are underway to uncover potential over-reporting on adherence measures or differing drug pharmacokinetics in these different populations. A companion trial is underway to explore the potential for HSV suppression in HIV-infected persons to prevent HIV transmission; results from this trial are expected within 1 year.

Male Circumcision

A number of ecological and observational studies previously suggested a beneficial effect of male circumcision in preventing HIV acquisition in heterosexual men. Then, over the past several years, results from 3 randomized controlled trials in South Africa, Uganda, and Kenya demonstrated that adult male circumcision cut the rate of HIV acquisition by 60% in heterosexual men. This year's conference included new data on beneficial effects of male circumcision for HIV-seronegative men and their female partners but also concerns about potential harm to the female partners of HIV-seropositive men who are circumcised as adults.

Tobian and colleagues (Abstract 28LB) presented data from the randomized controlled trial of adult male circumcision in Rakai, Uganda. In that trial, HIV-seronegative adult men underwent randomization to immediate male circumcision (intervention arm) or circumcision delayed for 24 months (control arm). Circumcision was associated with a 24% reduction in HSV-2 acquisition among the 3516 men who were HSV-2-seronegative at enrollment. Acquisition rates of HSV-2 were 8.2% in the intervention arm and 10.8% in the control arm (RR, 0.76; 95% CI, 0.60-0.96).

Tobian also reported a significant decrease in sexually transmitted infections in the 1608 married women linked to male study volunteers, including a 24% reduction in genital ulcer disease (RR, 0.76; 95% CI, 0.60-0.97), 47% reduction in trichomoniasis (RR, 0.53; 95% CI, 0.33-0.85), and 20% reduction in bacterial vaginosis, (RR, 0.80; 95% CI, 0.71-0.89). The prevalence of severe bacte-

rial vaginosis, development of bacterial vaginosis, and persistence of bacterial vaginosis were also reduced in intervention wives compared with control wives. All of these factors may have favorable effects on HIV acquisition rates in this population.

Wawer and colleagues presented data on a companion trial of male circumcision among HIV-seropositive men in Rakai, Uganda (Abstract 33LB). In this study, 922 HIV-seropositive men with CD4+ counts at 350 cells/ μ L or higher underwent randomization to immediate circumcision or circumcision delayed for 24 months. Of this group, 770 were married and 566 wives enrolled, 245 of whom were HIV-seronegative.

Among the 245 HIV-seronegative women, HIV infection rates were somewhat higher in the wives of men in the male circumcision arm than in wives of men in the intervention arm (14.4% vs 9.1%; incidence rate ratio, 1.59; 95% CI, 0.7-4.3), although these differences were not statistically significant. In the first 6 months of follow-up, HIV incidence was 27.3 per 100 person-years in wives of men in the circumcision arm and 17.8% in wives of men in the control arm, dropping in the 6- to 24-month period to 5.7 per 100 person-years in wives in the circumcision arm and 4.1 per 100 person-years in wives in the control arm.

It appeared that the risk was particularly concentrated among couples who resumed sexual activity more than 5 days before certification of wound healing; of this group, 5 of 18 women (27.8%) became infected, compared with 6 of 63 (9.5%) of those who did not resume sexual activity until 5 or fewer days before certification of healing or after certification. The latter rate was comparable to infection rates in the wives of uncircumcised men (6/68, 8.8%) in the first 6 months of follow-up.

There were no serious adverse events associated with male circumcision in this trial, and the rates of moderate circumcision-associated adverse events were comparable to those reported in HIV-seronegative men (3.1 for each study). Wound healing was slower in this trial of HIV-seropositive men than

in the previous trial in HIV-seronegative men, with 73% of the men in this trial having complete wound healing by 30 days postcircumcision but an 83% healing rate in the same time period in the HIV-seronegative men ($P < .001$). Results of this study suggest that even in relatively healthy HIV-seropositive men, male circumcision is associated with delayed healing and a potential for increased HIV transmission to uninfected female partners, particularly if sexual activity resumes before complete healing.

Auvert (Abstract 2) made a case for widespread implementation of male circumcision in HIV-uninfected men in sub-Saharan Africa. He pointed out that previous modeling exercises suggest that this procedure could avert 2 million to 8 million new HIV infections over 20 years and cost less than the treatment that would be required for those infected.

One of the barriers to widespread implementation is the low number of adequately trained medical practitioners to conduct this surgical procedure. Auvert and colleagues modeled the number and cost of providers if circumcision were made available in the 14 countries in sub-Saharan Africa, where the prevalence of male circumcision is less than 80% and HIV prevalence is greater than 5%. According to this model, 2357 circumcisers would be required in the first 5 years of roll-out, and 626 in years 6 through 10. Although cost would be \$965 million for the first 5 years, the program would save an estimated \$4 billion by year 20 because of reductions in the number of infected persons.

Preexposure Prophylaxis and Microbicides

Several presentations and posters focused on the use of various topical and oral agents, including antiretroviral drugs, to prevent HIV acquisition. Substantial work is being conducted in development of animal models to evaluate the safety of microbicide approaches. Mesquita and colleagues (Abstract 26) presented data from polarized epithelial cell cultures and murine

genital tract tissue that may explain results presented at last year's conference that cellulose sulfate, used as a topical microbicide, may be associated with an increased risk of HIV acquisition. In their model, cellulose sulfate caused epithelial disruption and loss of cellular junctions, leading to increased translocation of HIV across the epithelial barrier.

Denton and colleagues (Abstract 558) presented data, also published recently,¹ that humanized mice are susceptible to vaginal HIV infection; they used this model to demonstrate efficacy of systemically administered tenofovir/emtricitabine in protecting against vaginal HIV challenge. Veazey and colleagues (Abstract 560) provided data from nonhuman primate studies suggesting that recombinant RANTES (regulated upon activation, normal T-cell expressed and secreted) analogues may provide protection against simian-HIV (SHIV) acquisition.

An update on oral and topical administration of preexposure prophylaxis (PrEP) was provided by Kashuba (Abstract 95). She noted that although tenofovir and emtricitabine (2 drugs being used in current clinical trials of preexposure prophylaxis) are present in higher concentrations in genital fluid than in the blood, drug levels in the animal challenge models that were most highly protective were 2-log_{10} copies/mL higher than levels achieved in the genital compartment in standard dosing in women. She urged that additional studies be conducted to define intracellular levels of these agents systemically and in the genital tract in humans.

Karim also presented an overview of microbicides (Abstract 96), noting the shift in the field from broad-spectrum antimicrobial drugs to a greater focus on antiretrovirals. She also noted the shift to different formulations and modes of delivery, including strategies that would unlink the timing of microbicide use from sexual acts.

Data were presented from several clinical trials of PrEP. Analysis of one seroconverter from a PrEP trial in Africa found no evidence of tenofovir resistance mutations in this participant, who reported excellent adherence to

study medication (Abstract 570). Baseline data of risk behaviors reported by injection drug users (IDU) (Abstract 568) and MSM (Abstract 569) were also presented, suggesting that risk levels are high in these populations. Efficacy results will be available from 2009 to 2011 from these trials.

Paltiel and colleagues (Abstract 563) modeled the cost-effectiveness and impact of PrEP on a population level, suggesting that this approach could be cost-effective and reduce HIV infection rates if targeted to populations with seroincidence rates in excess of 2% per year, if cost is low, efficacy is very high, or both. Abbas and colleagues (Abstract 564) modeled the emergence and spread of HIV drug resistance if PrEP is used and found that this risk could be minimized by also targeting those at highest risk and using drugs with highest efficacy levels.

Prevention of HIV Transmission Through Breastfeeding

Several oral sessions and abstracts focused on prevention of mother-to-child transmission. Abstracts focused on strategies involving maternal or infant antiretroviral therapy are presented in the review article by Wilkin and colleagues in this issue (pp. 31-60); those presentations focused predominantly on breastfeeding practices are presented here.

Becquet and colleagues (Abstract 46) presented pooled data from Cote d'Ivoire and South African cohorts of 1195 breastfed infants. Infection rates in infants predominantly breastfed were similar to those exclusively breastfed, with one important distinction. The subgroup of infants who were exposed to solid foods at least once during the first 2 months of life had an increased risk of infection (hazard ratio 2.9; 95% CI, 1.1-8.0).

In Botswana, 1200 HIV-infected pregnant women underwent randomization to either breastfeeding (with infant zidovudine for 6 months) or formula feeding (with infant zidovudine for 1 month). By 24 months of age, 8.3% of infants in the breastfed arm and 10.5% of infants in the formula-fed arm had died. The pattern of mortality was dif-

ferent in the 2 arms; the majority of deaths occurred in the first 3 months in the formula-fed infants, but most deaths in the breastfed arm occurred between 6 and 12 months of age. Independent risk factors for infection in multivariate analysis included infant HIV infection, low birth weight, and lack of a latrine.

Data from the Kisumu Breastfeeding Study (KiBS) (Abstract 645) evaluated the uptake of breastfeeding recommendations among women who opted for exclusive breastfeeding for 6 months after an intensive educational program. Of 504 infants born to these mothers, 21% were mixed-fed before 5 months of age, but only 8% were breastfed beyond 6 months of age in the absence of HIV infection or antiretroviral use. This result suggests substantial progress, although reasons should be explored for departure from World Health Organization recommendations in a minority of women.

Thomas and colleagues (Abstract 646) reported on the success of a safe water system in reducing infant diarrhea in the KiBS study. The safe water system (education, point-of-use water chlorination, and safe water storage vessels) led to significant reductions in infant diarrhea (RR, 0.72; 95% CI, 0.57-0.91), although most of the effect was seen before weaning. Peri-weaning infection rates were quite high both before and after implementation of the safe water system.

Several studies evaluated the properties of breast milk that may contribute to HIV transmission to infants. Semrau and colleagues (Abstract 650) presented data on the effects of mastitis on breast milk HIV RNA level. Among 38 HIV-infected Zambian women with mastitis, HIV RNA level significantly increased from baseline 2.57 log₁₀ copies/mL to 2.9 log₁₀ copies/mL during mastitis, then fell to rates similar to baseline levels after resolution (2.45 log₁₀ copies/mL). There was no statistically significant increase in the breast milk HIV RNA level in the unaffected breast, supporting the recommendation that HIV-infected women with mastitis breastfeed from the unaffected breast. Permar and colleagues

(Abstract 652) presented data from rhesus macaques suggesting that although the kinetics of the SIV-specific cellular immune response in breast milk mirrored that seen in blood, the magnitude of the peak response was more than twice as high in breast milk as in the blood, and the duration of the high-level response was longer. Permar also reported that the breast milk HIV RNA level was 1 to 2 log₁₀ copies/mL lower in breast milk than in blood, both at peak and setpoint, suggesting better control of viral replication in the breast milk compartment.

Factors Driving the US HIV Epidemic

One symposium at this year's conference focused on 4 populations at substantial risk for HIV infection and proposed strategies for reducing the epidemic within these populations (Abstracts 53–56). All 4 presenters in the symposium focused on intersecting epidemics (syndemics) of HIV, childhood sexual abuse, substance use, domestic violence, poverty, and social inequalities driving their respective epidemics. All also called for a broadening of research agendas beyond the individual-level interventions to include focus on partners, community, public health infrastructure, and government policy.

Stall and colleagues (Abstract 53) focused on the epidemic in MSM, the only group with continued increasing rates of HIV and AIDS in the United States. They modeled HIV prevalence rates based on data from 20 independent studies of HIV incidence. Among the general MSM population, they estimate that HIV prevalence rates are below 5% in 20-year-old men but rise steadily to 25% in 30-year-old men and 41% in 40-year-old men. Projections for African-American MSM are even worse, with prevalence rates estimated, at 40% by age 30 and 60% by age 40. Stall cites work by Millett that points to lower reported risk among African-American MSM but also lower rates of knowledge of HIV serostatus and lower rates of access to potent antiretroviral therapy. He likened the current focus on individual-level interventions to the

era of zidovudine monotherapy and called for prevention regimens that include interventions at the partnership, community, public health, and policy levels.

Adimora (Abstract 54) traced the epidemic in African-American women, where population prevalence rates are 1% in 18- to 39-year-olds and 2.8% in 40- to 49-year-olds according to the National Health and Nutrition Examination Survey. She also pointed to data for African-American women suggesting higher HIV infection rates, even when at comparable levels of risk with white women, and she noted the substantial proportion of women newly diagnosed with HIV who were unaware of partner risk. Adimora traced many of the population-level forces driving these increased infection rates, including factors leading to higher HIV prevalence in African-American men and forces driving concurrency of sexual partnerships.

Rosser (Abstract 55) addressed strategies to reduce HIV transmission from HIV-seropositive persons, arguing that once persons learn of their HIV-serostatus, most substantially reduce or stop risk activities with HIV-seronegative persons. He suggested that the upswing in the use of the Internet to increase the number and efficiency of finding sexual contacts argues for a need to build Internet-based prevention approaches, and he demonstrated one such intervention. Rosser also urged clinicians to provide HIV testing to identify infected persons unaware of their status and to counsel their HIV-seropositive patients about strategies to reduce HIV transmission. He, too, called for structural and environmental interventions to reduce HIV transmission rates in affected communities.

Finally, Vlahov (Abstract 56) addressed the role of recreational drugs in the HIV epidemic. Rates of HIV infection among IDUs have declined substantially since the beginning of the AIDS epidemic, but use of non-injection substances continues to play a major role in sexual transmission. Vlahov addressed the need to intervene on numerous levels and used as an example, evaluation of the Expanded Sy-

ringe Access Demonstration Program in New York. By intervening not only with the IDUs but also with pharmacists and the community, the program was able to improve perceptions of the program itself as well as decrease syringe exchange among IDUs. This type of multitiered intervention program may have a greater likelihood of suc-

cess than those focusing only on the drug user or the pharmacist.

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A list of all cited abstracts appears on pages 69-77.

Additional Reference

1. **Denton PW**, Estes JD, Sun Z, et al. Antiretroviral pre-exposure prophylaxis prevents vaginal transmission of HIV-1 in humanized BLT mice. *PLoS Med.* 2008;5:e16.

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Neurologic Complications of HIV Disease and Their Treatment

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*New data were presented at the 15th Conference on Retroviruses and Opportunistic Infections that further support the importance of considering the neuroeffectiveness of antiretroviral drugs when designing treatment regimens. Two studies linked antiretroviral therapy that had estimates of better neuroeffectiveness with better global neuropsychologic outcomes in life. A third study linked estimates of better antiretroviral therapy neuroeffectiveness, particularly nonnucleoside analogue reverse transcriptase inhibitors, with a lower prevalence of HIV-associated brain pathology at death. Additional findings presented at the conference focused on the correlates of HIV-associated neurocognitive disorders (HAND) and peripheral neuropathy. Supporting the concept that viral factors influence the pathogenesis of HAND, high frequencies of HAND were identified in people infected with HIV subtype D and in people infected with subtype B and having brain-specific mutations in V3 of gp160. Supporting the importance of host correlates of HAND, important data from a macaque study identified a strong link between a major histocompatibility complex class I allele, Mane-A*10, and simian immunodeficiency virus encephalitis. Supporting the importance of comorbidities in determining risk for HAND, high levels of lipopolysaccharide in blood, likely derived from the HIV-injured intestine and bacterial translocation, were linked to HAND. Coinfections with JC virus or Treponema pallidum were topics of other presentations, identifying a prognostic marker for PML (better CD8+ cytotoxic T-lymphocyte responses were associated with survival) and a diagnostic one for neurosyphilis (CXCL13 levels in CSF).*

Neuroeffectiveness of Antiretroviral Drugs

The effectiveness of antiretroviral drugs in the nervous system has been the subject of debate since the observation that zidovudine may more consistently benefit people with AIDS dementia than didanosine.^{1,2} Animal studies continue to support that some antiretroviral drugs do not treat HIV in the nervous system as well as they do outside the nervous system. At this year's conference, Annamalai and colleagues studied the effects of antiretroviral therapy on SIV in brain and lymphoid tissue in an accelerated rhesus macaque model of simian immunodeficiency virus (SIV) encephalitis (Abstract 386). The investigators compared HIV levels measured by real-time polymerase chain reaction (RT-PCR) in untreated macaques to those that had been treated with the com-

bination of the investigational drug PSI-5400 (a racemic mixture of emtricitabine), and tenofovir for 28 days. In treated animals, HIV levels were significantly lower in all lymphoid tissues (spleen, bone marrow, lymph nodes) but in only 1 (frontal cortex) of 4 brain regions (frontal cortex, putamen, hippocampus, and brainstem). Potential explanations for these tissue-specific differences include the limited neuroeffectiveness of tenofovir (and perhaps PSI-5400) and the longer half-life of the principal target cells in the brain (macrophages) than in lymphoid tissues (lymphocytes).

Human data supporting the limited neuroeffectiveness of tenofovir in the nervous system were presented by Best and colleagues (Abstract 131). Tenofovir concentrations were measured in body fluids from 187 volunteers of the CHARTER (Central Nervous System HIV Antiretroviral Therapy Effects Research) study, identifying that the concentrations in cerebral spinal fluid (CSF) were low (median 5.5 ng/mL, interquartile range 2.7-11.3 ng/mL) and averaged only 5% of the concentrations in blood plasma. Compare these concentrations with the higher concentrations of 2 nucleoside analogue reverse transcriptase

inhibitors (nRTIs), abacavir (median concentration in CSF, 128 ng/mL; mean CSF-to-plasma ratio, 36%)³ and lamivudine (median concentration in CSF, 470 nM; mean CSF-to-plasma ratio, 15%).⁴ In the tenofovir analysis, two-thirds of CSF specimens had concentrations below 7 ng/mL, and 30% of these specimens had HIV RNA levels in CSF above 50 copies/mL. In the one-third of CSF specimens that had tenofovir concentrations above 7 ng/mL, only 5% had HIV RNA levels above 50 copies/mL ($P = .02$ for the comparison between the 2 groups). Together, these data support that the neuroeffectiveness of tenofovir is limited and may be inferior to abacavir or lamivudine, although a direct comparison is needed to confidently reach this conclusion.

Data such as these support development of strategies for selection of neuroeffective regimens in the clinic. Strategies that might have clinical utility have used pharmacokinetic and other data to rank individual drugs and regimens for their likely neuroeffectiveness. Such strategies are particularly useful for clinicians in managing their patients who have common neurologic complications, such as HIV-associated neurocognitive disorders (HAND), pro-

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gressive multifocal leukoencephalopathy (PML), or cryptococcal meningitis.

One strategy was previously validated by demonstrating that higher regimen estimates of neuroeffectiveness were associated with lower HIV RNA levels in CSF.⁵ At this year's conference, investigators from the National Institute of Infectious Diseases (Rome) further validated this CNS penetration-effectiveness (CPE) ranking approach, also known as CHARTER ranks, by comparing it with another system they had used in previously published analyses. In this observational study of 185 HIV-infected volunteers, neuropsychologic test batteries were administered before antiretroviral therapy initiation and at follow-up (Abstract 391). Results using the 2 ranking systems were compared with changes in normatively adjusted neuropsychologic summary scores from baseline to the last observation. Half (50%) of the subjects had impaired neuropsychologic performance at baseline. Higher CPE rank, consistent with greater neuroeffectiveness, correlated with greater improvements in neuropsychologic performance. In contrast, higher estimates of neuroeffectiveness with the alternative ranking approach did not show such correlation.

These findings were confirmed by another longitudinal study (Abstract 68). In this analysis of volunteers with HAND, Letendre and colleagues also identified that higher CPE rank was associated with greater improvement in neuropsychologic performance. Of note, application of the CHARTER ranking system to the treatment of people with HAND is being tested in an ongoing, National Institutes of Health-funded, prospective, randomized clinical trial.⁶

The importance of considering the neuroeffectiveness of antiretroviral therapy was highlighted by 2 other studies. Everall and colleagues (Abstract 67) presented data from 374 volunteers who enrolled in the National NeuroAIDS Tissue Consortium (NNTC) before dying with HIV and AIDS. Neuropathologists from NNTC examined brain tissue obtained at autopsy, identifying that 76 (20%) had evidence of HIV-associated brain pathology, defined

as evidence of HIV leukoencephalopathy or HIV micro-gliar nodular encephalitis. Those who had HIV-associated brain pathology at autopsy had more advanced immunosuppression (lower current and nadir plasma CD4+ cell counts) and higher plasma HIV RNA levels before death and, consistent with these findings, were less likely to report use of antiretroviral therapy during the antemortem observation period. This analysis used a variation of the CPE ranking approach, summing the CPE ranks for all antiretroviral drugs reported during the antemortem observation period rather than for a single regimen. Estimates of greater cumulative neuroeffectiveness (ie, higher CPE ranks) were associated with a lower likelihood of HBP at autopsy ($P = .03$).

An interesting additional finding was that volunteers who reported use of a nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) during the antemortem observation period had a substantially lower likelihood of HIV-associated brain pathology at autopsy (NNRTI-containing regimen, 12%, vs protease inhibitor [PI]-containing regimen without an NNRTI, 22%, vs no antiretroviral therapy, 28%; $P = .03$). The neuroeffectiveness of NNRTIs, like nevirapine, is supported by this analysis of nearly 400 people, but the current analysis does not distinguish whether the observed associations might be attributable to other factors linked to NNRTI use, like less antiretroviral experience, better antiretroviral adherence, or the theoretically reduced neuro-pathogenicity of some drug resistance mutations in the brain.

The idea that some drug resistance mutations are less neuropathogenic than others was supported by data presented by Hightower and colleagues (Abstract 394). This analysis builds on the observations that some antiretroviral resistance mutations result in reduced replication capacity and may be associated with lower viral loads and decreased virulence (eg, see references⁷⁻⁹). In this study of 94 volunteers, drug resistance mutations were detectable in 48 (51%), and the most common resistance-associated mutations were M184V/I (20%) and K103N (15%). Drug resistance, par-

ticularly M184V/I, was associated with lower HIV RNA levels in CSF (2.6 vs 3.3 \log_{10} copies/mL, $P = .009$)—but not in plasma—and better neuropsychologic performance, particularly among those who had definite normal or definite impaired performance ($P = .05$). This analysis also identified that higher HIV RNA levels in CSF were associated with worse neuropsychologic performance but only among those who did not have drug resistance mutations, providing a possible explanation for the weakening of this relationship in the combination antiretroviral therapy era (eg, see reference¹⁰).

Using data from the FHDH (French Hospital Database on HIV) cohort, Gagnault and colleagues showed that the benefits of neuroeffective antiretroviral therapy may not be limited to the neurologic complications of HIV alone but may also improve survival in those who have CNS opportunistic diseases (Abstract 385). In a retrospective analysis of more than 1400 individuals, they found that survival after a PML diagnosis improved dramatically in the combination antiretroviral therapy era as compared with earlier treatment periods.

Only 20% of individuals who were diagnosed with PML between 1992 and 1995 survived 1 year. In comparison, 54% of individuals survived 1 year for the other 3 treatment periods (1996-1998, 1999-2002, 2003-2004). Survival was lowest among those who did not take antiretroviral therapy. Among those who did take antiretroviral therapy, regimens with better estimated neuroeffectiveness (CPE ranks of at least 1.5) had a 6-fold lower risk of death even after adjusting for other potentially influential demographic factors, such as age, AIDS diagnosis before PML diagnosis, nadir plasma CD4+ cell count, sex, and HIV transmission risk factor.

These results suggest that control of HIV replication in the CNS plays a role in recovery from PML. A limitation of this study was its failure to account for the number and potency of antiretroviral drugs in patients' regimens; this information would provide some assurance that the effects were the result of potency in the CNS specifically, rather than simply overall systemic efficacy or immune recovery. For instance, Gagnault

also demonstrated a survival benefit (77% at 6 months) in an interim analysis of 26 individuals who enrolled in a trial of intensified antiretroviral therapy (tenofovir-emtricitabine-efavirenz-lopinavir-ritonavir-enfuvirtide) for PML that was reported at the 2007 conference.¹¹ Although the study regimen selected for this trial included drugs that are more (lopinavir-ritonavir, emtricitabine) and less (tenofovir, efavirenz, enfuvirtide) neuroeffective, survival was linked to recovery of JC virus (JCV)–specific immune responses, emphasizing that recovery from PML probably requires both viral and host factors.

A contrasting viewpoint to the idea that some antiretroviral drugs are neuroprotective is that some may directly or indirectly injure the brain. Data from Husstedt and colleagues support direct injury by some antiretroviral drugs, namely the dideoxy-nRTIs (DDNs) didanosine, stavudine, and zalcitabine (Abstract 389). The toxic effects of these drugs on the brain have long been suspected based on their link to peripheral neuropathy (eg, see reference¹²) and to a neuromuscular weakness syndrome (stavudine¹³).

In a retrospective, cross-sectional analysis, data from 60 individuals taking antiretroviral therapy that included DDNs (mean duration, 19 months) were compared with those of controls taking antiretroviral therapy without DDNs. Use of DDNs was associated with prolonged event-related potentials (P3 component, 448 milliseconds, vs 431 milliseconds; $P < .02$) and a higher prevalence of impaired neuropsychologic performance ($P < .009$). These findings need to be confirmed in longitudinal and interventional studies but, if confirmed, would have important implications for the use of DDNs, which continue to be commonly used in resource-limited settings.

Favoring the concept of indirect injury of the brain by antiretroviral therapy, Letendre and colleagues presented data supporting that an intended consequence of effective antiretroviral therapy, immune recovery, might injure the brain under certain circumstances, such as when individuals have preexisting HAND (Abstract 68). In this

analysis, 25 individuals with HAND initiated a new antiretroviral therapy regimen and were observed for 24 weeks. Nearly all subjects (88%) had improved neuropsychologic performance by 24 weeks, but the extent of improvement varied widely between individuals (change in the Global Deficit Score, median, -0.53 , interquartile range, -0.79 to -0.19). The neuropsychologic performance of 15 (60%) normalized by 24 weeks. Those who improved the least (or not at all) had lower nadir blood CD4+ cell counts and higher HIV RNA levels in CSF before treatment and greater increases in blood CD8+ cell counts during treatment (linear regression model, r^2 , 0.48; $P = .0001$).

This combination of lower CD4+ cell counts before treatment, higher antigen levels within the CNS, and greater expansion of CD8+ cells, which can home to and injure the nervous system,¹⁴ suggests that recovery from HAND may be limited by a neuroimmune process directed at HIV antigens that is similar to the immune reconstitution inflammatory syndrome (IRIS, eg, see references^{15,16}). Thus, antiretroviral therapy might be a double-edged sword that can either benefit or injure the brain depending on clinical circumstances.

A combination of viral, host, and comorbid factors is thought to contribute to HAND. For instance, highly neurotropic HIV isolates can be isolated from brain tissue from individuals dying of HAND, and these isolates replicate with reduced dependence on CD4¹⁷ and enhanced macrophage tropism.¹⁸ Host factors, such as variability in the chemokine CCL2, have also been linked to the risk of HAND.^{19,20} Comorbidities are a third important determinant of risk and include disparate conditions such as coinfection with other pathogens (eg, hepatitis C virus [HCV]²¹), use of recreational stimulants (eg, methamphetamine²²) and advancing age.²³

Susceptibility to NeuroAIDS: HIV Correlates

The importance of the HIV envelope in HAND was supported by work from Pillai and colleagues from the CHARTER

Group. To validate their previous finding that a serine at position 5 of the V3 loop of HIV-1 *gp160* (N300S) was associated with HAND,²⁴ the investigators used clonal RNA sequencing of *C2-V3 env* to identify this mutation in matched CSF and blood plasma specimens from 39 volunteers, 19 of whom had HAND. As hypothesized, the N300S mutation was more common in volunteers who had HAND ($P < .032$) than in those without HAND. The positive predictive value of this mutation for the presence of HAND was high (86%), although the sensitivity was low (33.3%). Thus, the investigators confirmed their prior finding in an independent cohort, but the poor sensitivity in this analysis argues against the clinical utility of this mutation for identifying presence or risk of HAND.

HIV enters macrophages and microglia, its major target cells in the brain, primarily via CCR5.²⁵ Consistent with this, several studies have identified that brain-derived HIV isolates from people dying of AIDS-related complications are more likely than not to use CCR5²⁶ and be macrophage-tropic even when isolates from tissues outside the nervous system, such as the spleen, used CXCR4 and replicated in T-cell lines.²⁷

Dual-mixed HIV strains have only been infrequently isolated from brain tissue so Gray and colleagues characterized isolates from 2 individuals (1 with HAND, 1 with CNS lymphoma) to better understand how they influence the HIV neuropathogenesis (Abstract 397). Even though the envelope proteins derived from brain were dual-mixed, they had greater fusogenicity with CCR5. In contrast, matched dual-mixed envelope proteins from spleen or blood had greater fusogenicity with CXCR4. The investigators identified that all clones from brain tissue of the individual dying with HAND were missing an asparagine residue at position 11 in the V3 loop (R306S), but that it was conserved in spleen clones. They then mutated the brain-derived clones to 306R and the spleen-derived clones to 306S, demonstrating reduced CCR5-mediated fusion of the brain clones and reduced CXCR4-mediated

fusion of the spleen clones, which supported the importance of this mutation in determining coreceptor usage in compartmentalized brain isolates. Together, these findings support that dual-mixed HIV isolates still predominantly use CCR5 in the brain, which has implications for the neuroeffectiveness of CCR5 inhibitors like maraviroc and vicriviroc even when dual-mixed HIV is present in blood.

In addition to *env*, other HIV genes, such as *tat*, have been implicated in neuropathogenesis. Most of the investigations supporting the role of HIV genes derive from the United States and Europe, where subtype-B HIV infections predominate, but non-subtype-B infections are more common in the rest of the world. The genetic differences between HIV clades may influence neuropathogenicity.²⁸ Three studies at this year's conference assessed the potential influence of viral diversity on HIV neurologic complications.

Sacktor and colleagues studied HIV-infected individuals in Uganda, where HIV clades A, C, and D are common (Abstract 404b). Sixty antiretroviral therapy-naïve, HIV-seropositive individuals from Kampala who had blood CD4+ counts below 200 cells/ μ L were evaluated. Subtype assignments were generated by sequence analysis based on portions of *gag* and *gp41*. Evaluations included a neurological examination, an 8-part neuropsychologic test battery, and assessments of daily function. A higher proportion of subjects infected with HIV subtype D met study criteria for dementia (8/9, 89%), compared with only 24% (7/33) of those infected with subtype A. This difference was not explained by group differences in age, education, sex, blood CD4+ cell counts, or plasma HIV RNA levels. The mechanism by which subtype D may confer greater neurovirulence is yet to be determined. A strength of this study was that all patients were from the same geographic region, reducing the impact of factors other than subtype that could lead to observed differences in HIV-associated neurologic disease.

Robertson and colleagues reported the baseline findings of a multisite, international study performed in Brazil,

India, Malawi, Peru, South Africa, Thailand, and Zimbabwe (Abstract 388), the most widely representative assessment of neurocognitive complications of HIV in international settings to date. Before initiation of antiretroviral therapy, subjects underwent a structured neurologic examination and a brief neuropsychologic assessment that focused on motor performance.

In contrast to studies using more comprehensive neuropsychologic assessments, these screening tests revealed a low prevalence of HIV dementia (2 cases, 0.2%) and minor neurocognitive disorder (19 cases, 2.2%) among the 860 enrolled patients. In contrast, 87 subjects (10%) had evidence of peripheral neuropathy. Of note, neurocognitive test performance varied substantially between countries, which might be explained by many factors, including host genetics, cultural customs, opportunistic infections, coinfections, substance use, HIV subtypes, or variation in test administration.

In a third international study, Valcour and colleagues performed 2 analyses of data from Thai volunteers infected with the AE circulating recombinant form (CRF, or CRF01_AE) of HIV (Abstract 387). First, in a cross-sectional analysis of data from the SEARCH 005 study, 36% (8/22) of a cohort with undetectable plasma HIV RNA levels who were nested in the 2NN clinical trial,²⁹ had mildly impaired global neuropsychologic performance. Second, in a prospective, treatment trial (SEARCH 001),³⁰ antiretroviral therapy was administered to 30 volunteers, half of whom had HAND. Even though HIV RNA levels were reduced below detection, those who had HAND continued to perform worse at 6 months ($P = .08$) and 12 ($P = .17$) months, confirming the limited effectiveness of combination antiretroviral therapy in individuals infected with CRF01_AE.

Susceptibility to NeuroAIDS: Host Correlates

Genetic variants that influence the phenotype of CNS disease in humans are well known, particularly in neuroimmunology. For example, multiple scler-

osis is associated with certain susceptible major histocompatibility complex (MHC) haplotypes. The MHC is present in many species, and the human form is termed the human leukocyte antigen (HLA) system. This group of genes resides on chromosome 6 and encodes cell-surface antigen-presenting proteins and other genes. The major HLA antigens are essential elements in immune function and are broadly categorized as either class I or class II. Class I antigens (A, B, and C) present peptides from inside the cell (including viral peptides), and class II antigens (DR, DP, and DQ) present phagocytosed antigens from outside of the cell to T cells. Previous analyses have identified that MHC class II expression was elevated in the brains of individuals dying with HIV encephalitis³¹ and was restricted to macrophages and microglia, the primary target cells of HIV in the brain.

In this context, Mankowski and colleagues reported an HLA haplotype that may specifically affect CNS retroviral disease (Abstract 72). They studied an accelerated simian immunodeficiency virus (SIV) encephalitis model in pigtailed macaques. This animal model is characterized by a shortened asymptomatic interval and an increased incidence of CNS disease compared with other SIV models. In 60 macaques, an MHC allele, *Mane-A*10*, seemed to protect animals from SIV encephalitis (24% vs 67%; odds ratio, 6.0; $P = .003$) but was unrelated to plasma SIV RNA levels or blood CD4+ cell counts, suggesting that protection from CNS disease was not related to slower immune disease progression but rather to a CNS-specific action of the allele. This concept was supported when lower levels of SIV RNA, activated (CD68+) macrophages, and amyloid precursor proteins were identified in the brains of macaques that had the protective *Mane-A*10* allele than in the control animals.

Migration of lymphocytes and macrophages is an important component of the host response to HIV in the nervous system and can lead to persistent immune-mediated injury despite apparent control of HIV in blood by antiretroviral therapy. Even though CD8+

T cells, such as effector memory and cytotoxic T cells, play important roles in control of HIV in the brain and other organs, they can also cause injury to host tissues, particularly in the context of antiretroviral therapy–induced immune recovery.

Two studies provided supportive evidence of the importance of CD8+ T cells in the nervous system by surface-phenotyping cells from CSF. Sadagopal and colleagues (Abstract 396a) assessed the frequency of HIV-specific CD8+ T cells and their maturation phenotypes (CD45RO, CD57, and CCR7) using 9-color flow cytometry in 7 volunteers who had very low levels of HIV replication in plasma and very slowly progressive HIV disease (“immune controllers”). The frequencies of HIV-specific CD8+ T cells in CSF averaged 2.4-fold greater than in blood ($P = .0004$). The CSF cells were also expanded with phytohemagglutinin and evaluated for frequency of HIV-specific T cells by flow cytometry and for interferon gamma production to HLA-class I–restricted optimal peptides by enzyme-linked immunosorbent spot assay. Expanded cells from CSF responded to a greater number of HIV-specific HLA class I–restricted optimal peptides ($P = .036$) and at higher frequencies than expanded cells from blood ($P = .012$). The enrichment of HIV-specific CD8+ T cells in CSF relative to blood in these individuals, who were immunocompetent and had low levels of HIV RNA in CSF and no neurocognitive symptoms, argues that these cells are important for control of HIV in the CNS. These findings, however, also reinforce concerns that the expansion of CD8+ T cells after initiation of antiretroviral therapy may lead to a robust immune response to HIV antigens in the brain with resulting injury.

In a second study, Spudich and colleagues (Abstract 411) compared activation markers of blood and CSF T cells obtained from individuals recently infected with HIV with those who were chronically infected. The investigators identified high levels of CD8+ T-cell activation in cells from CSF, but the relationship with HIV RNA levels varied by disease stage. Consistent

with the idea that CD8+ T cells help control HIV in the CNS, volunteers who had early HIV infection and high levels of activated CD8+ T cells in CSF had low levels of HIV RNA in CSF. In contrast, volunteers who had chronic HIV infection and high levels of activated CD8+ T cells in CSF had high levels of HIV RNA in CSF, suggesting that the T cells were homing to the CNS in response to HIV antigens but were ineffective in controlling replication. Together, the findings from these 2 studies suggest that CD8+ T cells help control HIV replication in the nervous system in early disease, but when HIV disease advances to later stages, the frequency and activation of these cells increase in the nervous system, possibly tipping the scales in favor of injury rather than control.

Susceptibility to NeuroAIDS: Comorbidities

Recent findings indicate that the majority of all CD4+ T lymphocytes are lost during acute HIV infection, with mucosal compartments being most severely affected. The frequency of infection is very high in gut CD4+ T cells and is associated with increased gut permeability and microbial translocation, which is evident as circulating lipopolysaccharide (LPS).³² Higher LPS levels in blood correlate with CD8+ T-cell activation³³ and so may help drive HIV disease progression. Because LPS can also damage the blood-brain barrier and increase monocyte trafficking into the nervous system, Ancuta and colleagues studied its effect in 119 HIV-seropositive volunteers, 82 of whom had neurocognitive impairment (Abstract 69). They found that plasma levels of LPS were higher in subjects who had HIV-associated dementia (> 79 pg/mL; odds ratio, 3.8; $P = .007$) but not milder forms of HAND and that this association remained statistically significant even after adjusting for CD4+ cell counts and plasma HIV RNA levels. Thus, immune activation stemming from HIV-mediated injury of the gut and microbial translocation may be an important determinant of risk for progression to both AIDS and neuroAIDS.

Ancuta and colleagues also identified that plasma LPS levels were higher in individuals coinfecting with HCV, supporting that this may be another mechanism by which this common comorbidity may injure the brain. Two studies supported the continued importance of HCV coinfection as a risk factor for HAND. Letendre and colleagues presented data from 401 volunteers in Anhui, China, in collaboration with Peking University and the National Center for AIDS/STD Control and Prevention in China (Abstract 413). In this cohort of former plasma donors, the prevalence of HCV seropositivity was high (46% if HIV-seropositive, 26% if HIV-seronegative) even though none of the volunteers used injection recreational drugs. Among all subjects, those who had impaired neuropsychologic performance were much more likely to be HCV coinfecting (50% vs 31%, $P < .001$). Among those who were HIV-seropositive, HCV and AIDS were independently associated with HAND (50% of those who had both conditions also had HAND). Thus, in former plasma donors in China, HCV may be an even more important comorbidity predisposing HIV-seropositive individuals to brain injury than it is in the United States and Europe.

Fishman and colleagues presented important new evidence that HCV can adapt to cells in the CNS compartment (Abstract 414). They found that HCV was present in brain tissue from 7 of 13 viremic patients (54%), as determined by 5′-untranslated-region and *E1*-envelope-gene analysis. They also identified that *N*-linked glycosylation sites were mutated in the consensus brain sequences of 4 patients and that these differed from sequences obtained from plasma and liver. Quasispecies analysis revealed that several mutations present in clones from more than 1 brain region, such as the A113G mutation found in 10% of cerebellum and medulla amplicons, were absent from amplicons derived from liver and plasma. These findings further support the idea that the brain injury evident on neuropsychologic testing and neuroimaging of HCV-seropositive individuals may be attrib-

utable, at least in part, to infection of glial cells, rather than merely a consequence of liver disease and systemic inflammation.

Peripheral Neuropathy

Neuropathic pain is a frequent neurologic problem affecting HIV-infected patients. Unfortunately, successful virologic suppression and immune restoration with antiretroviral therapy does not necessarily reverse or ameliorate this disabling condition. To complicate matters, some antiretroviral drugs, such as the DDNs, can also damage peripheral nerves. This toxicity of DDNs is well recognized, but recent epidemiologic and in vitro data have also linked PIs to neuropathy. Ellis and colleagues in the CHARTER study group assessed this association in 1159 HIV-infected subjects enrolled in a large, prospective, observational, multicenter North American study (Abstract 393). Over half (58%) met criteria for HIV-associated distal sensory polyneuropathy (DSPN) by neurologic examination, and most (58%) of those with clinical examination findings indicating DSPN also had distressing sensory symptoms. Subjects were grouped into categories according to past and current exposure to any antiretroviral drugs and to PIs. Disease indicators such as nadir blood CD4+ cell count, plasma viral load, and duration of HIV infection, as well as advancing age and exposure to DDNs, were compared with DSPN in multivariate models.

In univariate analyses, both past and current PI exposure did increase the risk of DSPN. After adjusting for previously validated concomitant risk factors in multivariate models, however, the investigators found that PI exposure did not confer an increased risk of DSPN over that in subjects who had never used antiretroviral therapy. Neither duration of PI use nor exposure to individual PI drugs was associated with DSPN in multivariate models. These data suggest that the independent risk attributable to PIs, if any, is very small. This risk must be weighed against the important role of PIs in modern antiretroviral therapy regimens.

Other Neurologic Infections

Cryptococcal Meningitis

Two abstracts examined the role of antiretroviral therapy in prognosis of cryptococcal meningitis and of quantitation of serum cryptococcal antigen in diagnosis and prognosis of cryptococcal meningitis. Bisson and colleagues reviewed patients with first episodes of cryptococcal meningitis in Botswana to examine the effects of prior antiretroviral therapy on outcomes of cryptococcal meningitis therapy (Abstract 1010). Of 92 treated patients, 26 had received antiretroviral therapy for an average of about 3 months before their cryptococcal meningitis diagnosis. All patients were induced with amphotericin B (1 mg/kg/day) for 2 weeks, followed by consolidation with fluconazole 400 mg per day, followed by prophylaxis with 200 mg per day.

In-hospital mortality was lower (8% vs 21%) in those who took prior antiretroviral therapy than in all others. This difference was statistically significant in an age- and sex-adjusted analysis (odds ratio, 0.19; $P = .05$). This and another study from South Africa³⁴ showed that antiretroviral therapy at the time of a first admission with cryptococcal meningitis is associated with lower risk of death during antifungal therapy. Fear of inducing IRIS-related complications of cryptococcal meningitis should not be a barrier to beginning antiretroviral therapy before development of an opportunistic infection. Although early initiation of antiretroviral therapy in cryptococcal meningitis patients who are not on antiretroviral therapy was not directly assessed by the study, these findings and the results of a randomized clinical trial (Abstract 142) argue in its favor.

In a retrospective review of 42 cases of cryptococcal disease over 7 years, Kandel and colleagues examined the predictive value of serum titers of cryptococcal antigen (sCrAg) in the initial diagnosis and prognosis of cryptococcal complications (Abstract 1011). Median titers of sCrAg were markedly higher in those with cryptococcal meningitis than in those with other com-

plications (1:512 vs 1:16, respectively). Over half (11 of 21) who met criteria for cryptococcal meningitis had 1 or more complications of death (2), intracranial hypertension (9), prolonged alteration of consciousness (3), or persistent hydrocephalus (1). Thus, adverse prognosis from cryptococcal meningitis was also associated with higher sCrAg titer. Patients with sCrAg titers of at least 1:2048 presenting with initial symptomatic cryptococcal infection have at least a 70% chance of developing complicated cryptococcal meningitis. If lumbar puncture must be delayed in such patients, regimens adequate for treating cryptococcal meningitis should still be used.

Progressive Multifocal Leukoencephalopathy

Two abstracts examined determinants of prognosis in PML. To develop biomarkers of PML prognosis, Marzocchetti compared 73 HIV-seropositive, PML-positive patients with 20 HIV-seropositive, PML-negative matched controls and 23 HIV-seronegative, PML-positive and 15 HIV-seronegative, PML-negative unmatched controls (Abstract 71). Concentrations of JCV DNA in peripheral blood mononuclear cells, plasma, and urine were measured by PCR-based assays, and CD8+ cytotoxic T-lymphocyte (CTL) responses against JCV VP1 protein were assessed by tetramer staining in HLA A*0201-positive persons and by chromium release assays in others. Survival was better in HIV-seropositive (77%) than in HIV-seronegative (60%) PML patients. In PML patients, JCV was detectable more frequently in plasma (56% vs 30%) and urine (61% vs 27%) than in matched HIV-seropositive controls, but JCV titers were similar. In HIV-seropositive, PML-positive patients, those who had detectable CTL responses within 1 year of diagnosis had markedly better survival than those who did not (83% vs 33%). Survival was also better in those with higher blood CD4+ counts at PML diagnosis (> 200 cells/ μ L, 92%, vs < 200 cells/ μ L, 70%).

Two studies highlighted manifestations of PML in the cerebellum. The

first described features of “unmasked” PML, that is, PML diagnosed within 6 months of starting antiretroviral therapy. Because IRIS usually occurs in the first months after starting antiretroviral therapy, it might play a role in cases of PML that occur during that period. In the first study, Sidhu and McCutchan examined records of 20 HIV-seropositive PML patients whose PML was diagnosed between 1996 and 2006 to assess the relationship of PML onset and potent antiretroviral therapy (Abstract 417). Unmasked PML was seen in 8 (40%) patients and was diagnosed a median of 80 days (range, 47-140 days) after starting antiretroviral therapy.

In comparison, PML was diagnosed in 6 patients before they started antiretroviral therapy, and the remaining 6 had undergone antiretroviral therapy for more than 6 months before receiving the PML diagnosis. Among the 8 cases of unmasked PML, disease was confined to the posterior fossa (cerebellum and peduncles) in 4, 3 of whom had cranial nerve palsies involving cranial nerves VI and VII. Only 3 of 8 had enhancement on magnetic resonance imaging, all improved, and 5 of 8 survived for more than 400 days (the 3 others were lost to follow-up at 10, 16, and 69 days). Unmasked PML does not require evidence of severe IRIS, as manifested by enhancement on magnetic resonance imaging, and appears to have a relatively good prognosis. Reasons for its unusually common localization to the posterior fossa (7% in another large pre-antiretroviral-therapy-PML case series and 50% in this series) are unclear.

A second study stems from a recently described,³⁵ progressive cerebellar disease of HIV-infected patients called JCV granule cell neuronopathy. This syndrome is distinct from PML, which commonly affects cerebral white matter. To determine the prevalence of JCV in granule cell neurons (GCNs) in HIV-seropositive patients, brains from 44 patients with HIV and PML and 44 controls with HIV but not PML were examined by Wuthrich and colleagues using immunohistochemical and immunofluorescence methods (Abstract 418). A substantial propor-

tion of the HIV-seropositive, PML-positive patients (72%) had detectable JCV in their GCNs compared with HIV-seropositive, PML-negative controls (0 of 44). The JCV VP1 protein, which is associated with productive infection, was found infrequently, supporting the presence of a latent or abortive JCV infection of GCNs. Because JCV infection of GCN occurred only in the context of PML in this series, the analysis does not support that this syndrome occurs independently of PML. However, restricted infection of GCNs may provide important insights into the initiation and progression of this debilitating disorder.

CNS Syphilis

The number of B cells is higher in the CSF of HIV-seropositive patients with neurosyphilis than in HIV-seronegative patients with neurosyphilis³⁶ or HIV-seropositive patients with uncomplicated syphilis.³⁷ To build on these observations, Marra and colleagues examined levels of CD19+ B cells and the B-cell chemokine CXCL13 in the CSF of 180 HIV-seropositive individuals who had either syphilis or neurosyphilis (Abstract 407). Levels of CSF CXCL13 and B cells were elevated in neurosyphilis, and their levels were highly correlated (r^2 , 0.69). Using a more inclusive definition of neurosyphilis (CSF VDRL-test-positive or CSF leukocyte level above 20/ μ L), the investigators found that higher levels of CSF CXCL13 (odds ratio, 15.5; $P < .001$) or CD19+ B cells (odds ratio, 12.8; $P < .001$) were each strongly associated with neurosyphilis, even after adjusting for antiretroviral therapy use. Although these data confirm the importance of B cells in treponemal neuropathogenesis, they also identify that measurement of CXCL13, which can be performed using a currently available commercial immunoassay, may be an important new diagnostic test for neurosyphilis.

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A list of all cited abstracts appears on pages 69-77.

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Complications of HIV Disease and Therapy

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Managing and preventing complications of HIV disease remain high priorities for research worldwide. At the 15th Conference on Retroviruses and Opportunistic Infections, continued areas of focus were on understanding the pathogenesis of complications, identifying risk factors for these problems, and defining optimal management strategies for complications and infections. As in past years, there was an increase in studies focused on problems predominantly occurring in resource-limited settings.

Morbidity and Mortality in the Potent Antiretroviral Therapy Era

As highlighted by Phillips in the opening morning plenary session of this year's conference, the greatest source of morbidity in the potent antiretroviral therapy era is undiagnosed and under-treated HIV infection. He discussed the relationship between serious non-AIDS events (cardiovascular disease and renal and hepatic events) and HIV infection, demonstrating that these events are both more common in patients with lower CD4+ cell counts and reduced in frequency by the use of antiretroviral therapy (see also Abstract 963). He concluded by suggesting that all-cause morbidity might be further reduced if treatment were started at higher CD4+ cell counts. Additional data from his group demonstrated a higher rate of mortality for treatment-naïve patients with CD4+ counts above 350 cells/μL than for the general population in the UK (Abstract 141). In this study, age-standardized mortality ratios for 47,474 antiretroviral therapy-naïve patients with CD4+ counts greater than 350 cells/μL were compared with ratios of the general population. For each risk group examined, men who have sex with men (MSM), injection drug users, and heterosexuals, the risk of death was higher for the HIV patients than for the controls, and the

excess mortality was greatest for injection drug users, possibly the result of non-HIV-related morbidity in this population. These data support the notion that earlier treatment of HIV infection should be explored with the hope of further improving the overall outcomes for people with HIV infection.

As treatment improves, it is clear that rates of failure and opportunistic infections remain low among those who are able to obtain and stay on therapy. This is not to say that toxicity and adverse events related to long-term HIV infection and its treatment are not important issues. In this article, we review some of the new data presented at this year's conference on managing complications of HIV disease and therapy.

Cardiovascular Disease

As patients with HIV age, there is ongoing concern about the long-term risk of cardiovascular disease in this population. Previously the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) collaboration, a prospective multicohort study, reported that each additional year of protease inhibitor (PI) treatment was associated with 16% excess risk of myocardial infarction (MI).¹ Preplanned analyses from this cohort were presented at this year's conference examining the association between the nucleoside analogue reverse transcriptase inhibitor (nRTI) component of therapy and MI risk (Abstract 957c).

At the outset, it is important to emphasize that the absolute risk of MI in this updated report from the DAD study is low, with 517 events among 33,400 patients (1.6%) during 5 years of follow-up. The investigators had hypothesized

that the thymidine nRTIs zidovudine and stavudine would be associated with an increased risk of MI because of the known relationship between these drugs and modest changes in dyslipidemia. An unexpected finding emerged from these analyses: both didanosine (relative risk [RR], 1.49) and abacavir (RR, 1.9) appeared to be associated with the risk of MI. Interestingly, the risk was not evident in patients who previously took abacavir and stopped it more than 6 months beforehand.

Careful analyses of these data suggested that patients who received abacavir had a greater burden of traditional cardiovascular risk factors, but after control for these factors, the relationship between recent abacavir use and MI persisted. Also, within the abacavir group, the excess risk was greatest for patients with a higher underlying risk of cardiovascular disease, which is a reminder to clinicians to screen and manage all patients for modifiable cardiovascular risk factors such as hypertension, dyslipidemia, and diabetes.

The results of this study will launch a closer look at the relationship between abacavir and didanosine exposure and MI in other large databases and clinical trials. In the interim, clinicians should interpret these unexpected findings cautiously while more data are compiled.

An active area of investigation is the relationship between chronic HIV infection, markers of inflammation, and cardiovascular risk. Sparked initially by data from the Strategies for Management of Antiretroviral Therapy (SMART) study that demonstrated a marginally increased risk of cardiovascular events among patients who interrupted therapy, interest is growing in the role of inflammation as a mediator of cardiovascular risk in HIV. Kuller and the SMART team reported a case-control study (Abstract 139) that examined the relationship among (1) the levels of the inflammatory markers interleukin-6, high-sensitivity C-reactive protein, and

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amyloids A and P; (2) the markers of thrombosis, d-dimer and prothrombin fragments 1 and 2, at the time of treatment interruption; and (3) cardiovascular events and overall mortality. They found a striking association between the levels of both interleukin-6 (odds ratio [OR], 12.6) and d-dimer (OR, 13.3) and all-cause mortality. They also found a statistically significant, but of lesser magnitude (OR, 2.0 for d-dimer) association between the markers of thrombosis and fatal and nonfatal cardiovascular events. These results suggest that among patients who stop antiretroviral therapy, increases in generalized immune activation may be associated with the excess morbidity observed.

Other studies examined the relationship between biomarkers of inflammation and endothelial activation and measures of subclinical cardiovascular and metabolic disease. Ross and colleagues reported higher levels of endothelial activation markers in untreated HIV patients than in uninfected controls (Abstract 954). In a second study (Abstract 949), these same investigators examined the association between several biomarkers and carotid intima media thickness (IMT) in a cross-sectional study of HIV-infected and -uninfected patients. They reported higher levels of the inflammatory cytokines and endothelial activation markers in the HIV-infected patients than in the controls and a correlation between the inflammatory cytokines (but not endothelial activation markers) and carotid IMT.

Data from one of the few longitudinal studies presented demonstrated higher levels of several endothelial activation markers (soluble intercellular adhesion molecule 1, soluble vascular cell adhesion molecule 1, tissue-type plasminogen activator inhibitor, and high-sensitivity C-reactive protein) among untreated HIV patients with an improvement (reduction in activation markers) during potent antiretroviral therapy (Abstract 953). After 12 months of potent antiretroviral therapy, the difference in endothelial activation markers between the HIV-infected and -uninfected groups was no longer statistically significant.

A novel approach to examining the relationships among HIV infection, viral replication, HIV treatment, and atherosclerosis was reported by Hsue and colleagues in a cross-sectional study comparing carotid IMT in HIV-infected patients with that of uninfected controls (Abstract 951). The novel aspect of this study was the inclusion in the HIV groups of patients in whom HIV replication was controlled without treatment as well as patients on potent antiretroviral therapy. After adjustment for traditional risk factors, both HIV infection and duration of PI therapy were associated with carotid thickness. Notably, the untreated HIV patients with controlled viral replication also had greater carotid thickness than the uninfected controls did, suggesting that factors other than viral replication or immunodeficiency may contribute to carotid thickness.

An intriguing pilot study by Gupta and colleagues at Indiana University examined the impact of pentoxifylline on endothelial function in HIV-infected patients (Abstract 955). Previous studies have suggested that impaired flow-mediated dilation (FMD) of the brachial artery is common in HIV-infected patients.² Pentoxifylline is known to reduce tumor necrosis factor production *in vivo* and *in vitro*; however, it did not have a significant impact on HIV replication when it was evaluated as a potential HIV treatment.³ In this single-arm study, a 400-mg, 3-times-daily dosage of pentoxifylline given to 9 HIV patients not on antiretroviral therapy was associated with an improvement in FMD of the brachial artery after 4 and 8 weeks, suggesting that systemic inflammation is likely to contribute to the abnormal FMD of the brachial artery seen among untreated patients. Controlled studies are needed to determine whether pentoxifylline has any role in reducing systemic inflammation during effective HIV therapy.

Dyslipidemia

Randomized trials of new or existing treatments in treatment-naïve patients now routinely include the measurement of fasting lipid levels,

as this information is important for the long-term management of HIV infection. The CASTLE study (Abstract 37) compared ritonavir-boosted atazanavir with lopinavir/ritonavir, both in combination with tenofovir/emtricitabine, in treatment-naïve patients; it demonstrated higher triglyceride, total cholesterol, and non-high-density-lipoprotein (HDL) cholesterol levels in the lopinavir/ritonavir-treated patients. In the MERIT study, in which zidovudine and lamivudine provided the nRTI backbone, efavirenz therapy was associated with high median increases in levels of total cholesterol (35 mg/dL vs 2 mg/dL), HDL cholesterol (13.5 mg/dL vs 6.9 mg/dL), triglyceride (20 mg/dL vs -9 mg/dL), and low-density-lipoprotein (LDL) cholesterol (20.7 mg/dL vs -9 mg/dL).

These results highlight the fact that first-line therapy with efavirenz, especially when combined with zidovudine plus lamivudine, is not lipid-neutral (Abstract 929). In the HEAT study, lipid changes in patients on abacavir plus lamivudine were comparable with those on tenofovir plus emtricitabine, both combined with once-daily lopinavir/ritonavir (Abstract 774).

Ritonavir is used in different doses to boost PIs and other drugs. Boffito and colleagues examined the relationship between low doses of ritonavir and values of triglycerides and HDL cholesterol (Abstract 930). Effects of ritonavir doses of 100 mg either once daily or twice daily were examined in uninfected volunteers over a 14-day period. Only the 100-mg, twice-daily dose of ritonavir was associated with an increase in triglyceride levels, and there appeared to be a relationship between ritonavir exposure and change in triglyceride level. In a small study ($n = 40$) comparing the lipid profiles of the new (tablet) and old (capsule) formulations of lopinavir/ritonavir, higher levels of triglycerides and lower levels of HDL were observed with the newer tablet formulation (Abstract 934). Higher lopinavir trough levels were seen during therapy with the tablet formulation; unfortunately, no information about ritonavir levels was available in this study.

Lipoatrophy and Lipohypertrophy

Factors associated with the development of a 20% loss of limb fat as measured by dual-energy x-ray absorptiometry (DEXA) scan were evaluated in the AIDS Clinical Trials Group (ACTG) 5142 study that compared 3 class-sparing regimens for initial treatment of HIV infection (Abstract 935). In this study, lipoatrophy was greater for efavirenz plus 2 nRTI arms (32%), more so with stavudine (43%) and zidovudine (27%) than with tenofovir and the lopinavir plus efavirenz arms (8%-10%). Independent of the antiretroviral therapy received, higher baseline CD4+ cell count and lower gain in body weight were associated with the development of lipoatrophy. Other factors associated with limb fat loss included male sex, absence of AIDS diagnosis at baseline, and smaller increases in total and LDL cholesterol levels. These results suggest that additional factors contribute to fat loss during treatment of HIV infection.

Currently, the most effective intervention for management of lipoatrophy is switching patients off zidovudine or stavudine to either an abacavir- or tenofovir-based regimen. Moyle reported his group's 48-week DEXA results from a randomized trial that enrolled 250 patients who were well suppressed on efavirenz and fixed-dose zidovudine/lamivudine and who underwent randomization to either remain on this treatment or change the nRTI component to tenofovir and emtricitabine (Abstract 938). Mean limb fat (as measured by DEXA) increased by 261 g in the tenofovir group compared with a 187-g decline in those remaining on zidovudine. Importantly, virologic control was maintained during follow-up, and no statistically significant differences were noted in a post hoc analysis of bone mineral density during the 48-week period.

Further support for the role of nRTIs in the pathogenesis of lipoatrophy and visceral fat accumulation comes from the MEDICLAS trial (Abstract 937). Antiretroviral-therapy-naïve men underwent randomization to lopinavir/ritonavir combined either with zidovudine plus lamivudine or with nevirapine.

Both DEXA and abdominal computed tomography measures were included, and follow-up to 24 months was reported. Lipoatrophy and abdominal fat accumulation were more common when lopinavir/ritonavir was added to the nRTI combination of zidovudine plus lamivudine. However, higher levels of total and LDL cholesterol were observed in the nRTI-sparing regimen of lopinavir/ritonavir plus nevirapine, indicating that alternative nRTI-sparing regimens should probably be explored.

Currently, weight loss and exercise are the mainstays in managing central fat gain during HIV treatment. Mun and colleagues conducted a randomized trial comparing the insulin sensitizer rosiglitazone with a diet-and-exercise intervention including either placebo or rosiglitazone (Abstract 944). Eligible patients had an elevated body mass index (BMI) and fasting insulin level at or above 16 $\mu\text{IU/mL}$. Treatment with rosiglitazone was associated with weight gain, which was ameliorated in the group who received the diet-and-exercise intervention with rosiglitazone. It was not possible to measure an additional benefit provided by rosiglitazone over the diet-and-exercise intervention in this small study.

The growth-hormone-releasing factor analogue tesamorelin is under investigation as a treatment for HIV-associated central fat gain. Previous 26-week results reported a decrease in visceral adipose tissue with a 2-mg daily dose of tesamorelin, compared with placebo. At this year's conference, 52-week results were presented that compared the long-term outcomes for patients who underwent rerandomization at week 26 to either discontinue or remain on treatment through 52 weeks (Abstract 943). Within the group that remained on treatment, loss of visceral fat was maintained without a significant loss in limb fat or evidence of worsening glucose tolerance. Unfortunately, the improvement in visceral adipose tissue seen during the first 26 weeks of therapy was not maintained in subjects who were switched to placebo, suggesting that continued treatment will be needed to maintain the benefit of this drug.

Bone Density

Low bone density is common among HIV-infected men and women; however, the role of antiretroviral treatment as a cause of osteopenia and osteoporosis remains controversial. Investigators from the Women's Interagency HIV Study (WIHS) evaluated changes in bone mineral density (BMD) among 114 HIV-seropositive and 74 HIV-seronegative premenopausal women over a 2-year period (Abstract 965). At baseline, the HIV patients were older and had lower BMI and—not surprisingly—also had lower BMD, most notably in the PI-treated group. During the 2 years of follow-up, however, the rate of bone loss and occurrence of fractures did not differ between the treatment groups. These results suggest that antiretroviral therapy-treated HIV patients may have comparable rates of bone loss to age-matched controls.

Two studies examined the role of different antiretroviral treatment regimens and bone loss within randomized clinical trials and produced somewhat conflicting results. Brown reported the results of a randomized trial comparing initial treatment with either efavirenz plus zidovudine plus lamivudine or lopinavir combined with zidovudine plus lamivudine and later simplified to lopinavir monotherapy (Abstract 966). After 96 weeks of treatment, the rate of bone loss (-2.3% , -2.5%) was similar in both groups. These results suggest that the loss of BMD that occurs after initiation of antiretroviral therapy is independent of the treatment regimen. In addition, the baseline data from this study confirm earlier observations that nonblack patients and those with lower baseline CD4+ cell counts are more likely to have lower BMD.

In contrast, Duvivier and colleagues (Abstract 967) compared rates of bone loss among patients who underwent randomization to a nonnucleoside analogue reverse transcriptase inhibitor (NNRTI)-PI combination or to therapy with either a PI or NNRTI combined with nRTIs. Follow-up in this study was 48 weeks, at which point bone loss at the hip and lumbar spine was greater in both of the PI-containing arms than

in the NNRTI arm. Clearly, larger studies with longer follow-up periods are needed to sort out the contribution of specific antiretroviral therapy regimens to bone loss. One point that all studies appear to agree on is the high prevalence of osteopenia among antiretroviral-therapy-naïve patients, suggesting a role for untreated HIV infection in the pathogenesis of bone loss (Abstracts 968, 969).

Renal Disease

A theme throughout this year's conference was the role of HIV infection and immunodeficiency in the pathogenesis of many important complications; renal disease is a prime example. Kirk and the EuroSIDA Study Group (Abstract 971) examined predictors of deterioration of renal function among 5526 patients observed prospectively with measurement of estimated glomerular filtration rate (GFR). Loss of renal function (25% decline) was observed in 2% to 3% of patients and appeared related to the level of immunodeficiency in addition to traditional risk factors (most notably hepatitis C virus [HCV] coinfection).

Data from the Multicenter AIDS Cohort Study (MACS) were used to examine predictors of GFR decline in HIV-infected men compared with uninfected controls (Abstract 973). In this study of 2163 men (1206 HIV-uninfected), GFR decline was not associated with HIV status or potent antiretroviral use but rather with black race, diabetes, hypertension, smoking, and HCV status. Proteinuria was identified as an important early marker of future decline in renal function.

Gupta examined the urine protein-to-creatinine ratio (P:Cr) in 2827 patients observed since 2002 in the ACTG Longitudinal Linked Randomized Trials (ALLRT) cohort and found a decline in P:Cr over time; notably, those with plasma HIV RNA levels below 400 copies/mL had reduced odds of clinically significant proteinuria (Abstract 974). Again, hypertension, diabetes, older age, and black race were important factors in predicting a decline in renal function over time.

Optimal methods for monitoring renal function in clinical practice are often debated, and the accuracy of different formulas for estimating creatinine clearance in HIV patients is unknown. Investigators from the PREPARE study compared a gold standard measure of GFR, that is, GFR measured by iodine¹²⁵-iothalamate using a 24-hour urine collection, with other estimates of GFR using either the Cockcroft-Gault method, the modification of diet in renal disease formula, or a measurement of cystatin C (Abstract 977b). Among this small group of predominantly male patients with preserved renal function, the Cockcroft-Gault method compared most favorably with the measured creatinine clearance using the isotope method. The reasons for the poor performance of the cystatin C measure in this study are unknown; however, the authors postulate that HIV-related inflammation may play a role.

Toxicity in Resource-limited Settings

Toxicities associated with stavudine, the most commonly used nRTI in first-line antiretroviral therapy in resource-limited settings, were the focus of the majority of abstracts on this topic. From a cohort of 305 patients receiving stavudine-containing antiretroviral therapy regimens for 2 years, Wong and colleagues reported that stavudine-specific toxicities were frequent and cumulative (Abstract 990). Peripheral neuropathy incidence rates were 0.27 and 0.22 (expressed as events per person-year) in years 1 and 2, respectively. Lactic acidosis incidence rates were 0.04 in year 1 and 0.06 in year 2 of follow-up. Lipodystrophy presented more commonly in year 2 with an incidence rate of 0.21. Ninety percent of the 60 regimen changes in this cohort were because of toxicity, with lipodystrophy (37%), peripheral neuropathy (32%), and lactic acidosis (15%) accounting for the majority of the regimen switches. The concern for lactic acidosis among patients has led to the development of methods to measure lactate that are feasible in a resource-limited setting. Hand-held, point-of-care lactate analyzers compared favorably with traditional

laboratory evaluations of lactate, and authors concluded that these devices were useful for evaluating patients with symptoms consistent with symptomatic hyperlactemia (Abstracts 991, 992).

Substituting zidovudine for stavudine to limit toxicity is standard practice in resource-limited settings, but few studies have evaluated outcomes of this approach. Mwima and colleagues reported outcomes of 860 adults in Uganda who developed peripheral neuropathy after starting antiretroviral therapy with a stavudine-based regimen (Abstract 988). Thirty-six percent of adults reported symptoms of neuropathy a median of 28 days after antiretroviral therapy initiation, and 143 patients with mild neuropathy remained on stavudine, with 54% reporting improvement, 40% remaining the same, and 6% worsening. One hundred fifty-three subjects with grade 3 or 4 neuropathy switched to zidovudine, of whom 75% had improvement in their neuropathy at follow-up. Improvement in neuropathy was most likely when the CD4+ count was above 200 cells/ μ L and the subject was not receiving isoniazid. Although these data demonstrate improvement in many individuals after discontinuation of stavudine, many individuals did not improve, and many progressed, underscoring the need for the use of alternatives to stavudine.

Risks for lipodystrophy and the metabolic syndrome in a cohort of 171 patients living in Abidjan, Cote d'Ivoire (West Africa), were reported by Eholie (Abstract 947). Lipodystrophy was defined by 1 or more signs of peripheral lipoatrophy and central lipohypertrophy. Metabolic syndrome was defined as the presence of abnormalities in at least 3 of the following laboratory measures: triglycerides, HDL, glucose, waist circumference, and blood pressure. The 2 most commonly used antiretroviral therapy regimens were efavirenz plus zidovudine plus lamivudine (57%) and nevirapine plus stavudine plus lamivudine (21%). The cumulative incidence of metabolic events after a mean follow-up period of 16 months was: blood pressure increase, 38%; waist hypertriglyceridemia, 16%; circumference increase, 14%; and hyperglycemia, 2%. Lipohy-

pertrophy was reported in 23% and lipotrophy in 4%. Although the absence of standardized case definitions in the field make comparison between studies challenging, these data contribute to accumulating evidence that metabolic abnormalities are not uncommon among patients receiving standard first-line regimens in resource-limited settings.

Toxicities to stavudine continue to follow a predictable pattern in resource-limited settings, and the high cost of alternative drugs is the major reason for its continued use. One modeling study suggested that only modest reductions in tenofovir prices would be enough to make it cost-neutral to stavudine, when the costs of stavudine toxicity are considered (Abstract 989). Tenofovir is now included as first-line therapy in the World Health Organization guidelines, and all data continue to point to the importance of avoiding cumulative exposure to stavudine.

Aging

With the improved long-term prognosis of treated HIV patients comes an awareness of the intersection between normal aging and the management of HIV infection. A 2-hour symposium at this year's conference highlighted the special considerations about aging in the setting of HIV infection. With speakers focused on epidemiology (Ledergerber), immunology (Effros), pharmacology (Flexner), and clinical management (Powderly), an array of special issues were reviewed.

The session addressed the growing number of patients with established HIV infection who are aging, along with the importance of identifying new infections among the over-50-year-old population. Data suggesting that people older than 50 years are more adherent to therapy were counterbalanced by evidence of limited immune reserve and blunted CD4+ cell responses in older patients. Immune exhaustion in chronic HIV infection and normal aging were explored, with an emphasis on the role and measurement of CD8+ T-cell exhaustion as an important issue for the aging HIV-infected population. Special issues related to diseases of aging such as diabetes, hypertension, os-

teoporosis, and cardiovascular disease were highlighted, as was concern about polypharmacy and drug interactions. Finally, optimal systems of care for the management of an aging HIV-infected population were brought into question. Viewing of this session on the webcast is highly recommended for those with an interest in this important new area of investigation.⁴

Tuberculosis Coinfection

Drug-resistant Tuberculosis

The toll and spread of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) were reviewed by Friedland in the tuberculosis symposium (Abstract 112). Friedland provided an update on the South African situation in Tugela Ferry, KwaZulu-Natal province, since the original report of the epidemic. Between January 2005 and September 2007, there have been an additional 471 cases of drug-resistant TB. The outcomes continue to look grim, with mortality rates in the 60% to 80% range. Strains of MDR-TB have not been limited to Tugela Ferry. In mid-2007, XDR-TB cases had been identified from 60 facilities in KwaZulu-Natal. Of the 5019 cases identified in the province, over half were outside Tugela Ferry. Only 25% of the total cases had records of care at the MDR referral hospital, the only location where second-line TB drugs are available. An additional 9 South African provinces had identified cases of XDR-TB. There are also reports of resistant strains in neighboring Mozambique and Botswana. Studies are ongoing to define the extent of this emerging epidemic in sub-Saharan Africa.

Reminiscent of the outbreaks of MDR-TB in the United States in the 1980s, new data presented by Andrews and colleagues documented that some patients acquire MDR- or XDR-TB in health care facilities, and that many of these infections represent TB reinfections among patients already being treated for drug-susceptible TB (Abstract 143). This group examined baseline and follow-up TB cultures from 17 individuals from Tugela Ferry who de-

veloped drug-resistant TB after initiating TB treatment. Results of spoligotyping of the culture pairs demonstrated that the patients were reinfected with a drug-resistant TB strain. All 17 patients were hospitalized at the same facility. Supporting the conclusion of nosocomial reinfection, unique TB strains for each patient were identified at the start of therapy, and common MDR- or XDR-TB strains were found to account for reinfection. Infection-control measures are nonexistent in most parts of Africa. These data call for rapid implementation of measures to reduce in-hospital transmission.

High prevalence of TB drug resistance is not limited to Africa. Eastern Europe has among the highest rates of drug-resistant TB in the world. In an epidemiologic survey from Ukraine, MDR-TB rates were 1.7-fold higher among HIV-infected than uninfected patients (Abstract 144). The overall prevalence of MDR-TB was alarmingly high in isolates from these individuals living in Ukraine. Among HIV-seropositive individuals, 28% of TB cases in the civilian sector and 58% in the prison sector harbored MDR strains of TB.

Tuberculosis Outcomes

The bulk of early mortality observed after initiation of antiretroviral therapy in Africa has been attributed to TB. Westreich and colleagues evaluated outcomes of 6080 adults initiating antiretroviral therapy in Johannesburg, South Africa (Abstract 145), of whom 17.3% had TB at the time of antiretroviral therapy initiation. In the multivariate analysis, TB was not associated with increased mortality nor loss to follow-up. However, individuals with low BMI, a CD4+ count below 50 cells/ μ L, and TB had increased mortality rates.

In this same cohort, Faesen reported a study comparing suppression rates of plasma HIV RNA levels among patients with TB receiving antiretroviral therapy with those of similar patients but without TB (Abstract 1002). As in reports from other cohorts, there was no difference in reductions in plasma HIV RNA levels between the patients with or without TB.

Immune Reconstitution Inflammatory Syndrome

The immunologic basis of TB-associated immune reconstitution disease has yet to be elucidated. Meintjes and colleagues evaluated sequential interferon gamma (IFN- γ) enzyme-linked immunosorbent spot (ELISpot) data from 63 adults with TB who were initiating antiretroviral therapy, as well as a cross-sectional cohort of 42 persons with TB-associated immune reconstitution inflammatory syndrome (IRIS). In the longitudinal cohort, IRIS developed in 22% of persons. Although IFN- γ responses to a number of TB antigens increased after antiretroviral therapy, these changes did not predict development of TB-IRIS (Abstract 1006). Similarly, Tieu and colleagues examined T_H1 cytokine responses and IFN- γ responses among 51 Thai patients with TB who initiated antiretroviral therapy. In this cohort, 21.6% developed TB-IRIS, with 8 requiring corticosteroid treatment (Abstract 1008).

Similar to the South African study, Boulware and colleagues found no association between the immunologic markers tested and the development of TB-IRIS (Abstract 1007). Gazzola and colleagues presented an interesting poster on FoxP3 (T-regulatory)-expressing cells (Abstract 1003). These investigators examined lymph nodes for FoxP3 expression from patients with and without HIV and with and without TB. They found the lowest expression of FoxP3 markers to be among patients with TB and HIV. They suggested that fewer T-regulatory cells may result in the poorer control of inflammatory responses and increased inflammation observed with TB among HIV patients, particularly during IRIS events.

Numerous posters and a poster discussion session (Session 29) highlighted the absence of a uniform, validated case definition for TB-IRIS. In addition, one of the requirements for the diagnosis of immune reconstitution disease, or transient worsening of TB after initial clinical improvement, is the exclusion of other possible causes of clinical deterioration.

In this regard, one of the most important TB-HIV presentations at this year's

conference was the report by Meintjes and colleagues (Abstract 1009), who prospectively evaluated 100 suspected TB-IRIS cases between February 2005 and July 2006. In 7 cases, an alternative opportunistic infection was the explanation for the clinical deterioration. In 12 cases, rifampin resistance, either alone or as a part of an MDR-TB infection, was present at baseline and was the reason for the clinical worsening. In 8 cases, the clinical deterioration was the manifestation of an inadequate treatment regimen in a patient with rifampin resistance. This report, along with the TB reinfection data cited above, indicate that suspected TB-IRIS may be the result of failure of a drug-resistant first-line regimen or reinfection with a second drug-resistant strain. Rapid diagnostic tests for drug resistance are urgently needed, both for clinical care and research studies in this population.

Pharmacokinetics

In resource-limited settings, efavirenz is recommended as the preferred NNRTI for patients requiring rifampin-based TB therapy because of the greater effect of hepatic enzyme induction by rifampin on nevirapine than on efavirenz. Matteelli evaluated 16 subjects from Burkina Faso, Italy, treated for TB, who started a nevirapine-based antiretroviral therapy regimen within 30 days of the start of TB therapy (Abstract 760). About 33% of the patients had subtherapeutic nevirapine trough levels in the presence of rifampin compared with about 12% when only nevirapine was present and rifampin had been discontinued. This sample size was too small to evaluate clinical outcomes, but the results add to the body of literature demonstrating the short-term effect of rifampin on nevirapine trough levels during rifampin administration.

Haas and colleagues evaluated the interaction between boosted atazanavir and rifampin (Abstract 766b). After 8 days of rifampin treatment, HIV-uninfected volunteers received twice-daily atazanavir 300 mg and ritonavir 100 mg. The study was halted after only 3 participants were entered. After starting the atazanavir/ritonavir treatment,

all subjects experienced severe nausea and vomiting and significant elevation in hepatic transaminase levels. Authors postulated that a toxic metabolite of either ritonavir or rifampin caused these effects.

Hepatitis C Virus

Epidemiology

Sexually transmitted HCV has been reported among MSM. Jones and colleagues reported reinfection with HCV among MSM who had been successfully treated previously for HCV. They identified 16 patients with hepatitis C viremia after either sustained virologic response (SVR) posttreatment or spontaneous clearance (Abstract 61LB). Among 8 individuals for whom paired samples of the 2 episodes were available, results of phylogenetic analysis suggested that 6 of the 8 patients were reinfected with a new strain of HCV, and 2 had late relapses. All of the subjects had ongoing high-risk sexual activity. Although there is the possibility that the patients were initially infected with more than 1 strain, these data suggest that even patients for whom the HCV achieves SVR or spontaneous clearance are at risk for HCV reinfection.

In a second epidemiologic study of HCV in MSM, van de Laar and colleagues used results of phylogenetic analysis to characterize ongoing new HCV outbreaks (Abstract 1066). They evaluated 200 isolates from MSM with acute HCV infection from England, the Netherlands, Germany, and Australia. Results of phylogenetic analysis revealed 12 HCV clusters. Data were consistent with clusters within Europe but not between Europe and Australia. These data underscore the importance of including HCV evaluations among sexually active MSM and targeting prevention messages to this population.

Outcomes

Sustained virologic response is the goal of HCV therapy. Few studies have attempted to quantify outcomes in patients whose treatment did and did not achieve SVR. Berenguer and colleagues

examined outcomes from 711 HIV-infected patients from 11 clinical centers in Spain who received HCV treatment with interferon alfa (including pegylated forms) plus ribavirin (Abstract 60). The follow-up period was approximately 2 years, during which SVR was achieved in 31% of subjects. Mortality was 6.9% among non-SVR patients and 0.9% in the SVR group. Liver decompensation was 9.1% and 0.5% in the non-SVR and SVR groups, respectively. Liver transplants were performed in 2.2% and 0.5% of patients in the non-SVR and SVR groups, respectively. These data, which demonstrate 20-fold higher rates of liver decompensation and 9-fold increased rates of mortality among patients for whom treatment failed to achieve SVR compared with those for whom treatment did achieve SVR, underscore the value of achieving SVR and the urgent need for better HCV treatments.

Lars Peters and colleagues evaluated HIV treatment outcomes among patients with and without HCV in the EuroSIDA cohort (Abstract 1069). They specifically examined whether the presence of HCV infection influenced CD4+ cell count changes among HIV-infected patients who had 2 consecutive test results of plasma HIV RNA values below 50 copies/ μ L. In this analysis of 3892 patients, 21% were HCV-seropositive. After adjusting for potential factors associated with influencing CD4+ cell count recovery or viral load suppression, there was no difference in CD4+ cell count recovery among patients with and without HCV antibody.

Treatment

The value of maintenance therapy with peginterferon alfa in HCV patients whose infection failed to achieve an early virologic response (EVR) is not known. Some data suggested that continued interferon therapy for such patients could potentially provide improvement in histologic disease progression. To test that hypothesis, patients for whom treatment with peginterferon alfa and weight-based ribavirin had failed to achieve EVR (defined as a 2- \log_{10} reduction in plasma

HCV RNA levels at 12 weeks) underwent randomization to either peginterferon alfa or no therapy (Abstract 59).

Sherman and colleagues used sequential liver biopsies to assess liver disease progression. The study was prematurely halted because of the slow rates of progression in the observation (control) arm that received no interferon. The expected rate of change of fibrosis in the control arm was 0.18 metavir units/year, and the observed rate was undetectable. Possible explanations for these results include the influence of high rates of SVR suppression during the initial treatment phase, a duration of follow-up that was not long enough, or that the differences were too modest to detect by this study. These data do not support maintenance interferon alfa therapy among patients for whom prior treatment with interferon alfa and weight-based ribavirin failed to lead to EVR.

Rapid virologic response (RVR), defined as HCV titers below 50 IU/mL at 4 weeks, has been utilized to predict HCV treatment responses in HCV-monoinfected patients. Rodriguez-Torres and colleagues examined RVR and EVR among 271 HIV-coinfected patients who underwent treatment for HCV (Abstract 1073). Rates of SVR were highest in those with RVR. When the researchers stratified results of those with EVR into “complete” EVR (defined as plasma HCV RNA levels below 50 IU/mL at week 12, not week 4) and “partial” EVR (defined as a 2-log reduction in HCV titer at week 12 and plasma HCV RNA titer above 50 IU/mL), they found higher SVR rates in the complete than in the partial EVR subjects. Matthews and colleagues examined RVR as a predictor of SVR among patients with acute HCV infection (Abstract 1070). They had 96 patients, 28 of whom were coinfecting with HIV. An RVR occurred in 39% of HCV-HIV-coinfecting subjects and in 49% of HCV-monoinfected subjects. Sustained virologic response was achieved in 100% of subjects with RVR and in 56% of subjects without RVR. There was no difference in the positive predictive value of EVR for SVR between the HIV-infected and -uninfected subjects.

Finally, 3 abstracts from Spain evaluated the potential effect of nRTIs on HCV infection outcomes. There are conflicting data on whether abacavir-containing regimens reduce HCV response rates.

Mira and colleagues compared HCV treatment outcomes among 256 patients receiving either antiretroviral therapy with an abacavir plus lamivudine regimen or a tenofovir plus lamivudine or emtricitabine regimen (Abstract 1074). In the intention-to-treat analysis, 29% and 45% of subjects achieved SVR with the abacavir and tenofovir regimens, respectively ($P = .02$). The differences between SVR rates for abacavir and tenofovir were most pronounced among patients with high plasma levels of HCV RNA genotypes 1 and 4 and among patients who received daily as opposed to weight-based regimens of ribavirin.

Gonzalez-Garcia and colleagues evaluated the association between SVR and the use of tenofovir versus nontenofovir drugs among patients undergoing HCV treatment (Abstract 1076). In a model controlling for variables that predict SVR, the use of a tenofovir regimen and not a nontenofovir regimen was associated with SVR. As reported previously, zidovudine use, which often coincides with ribavirin dose reduction, was associated with lower rates of SVR. In this analysis, abacavir was not associated with lower rates of SVR.

Moreno and her group examined nRTI backbone as a predictor of SVR. They found that plasma HCV genotype, HCV RNA level, and fibrosis scoring were associated with SVR (Abstract 1075), and the use of abacavir versus tenofovir versus triple-nRTI had no effect on SVR. These seemingly conflicting data do not provide a definitive answer to the question of when to avoid using certain nRTIs, including guanosine analogues such as abacavir.

Opportunistic Infections and Timing of Antiretroviral Therapy

In a plenary presentation, Phillips highlighted that even in the developed world, presentation of HIV-infected patients to care at the time of severe im-

immune compromise concomitant with an opportunistic infection or malignancy remains common (Abstract 8). The optimal time to initiate antiretroviral therapy in such individuals is not known. Although immediate administration of antiretroviral therapy should slow HIV progression, the absence of randomized data creates concerns about toxicity, drug interactions, and more severe immune reconstitution syndromes and has led many clinicians to defer therapy until after resolution of an acute infection.

In ACTG A5164, 282 adults with an acute infection underwent randomization to immediate (within 2 weeks of the acute event) or deferred (4 weeks after randomization) antiretroviral therapy (Abstract 142). Persons with TB were excluded. Events that occurred within 30 days of randomization were not included in the analysis. The study population included 63% of patients with *Pneumocystis jirovecii* pneumonia, 13% with cryptococcal meningitis, and 10% with non-*Pneumocystis* pneumonia. Median entry CD4+ count was 29 cells/ μ L and plasma HIV RNA level was 5 log₁₀ copies/mL. Immediate and deferred antiretroviral therapy started at a median of 12 days and 45 days, respectively. There was no difference between the 2 arms in the primary endpoint, which was defined as an ordered categorical variable of (1) death or AIDS progression, (2) no progression and plasma HIV RNA level above 50 copies/mL, and (3) no progression and plasma HIV RNA level below 50 copies/mL. However, the time to progression to AIDS or death was significantly shorter in the immediate than in the deferred antiretroviral therapy arm ($P = .035$).

Immediate antiretroviral therapy was associated with more rapid time to CD4+ count above 50 cells/ μ L and

virologic suppression but more therapy changes. Immediate antiretroviral therapy was not associated with a greater risk for IRIS, toxicity, worse adherence, or hospitalizations. For patients with the spectrum of infection and illness included in this study, these data strongly support the early institution of antiretroviral therapy to prevent further HIV disease progression.

Immune Reconstitution

The spectrum and frequency of IRIS among children living in Africa has not been well characterized. Smith and colleagues reported findings from a South African cohort of HIV-infected children less than 2 years of age who were starting antiretroviral therapy with a lopinavir/ritonavir-based regimen (Abstract 75). Twenty-five of 148 children were classified as having IRIS events, and median time to first IRIS event was 15 days. Multiple events occurred in 5 children. Twenty of 25 children had BCG-vaccine-injection-site inflammation or adenitis with abscess. There were an additional 7 children with TB and other pneumonias and dermatologic events. Younger age and lower CD4+ cell count were associated with more frequent incidences of IRIS. Rabie reported on IRIS events associated with BCG vaccine in the Children with HIV Early Antiretroviral (CHER) trial, in which children underwent randomization at 6 weeks to 12 weeks of life to either early or deferred antiretroviral therapy, based on CD4+ cell counts or clinical criteria (Abstract 600). All children received BCG vaccination. Incidence of BCG-vaccine adenitis did not differ between the early (6.9%) and the deferred (10.4%) arms. No BCG-vaccine adenitis was observed in an HIV-uninfected contemporary cohort of children, but rates of local BCG-vac-

cine reactions were similar between the 2 groups. There was 1 death attributed to BCG vaccine in the deferred antiretroviral therapy arm. These data demonstrate that BCG-vaccine adenitis is associated with antiretroviral therapy initiation, but that early antiretroviral therapy did not appear to increase risk of BCG-vaccine adenitis.

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A list of all cited abstracts appears on page 69-77.

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Advances in Antiretroviral Therapy

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The 15th Conference on Retroviruses and Opportunistic Infections maintained its place as the premier meeting for presentation of the state of the art of antiretroviral therapy. This year brought together data on new antiretroviral agents in the pipeline, updated our knowledge base of agents approved in the past year (eg, maraviroc, raltegravir, etravirine), delineated approaches to management of treatment-naïve and -experienced patients and the use of drugs for prevention of maternal-to-child transmission, and refined our expanding knowledge of drug resistance. A particular highlight of this year's conference was the progress made in antiretroviral treatment and research in resource-limited settings as reflected in both the number and quality of presentations emanating from the developing world.

Investigational Agents

CCR5 Antagonists

SCH 532706. Pett and colleagues presented a phase I study of the CCR5 antagonist SCH 532706 in HIV-infected men (Abstract 38). The study was an open-label, nonrandomized, single-center study of 12 subjects receiving SCH 532706 60 mg twice daily with ritonavir 100 mg daily for 10 days. The mean changes in plasma HIV RNA level at day 10 and day 15 were $-1.31 \log_{10}$ copies/mL and $-1.62 \log_{10}$ copies/mL, respectively. The drug was generally well tolerated. One serious adverse event, pericarditis, occurred 13 days after dosing was completed and was considered possibly related to the study drug. This event resolved without sequelae. The authors noted that the drug was suitable for once-daily dosing with ritonavir.

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Nucleoside Analogue Reverse Transcriptase Inhibitors

Translocation-deficient reverse transcriptase inhibitors. Existing nucleoside analogue reverse transcriptase inhibitors (nRTIs) lack a 3'OH group and thus terminate the growing DNA chain once incorporated. Marchand and colleagues presented data on a new nRTI, 4'-ethynyl,2-fluorodeoxyadenosine (4'-E-2FdA) (Abstract 726a). The compound has a 3'OH group but appears to act as a chain terminator. The authors presented evidence that once the compound is incorporated into the growing DNA, translocation and resulting incorporation of the subsequent DNA base pair are inhibited. This appears to be a new mechanism within the nRTI class of compounds.

OBP-601 (4'-Ed4T). Weber and colleagues presented data on OBP-601, a new nRTI related to stavudine (Abstract 726b). The in vitro data showed that OBP-601 was active against a broad panel of recombinant viruses. Some nRTI resistance mutations conferred mild to moderate resistance. Viruses containing the Q151M mutation appeared hypersusceptible to the drug, however. The compound exerted synergy with the other antiretroviral agents tested.

3'-Azido-2',3'-dideoxypurines. Sluis-Cremer presented data on 2 related com-

pounds: 3'-azido-2',3'-dideoxyadenosine and -dideoxyguanosine (Abstract 727). The compounds appeared to have minimal cytotoxicity or effect on mitochondria. Both compounds exhibited potent activity in vitro. The inhibitory concentration was not affected when tested against viruses containing the K65R, L74V, M184V, or 3 or more thymidine analogue-associated mutations (TAMs).

Nonnucleoside Reverse Transcriptase Inhibitors

UK-453,061. Mori and colleagues presented data on a new nonnucleoside analogue reverse transcriptase inhibitor (NNRTI), UK-453,061 (Abstract 728). This NNRTI was tested against 62 clinically derived viruses from treatment-naïve patients with transmitted NNRTI resistance including viruses from a broad range of subtypes. The compound retained activity against 61 of 62 isolates, defined as a fold-change of the 50% inhibitory concentration (IC_{50}) of less than 10. The remaining virus contained the triple mutation K101E + V106I/M + Y188F/L. The compound was synergistic with the other tested drugs.

IDX899, RDEA427, and RDEA640. Richman and colleagues compared the in vitro development of resistance to efavirenz and IDX899, a new NNRTI, in a serial passage experiment (Abstract 729). High-level resistance to IDX899 took considerably longer to develop than for efavirenz (26 to 30 passages vs 8, respectively). The efavirenz-resistant viruses typically remained sensitive to IDX899, as did all single or double mutants. Similarly, Raney and colleagues presented data on the investigational NNRTIs RDEA427 and RDEA640, which were found to have minimal cytotoxicity, good activity against NNRTI-resistant virus, and a low potential for induc-

tion of cytochrome P450 3A4 (CYP3A4) activity (Abstract 730).

Protease Inhibitors

Dimerization inhibitors. Dimerization of the 2 protease polypeptide monomers is essential for protease's activity. Koh and colleagues presented evidence that this process can be inhibited with small molecules (Abstract 733). In fact, they found that tipranavir and darunavir acted as dimerization inhibitors at low concentrations, whereas other protease inhibitors (PIs) did not. Protease with an A28S mutation or 4 mutations (V32I, L33F, I54M, I84V) could dimerize even in the presence of these compounds. The authors concluded that these 2 PIs differ substantially from other PIs and that protease dimerization should be investigated further for drug development.

Integrase Inhibitors

Integrase-LEDGF/p75 interaction. Integration of HIV is a multistep process. Christ and colleagues presented data on the interaction of HIV integrase with the host protein LEDGF/p75 (Abstract 735). They developed a high-throughput assay to discover inhibitors of this interaction and found compounds with low micromolar activity. They consider this interaction a viable target for drug development.

Nanoparticles

TMC278. Klooster and colleagues presented data on a depot formulation of TMC278, an investigational NNRTI (Abstract 134). TMC278 was administered to 48 HIV-seronegative volunteers as a nanosuspension that slowly released drug over an extended period. Subcutaneous or intramuscular injections of TMC278 200 mg, 400 mg, or 600 mg or of placebo were studied. The intramuscular injection appeared better tolerated and not appreciably different from placebo. The TMC278 levels were detectable for approximately 12 weeks. The peak plasma level after intramuscular injection of 600 mg occurred at

approximately 3 days and was comparable to that of 25 mg orally once daily. One month after intramuscular injection of 600 mg, the plasma levels were similar to that of the expected trough of 25 mg orally once daily. These results suggest the potential for once-monthly dosing.

Efavirenz/Lopinavir/Ritonavir. Destache and colleagues discussed the in vitro study of ritonavir, lopinavir, and efavirenz nanoparticles (Abstract 743). Nanoparticles are pure drug in particle size of 340 nM. These particles slowly released drug in the in vitro system. The level at day 14 for each drug was greater than 1.0 µg/mL. These results are promising for future studies of infrequent parenteral dosing of antiretroviral therapy.

Clinical Trials of Antiretroviral Therapy in Treatment-naïve Subjects

Atazanavir/Ritonavir Versus Lopinavir/Ritonavir

Molina and colleagues presented data from the CASTLE study, which compared open-label, once-daily atazanavir/ritonavir to lopinavir/ritonavir soft-gel capsules, each given with fixed-dose tenofovir/emtricitabine to 883 antiretroviral therapy-naïve subjects with a plasma HIV RNA level of at least 5000 copies/mL (Abstract 37). The median CD4+ counts in the atazanavir/ritonavir and lopinavir/ritonavir groups were 205 cells/µL and 204 cells/µL, respectively, and the mean plasma HIV RNA levels were 5.01 log₁₀ copies/mL and 4.96 log₁₀ copies/mL, respectively. The median ages were 34 years and 36 years, respectively, and 31% were women.

Seventy-eight percent of subjects who underwent randomization to atazanavir/ritonavir achieved a plasma HIV RNA level below 50 copies/mL at week 48 compared with 76% for the lopinavir/ritonavir arm (difference, 1.7%; 95% confidence interval [CI], -3.8% to 7.1%). This excluded the prespecified noninferiority boundary of -10%, and atazanavir/ritonavir was declared noninferior to lopinavir/ritonavir. No

statistically significant difference occurred between arms for subjects with baseline plasma HIV RNA levels above 100,000 copies/mL (74% vs 72%). The efficacy of lopinavir/ritonavir seemed lower in subjects with lower CD4+ cell counts, however. The authors suggested that this result stemmed from increased discontinuations because of side effects from lopinavir/ritonavir among those with the lowest CD4+ counts. The authors also noted that atazanavir/ritonavir resulted in more favorable lipid profiles than lopinavir/ritonavir did, as judged by fewer subjects initiating lipid-lowering therapy on the former (2% vs 8%, respectively) and a lower proportion of subjects with a total cholesterol to high-density lipoprotein ratio greater than 5 (12% vs 20%, respectively). Overall discontinuations as a result of side effects were low in both arms (2% vs 3%, respectively).

Fixed-dose Abacavir/Lamivudine Versus Tenofovir/Emtricitabine

Only limited data directly compare the 2 once-daily fixed-dose nRTI combinations of abacavir/lamivudine and tenofovir/emtricitabine. Smith and colleagues presented data comparing fixed-dose combinations of these nRTIs, each given with once-daily lopinavir/ritonavir soft-gel capsules (Abstract 774). This was a randomized, double-blind, placebo-matched trial. No HLA-B*5701 testing was performed. The primary outcome measured was the proportion of subjects with plasma HIV RNA levels below 50 copies/mL at week 48. Missing subjects and subjects switching antiretroviral therapy counted as failures. The trial enrolled 688 subjects (median age, 38 years; 18% female). In the abacavir/lamivudine and tenofovir/emtricitabine groups, the median baseline CD4+ count was 214 cells/µL and 193 cells/µL, respectively, and the median plasma HIV RNA level was 4.90 copies/mL and 4.84 copies/mL, respectively. At week 48, 68% and 67% of subjects had plasma HIV RNA levels below 50 copies/mL (difference, -6.6% to 7.4%). This excluded the prespecified noninferiority boundary of -12%, and abacavir/lamivudine was

declared noninferior to tenofovir/emtricitabine. Fourteen subjects receiving abacavir/lamivudine discontinued early because of suspected abacavir hypersensitivity compared with 3 in the tenofovir/emtricitabine group. Three subjects discontinued tenofovir/emtricitabine because of proximal renal tubular dysfunction. Subsequent to this presentation, a separate double-blind, placebo-controlled comparison of these 2 fixed-dose combinations was partially unblinded by the study's Data and Safety Monitoring Board because of a higher rate of virologic failure among subjects randomized to abacavir/lamivudine whose prerandomization plasma HIV RNA level was greater than 100,000 copies/mL (http://www3.niaid.nih.gov/news/news_releases/2008/actg5202bulletin.htm).

Once-daily Versus Twice-daily Dosing of Lopinavir/Ritonavir

Gathe and colleagues presented data from an open-label, randomized controlled trial of once-daily versus twice-daily dosing of lopinavir/ritonavir given with fixed-dose tenofovir/emtricitabine (Abstract 775). They randomized 664 subjects with a mean plasma HIV RNA level of 5 log₁₀ copies/mL and CD4+ count of 216 cells/μL in the 2 arms. Plasma HIV RNA level was below 50 copies/mL 48 weeks after randomization in 77% and 75% of the once- and twice-daily groups, respectively (difference, 3%; 95% confidence interval [CI], -4.8% to 8.1%). They excluded the noninferiority boundary of -12% and declared once-daily dosing of lopinavir/ritonavir noninferior to twice-daily dosing. The adverse event rate and discontinuations because of adverse events were similar between groups. Among subjects with virologic failure, no PI resistance-associated mutations were found.

Maraviroc

Heera and colleagues presented a detailed analysis of subjects with virologic failure during the Maraviroc in Treatment-naïve Patients (MERIT) trial, which compared maraviroc to efavirenz, each given with fixed-dose zidovudine/lamivudine (Abstract 40LB).

This study enrolled 724 subjects with CCR5-using virus at a screening. At the time of randomization, 25 of the 724 subjects (3.5%) were found to have dual-tropic or mixed-tropic populations. These 25 subjects were less likely to have plasma HIV RNA levels below 50 copies/mL at week 48: 6 of 11 (56%) of those randomized to efavirenz had less than 50 copies/mL at week 48, as did 1 of 14 (7%) of those who underwent randomization to maraviroc. There were 43 subjects who discontinued maraviroc because of lack of efficacy. At the time of failure, 19 of 43 had dual-tropic or mixed HIV populations. Twenty-nine of 43 patients had the M184V mutation, and 7 had other nRTI resistance mutations in addition to M184V. These mutations were more common among those whose treatment failed and who had dual-tropic or mixed-tropic HIV populations (eg, 19/19 subjects with virologic failure and dual-tropic or mixed HIV populations had M184V). Among the subjects for whom maraviroc failed and who had CCR5-using HIV, 2 had resistance to maraviroc.

Once-daily Emtricitabine, Didanosine, and Efavirenz in HIV-infected Children and Adolescents

Rathore and colleagues enrolled 37 children in this single-arm, open-label trial. After 144 weeks of follow-up, 24 (65%) had plasma HIV RNA levels below 50 copies/mL (Abstract 581). The CD4+ count increased a median of 308 cells/μL, and the CD4+ percentage increased by 16%. The treatment appeared generally safe and well tolerated.

Clinical Trials in Treatment-experienced Subjects

Table 1 lists the results of selected clinical trials in treatment-experienced subjects. The 48-week updates are presented here for clinical trials involving raltegravir, maraviroc, and etravirine. The 16-week or 24-week results for each of these trials have been presented previously.

Vicriviroc

Zingman and colleagues presented data on the virologic efficacy of vicriviroc, an investigational CCR5 antagonist (Abstract 39LB). This study evaluated higher doses of vicriviroc (20 mg and 30 mg daily) than had been studied in a prior trial of vicriviroc, AIDS Clinical Trials Group (ACTG) 5211 (5 mg, 10 mg, and 15 mg). This study enrolled 116 subjects (78% men) with 3-class antiretroviral experience and plasma HIV RNA levels greater than 1000 copies/mL. Subjects were required to have only CCR5-using virus. Vicriviroc (20 mg or 30 mg) or placebo was given with an optimized background regimen that was required to have a ritonavir-boosted PI. Of 39 subjects who underwent randomization to the higher dose of vicriviroc, 22 (56%) had plasma HIV RNA levels below 50 copies/mL at week 48; the same was true for 21/40 (52%) of those who underwent randomization to 20 mg and for only 5/35 (14%) of those who underwent randomization to placebo. Among subjects receiving vicriviroc, those achieving a minimum concentration greater than 100 ng/mL were more likely to have a plasma HIV RNA level below 50 copies/mL. This level was achieved more commonly among subjects receiving the 30-mg dose of vicriviroc. No safety concerns arose from this study. The 30-mg dose was chosen for subsequent phase III studies of vicriviroc.

Apricitabine

Cahn and colleagues presented a phase IIB study of apricitabine in treatment-experienced subjects with the M184V mutation whose antiretroviral regimen was failing (Abstract 793). Apricitabine is a cytidine analogue that retains activity against HIV with resistance to lamivudine and emtricitabine. This study randomized 50 subjects to either continue lamivudine treatment or change lamivudine to apricitabine 600 mg or 800 mg twice daily. The primary endpoint was the change in plasma HIV RNA level at day 21, as previously reported.¹ Subjects optimized their antiretroviral regimen at day 21 according

to baseline genotype while continuing lamivudine or apricitabine. At week 24, 72% and 73% of subjects in the 2 apricitabine arms had plasma HIV RNA levels below 50 copies/mL, compared with 58% of the lamivudine subjects. This study was not powered for this endpoint, and the results did not reach statistical significance.

Therapeutic Drug Monitoring with Subsequent Protease Inhibitor Dose Escalation

Demeter and colleagues presented data from ACTG 5146 of a randomized, controlled trial of the effect of therapeutic drug monitoring and PI dose escalation on virologic efficacy (Abstract 35). Eligible subjects had experienced failure of at least 1 prior PI-based regimen and had a plasma HIV RNA level of 1000 copies/mL or higher. Subjects initiated a new PI-based regimen chosen according to results of resistance testing. After 2 weeks, subjects returned for testing of plasma trough PI concentration. Results of the resistance test before starting the new regimen and the trough concentration were used to calculate the value of the normalized inhibitory quotient (nIQ). Lower trough concentrations and increasing resistance lead to a lower nIQ value. An nIQ value below 1 was hypothesized to increase risk of virologic failure.

Four weeks after initiating the new regimen, 183 subjects with an nIQ value below 1 underwent randomization to either maintain the standard PI dose (standard-of-care arm) or increase the PI dose (therapeutic-drug-monitoring arm). The dose escalation was successful in raising the trough concentration (and thus the nIQ value) for all PIs except for fos-amprenavir, for which dose escalation did not change the trough concentration. The change in plasma HIV RNA level was not statistically significantly different between the 2 arms. On subgroup analysis, however, subjects with an nIQ value of 0.7 to 1.0 (ie, less severe resistance and/or higher plasma trough concentrations) benefited from therapeutic drug monitoring (TDM) with resulting dose escalation. Black and Hispanic subjects also

appeared to benefit from TDM with a greater decrease in plasma HIV RNA level with PI dose escalation. The reason for this association with race and ethnicity is unclear.

Change from Enfuvirtide to Raltegravir

Harris and colleagues presented observational data on patients with sustained virologic suppression (plasma HIV level RNA below 50 copies/mL) and treatment-limiting, injection-site reactions on an enfuvirtide-containing regimen (Abstract 799). All such subjects at their clinical site were offered to switch from enfuvirtide to raltegravir. Subjects were highly treatment-experienced. Thirty-six subjects made the switch and were observed with routine virologic monitoring for a median of 7 months. The plasma HIV RNA levels of 34 of 35 subjects were still below 50 copies/mL at their most recent assessment. The remaining subject had a level of 60 copies/mL. No subjects discontinued raltegravir treatment. The authors concluded that this drug substitution was safe and effective in subjects receiving enfuvirtide.

Antiretroviral Treatment Strategies

Consequences of Treatment Interruption

This year's conference offered new insights into the consequences of strategic treatment interruptions. El-Sadr presented data on behalf of the Strategies for Management of Antiretroviral Therapy (SMART) trial investigators on the risk of opportunistic disease or death following treatment reinitiation after treatment interruption (Abstract 36). The SMART trial randomized 5472 participants with CD4+ counts above 350 cells/ μ L to 1 of 2 strategies: virologic suppression, which entailed continuous use of antiretroviral therapy to maintain the lowest possible plasma HIV RNA level; or drug conservation, which consisted of deferred antiretroviral therapy until CD4+ count was less than 250 cells/ μ L, followed by episodic

potent antiretroviral therapy to raise CD4+ counts above 350 cells/ μ L, followed by further treatment interruption.

Enrollment in the trial was stopped on January 11, 2006, when the study group found the hazard ratio (HR) for opportunistic disease or death for the drug conservation group compared with the virologic suppression group to be 2.52 (95% CI, 1.82-3.51), representing a statistically significant increased risk in the drug conservation group. At that point, the protocol was discontinued, and all study participants who met criteria for antiretroviral initiation were encouraged to start treatment. The investigators continued to observe all participants through July 11, 2007.

At the time of study modification, notable characteristics of the drug conservation compared with the virologic suppression groups, respectively, were as follows: current use of antiretroviral therapy, 36% versus 94%; plasma HIV RNA level less than 400 copies/mL, 35% versus 82%; and mean CD4+ count, 425 versus 625 cells/ μ L. By the study's close, 84% of participants in the drug conservation group and 95% of participants in the virologic suppression group were receiving antiretroviral therapy. The HR for opportunistic disease or death after study modification was 1.37 (95% CI, 0.96-1.94), which had a *P* value for difference from the premodification HR of .02. Similar trends were observed for death, opportunistic disease alone, or major cardiovascular, renal, or hepatic disease. In subgroup analyses, participants in the drug conservation group who were on antiretroviral therapy for greater than 85% of the time after study modification had an HR for opportunistic disease or death of 0.9, compared with the virologic suppression group. This normalization of the HR did not occur among participants in the drug conservation group on antiretroviral therapy between 75% and 85% of the time, or less than 75% of the time after study modification. The investigators also noted that the proportion of participants with plasma HIV RNA levels less than 400 copies/mL in July 2007 still differed by study group: 73% for the drug conservation

Table 1. Selected Clinical Trials of Antiretroviral Drugs in Treatment-experienced Patients

| Study Name Abstract No. Description | Regimen(s) (No. Patients) | Population | Baseline CD4+ count (cells/ μ L) | Baseline HIV RNA (log ₁₀ copies/mL) |
|--|--|---|---|---|
| BENCHMRK-1 Abstract 788 Phase III, randomized, placebo-controlled trial of raltegravir | Raltegravir 400 mg bid (n = 232) or placebo with OBR (n = 118) | Genotypic or phenotypic resistance to at least 1 drug from all 3 current classes, plasma HIV-1 RNA > 1000 copies/mL | 153–156 (mean) | 4.5–4.6 (mean) |
| BENCHMRK-2 Abstract 789 Phase III, randomized, placebo-controlled trial of raltegravir | Raltegravir 400 mg bid (n = 230) or placebo with OBR (n = 119) | Genotypic or phenotypic resistance to at least 1 drug from all 3 current classes, plasma HIV-1 RNA > 1000 copies/mL | 146–163 (mean) | 4.5–4.6 (mean) |
| Combined analysis of MOTIVATE 1 and MOTIVATE 2 Abstract 792 Phase IIb/III randomized, double-blind trials of maraviroc, an oral CCR5 inhibitor | Maraviroc 150 mg qd (n = 414) + OBR or maraviroc 150 mg bid + OBR (n = 426) vs OBR (n = 209) | 3-class experience, plasma HIV-1 RNA > 5000 copies/mL, CCR5-using virus | 150–182 (median) | 4.8–4.9 (mean) |
| DUET-1 Abstract 790 Phase III randomized, placebo-controlled trial of etravirine | Etravirine 200 mg bid, darunavir/ritonavir + choice of nRTIs +/- enfuvirtide vs placebo, darunavir/ritonavir + choice of nRTIs +/- enfuvirtide (n = 612 total) | Documented NNRTI resistance, \geq 3 primary PI resistance-associated mutations | 106 (median) | 4.9 (median) |
| DUET-2 Abstract 791 Phase III randomized, placebo-controlled trial of etravirine | Etravirine 200 mg bid, darunavir/ritonavir + choice of nRTIs +/- enfuvirtide vs placebo, darunavir/ritonavir + choice of nRTIs +/- enfuvirtide (n = 591 total) | Documented NNRTI resistance, \geq 3 primary PI resistance-associated mutations | 105 (median) | 4.8 (median) |
| VICTOR-E1 Abstract 39LB Phase II study of vicriviroc (investigational drug) | Vicriviroc 20 mg, vicriviroc 30 mg, or placebo with OBR containing ritonavir-boosted PI + nRTI | HIV-1 RNA > 1000 copies/mL, 3-class experience, CCR5-using virus | 202–226 (median) | 4.5–4.5 (mean) |

Abbreviations: bid, twice daily; OBR, optimized background regimen; qd, once daily; nRTI, nucleoside analogue reverse transcriptase inhibitor; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor.

group versus 84% for the virologic suppression group. Mean CD4+ counts by group also differed: 507 cells/ μ L, which was lower than baseline, and 648 cells/ μ L for the drug conservation and virologic suppression arms, respectively. The authors speculated that these differences may have led to the continued risk for opportunistic disease or death 1.5 years after study modification.

Mehandru and colleagues (Abstract 121) examined a different aspect of

treatment interruption by concentrating on the effects of treatment interruption on the CD4+ T-cell population in the gastrointestinal tract. They used a trial in which 10 patients received 3 monoclonal antibodies followed by treatment interruption, and received consent from 7 of the participants to perform rectosigmoid biopsies at 3 time points: baseline (3 to 0 days before treatment interruption), 5 to 7 weeks post-treatment interruption,

and 12 to 14 weeks post-treatment interruption. Of the 7 participants, 2 did not have virologic rebound after treatment interruption. Of the 5 who did, the decrease in CD4+ cell percentage in the gastrointestinal tract was more severe than the decrease in the peripheral blood. The CD4+ lymphocytes expressing the CCR5 coreceptor were preferentially targeted. The authors also found higher levels of immune activation, as measured by the percent-

| Follow-up Time (No. Weeks) | HIV-1 RNA Response | Comments |
|----------------------------|--------------------------------|---|
| 48 | 65% vs 31% < 50 copies/mL | Generally well tolerated |
| 48 | 60% vs 30% < 50 copies/mL | |
| 48 | 43%, 46% vs 17% < 50 copies/mL | Generally well tolerated |
| 48 | 60% vs 39% < 50 copies/mL | Generally well tolerated, rash was more common with etravirine (22% vs 11%) but rarely led to discontinuation |
| 48 | 61% vs 41% < 50 copies/mL | Generally well tolerated, rash was more common with etravirine (17% vs 11%) but rarely led to discontinuation |
| 48 | 52%, 56% vs 14% < 50 copies/mL | Trough concentration of 100 ng/mL was associated with response; this was achieved more reliably in 30-mg dose |

age of activated memory CD8+ T lymphocytes, in the gastrointestinal tract than in peripheral blood.

Immune-based Treatment Strategies

Schooley presented data from the ACTG 5197 study, a phase II, placebo-controlled trial examining the effects of treatment with an adenovirus 5 HIV Gag vaccine (Merck & Co, Inc) in HIV-infected participants before a 16-week

analytic treatment interruption (Abstract 87). The vaccine was given at weeks 0, 4, and 26. Twelve weeks after the last vaccine dose, participants initiated a 16-week treatment interruption, and they were observed for a total of 250 weeks. The inclusion criteria for participants were the following: two-thirds had a nadir CD4+ count above 300 cells/ μ L, and one-third had a nadir CD4+ count between 200 cells/ μ L and 300 cells/ μ L; all had plasma HIV RNA

levels below 50 copies/mL for at least 24 months, CD4+ cell counts greater than 500 cells/ μ L, and adenovirus 5 titers below 200 units. The investigators chose 2 predetermined endpoints: the time average of the area under the curve (AUC) for the plasma HIV RNA level from week 0 to 16 of treatment interruption and the mean plasma HIV RNA level at weeks 12 and 16 of treatment interruption (defined as the set point). The investigators specified that, to reject the null hypothesis, both endpoints needed to have *P* values less than .025 or 1 endpoint with a value less than .0125 and the other with less than .05.

The plasma HIV RNA level time-averaged AUC was 0.26 log₁₀ copies/mL less in the vaccine group than the placebo group (*P* = .024). The set point determination was also 0.27 log₁₀ copies/mL less in the vaccine group than in the placebo group (*P* = .059), but the 2 endpoints, taken together, did not reach statistical significance according to the prespecified cutoff level. The vaccine did stimulate CD4+ and CD8+ Gag-specific interferon gamma (IFN- γ)-producing cells but not Nef- or Pol-specific cells, and the number of CD4+ Gag-specific IFN- γ -producing cells predicted viral control.

Several groups presented data on the use of interleukin 2 (IL-2) as adjuvant therapy for HIV-infected individuals. Molina and colleagues presented 3-year, extended-follow-up data from the Interstart Agence Nationale de Recherche sur le SIDA (ANRS) 119 trial, which randomized 130 antiretroviral therapy-naïve, asymptomatic patients with CD4+ counts between 300 cells/ μ L and 500 cells/ μ L to IL-2 or no treatment (Abstract 702). In the treatment group, IL-2 was administered at a dose of 4.5 million international units subcutaneously twice daily for 5 days at weeks 0, 8, 16, and 24. The primary endpoint was a confirmed CD4+ count of less than 300 cells/ μ L, initiation of potent antiretroviral therapy, occurrence of an AIDS-defining illness, or death.

At 96 weeks, the rates of progression to the primary endpoint were 35% for the IL-2 arm and 59% for the placebo arm (*P* = .008). The researchers found that CD4+ count (HR, 0.59 per 50

cells/ μL ; $P = .01$) and plasma HIV RNA level (HR, 3.7; $P = .0006$) at baseline were both predictors of progression to the primary endpoint. The stratum of patients with baseline plasma HIV levels below 4.5 \log_{10} copies/mL had the most benefit from IL-2 therapy, with the probability of nonprogression at week 150 being 0.65 (95% CI, 0.48-0.78) in the IL-2 arm and 0.10 (95% CI, 0.02-0.27) in the control arm ($P < .0001$).

Two negative IL-2 trials provided a contrast to that presented above. The final results of the ANRS 123 ETOILE randomized trial, which added IL-2 to an optimized background treatment regimen in patients with virologic failure and no treatment options, found no statistically significant increase in CD4+ cell counts at week 52 (Abstract 703). The authors did find that the addition of enfuvirtide to the optimized regimen resulted in a statistically significant increase in CD4+ cell counts at week 52. Porter and colleagues evaluated whether IL-2 treatment can help maintain CD4+ cell counts in treatment-experienced patients undergoing a 6-month treatment interruption (Abstract 706). Forty-one participants, all of whom had a history of at least 3 prior cycles of IL-2 therapy and a CD4+ count above 500 cells/ μL , underwent randomization to treatment interruption with IL-2 every 8 weeks for those with CD4+ counts below 500 cells/ μL or continuous treatment. At the end of 6 months, all participants were given the option of interrupting treatment for an additional 6 months. Investigators determined that CD4+ counts at 6 months were lower in the treatment-interruption arm (866 cells/ μL ; 95% CI, 445-1698) than in the control arm (1246 cells/ μL ; 95% CI, 517-2253; $P = .001$). A 6-month treatment interruption had minimal impact on metabolic indices (total cholesterol levels, apolipoprotein AI levels, and hemoglobin A_{1c} concentration).

Antiretroviral Therapy in Resource-limited Settings

The 15th Conference on Retroviruses and Opportunistic Infections demon-

strated the impressive progress made over the past few years in antiretroviral treatment programs in resource-limited settings (RLS). This year's presentations included some of the first data on response to second-line therapy in RLS, important findings on reductions in loss to follow-up and mortality, and novel information on antiretroviral resistance in RLS.

Maartens led off the discussion on Sunday with a plenary session titled "ART in Africa: Beyond the Roll-out." He highlighted the fact that new infections in Africa continue to outpace the availability of antiretroviral treatment. Estimates from the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) are that 2,800,000 new HIV infections occurred in Africa in 2006 and 1,340,000 people were living with HIV on antiretroviral therapy. The same organizations note a growing funding gap between needs and availability of funding for antiretroviral treatment: a \$2.8 billion gap in 2005 and \$8.1 billion in 2007. High early mortality rates upon initiation of antiretroviral therapy were presented at last year's conference, but Maartens also mentioned recent data that demonstrate high death rates among patients awaiting antiretroviral therapy in South Africa, with a 6-month survival of 50% for those with CD4+ counts less than 200/ μL .² Adherence to antiretroviral therapy may be higher in Africa than in North America, according to a recent meta-analysis,³ and missed doses are frequently the result of system failures such as lack of medications in the pharmacy or inability to pay for medications.⁴

According to a WHO 2006 survey, first-line antiretroviral therapy in RLS is predominately with nevirapine, stavudine or zidovudine, and lamivudine. Antiretroviral substitutions for stavudine outpace all other medications, however, and 20.8% of patients receiving stavudine have switched therapy by 36 months.⁵ Finally, Maartens highlighted the need for further studies on the parameters that should determine a switch to second-line therapy and on the problem of the continual "brain drain" of health professionals

from Africa to the United Kingdom and the United States.

A symposium on individualizing patient management featured a talk by Mermin on "Optimizing Patient Management in Resource-limited Settings" (Abstract 155). Mermin reviewed insights from the literature over the past several years on structural issues affecting HIV care in RLS, including the decline in health care infrastructure in sub-Saharan Africa over the past 2 decades. In 2004, the United States had 1 physician for every 0.6 people living with HIV, whereas Malawi had 1 per 7435.⁶ Programs such as the Ugandan home-based care program, which allow for adherence counseling and treatment by nonphysician health care professionals, serve as safe and sometimes superior solutions to the physician shortage. Regardless, at the current pace of antiretroviral-drug scale-up, by 2017, only 18% of people needing antiretroviral therapy in Africa will be receiving it.⁷

Mermin outlined the need for a standard HIV care and prevention package in RLS. This would include interventions that have been associated with (1) significant decreases in morbidity and mortality for people living with HIV: cotrimoxazole prophylaxis, bed nets, safe water vessels, tuberculosis treatment and prevention, multivitamins, and herpes simplex virus (HSV)-2 suppression, and (2) decreases in HIV transmission: partner and family voluntary counseling and testing, and partner counseling, condom use, and circumcision.

Data from Large Clinical Cohorts

Selected studies on outcomes of antiretroviral treatment in RLS are summarized in Table 2, but several other investigations merit mention here. Researchers from the Antiretroviral Therapy in Lower Income Countries (ART-LINC) section of the International Epidemiologic Databases to Evaluate AIDS (IeDEA) evaluated changes in the demographic and clinical profiles of patients starting antiretroviral therapy in RLS over time (Abstract 820). Patients at least 16 years old who initiated potent antiretroviral therapy between 1996 and 2006 were included from 20 sites in sub-Saharan

Africa, Asia, and Latin America, for a total sample size of 37,841 people. The researchers found that CD4+ counts at antiretroviral initiation were higher for women than men (median difference, 22 cells/ μ L; 95% CI, 17-26) but showed no statistically significant increase over time, with CD4+ counts at initiation of antiretroviral therapy remaining consistently below 200 cells/ μ L.

Barnighausen and colleagues (Abstract 128) presented data on mortality from the Africa Centre catchment area of the Hlabisa subdistrict of Kwa-Zulu Natal Province, where antiretroviral therapy roll-out began in 2004 and the estimated HIV prevalence is 21%. More than 517,856 person-years of observation were documented, and the researchers investigated the cause in 7930 deaths. The authors noted a decline in all-cause and AIDS-related mortality among 25- to 49-year-olds starting in 2004. The all-cause mortality rate per 1000 person-years of observation was 28.9 in women and 37.3 in men from 2003 to 2004, and 22.7 in women and 29.8 in men between 2005 and 2006. This represents an encouraging trend that merits further investigation, particularly as antiretroviral uptake was reported to range from 8% to 16% within the region.

Outcomes in Women and Infants After Receiving Prophylaxis Against Mother-to-Child Transmission

Weidle presented 24-week data from the Nonnucleoside Reverse Transcriptase Inhibitor Response Study Team, a multicenter cohort of women in Zambia, Kenya, and Thailand enrolled from June, 2005, to January, 2007 (Abstract 48). The cohort included 878 women who were at least 18 years old, antiretroviral therapy-naïve, and ready to initiate NNRTI-based treatment by national guidelines; they were stratified by self-reported exposure to single-dose nevirapine. Participants were matched by CD4+ cell count and WHO clinical stage and were started on lamivudine, stavudine or zidovudine, and nevirapine. Efavirenz was used only for women receiving concomitant tuberculosis treatment. The primary analy-

sis defined success as remaining on an NNRTI and having a plasma HIV RNA level below 400 copies/mL. Failure was defined as having a plasma HIV RNA level of at least 400 copies/mL, death, discontinuation of antiretroviral therapy, withdrawal from the study, loss to follow-up, or change to a non-NNRTI-based regimen for any reason.

The results of this analysis at 24 weeks showed that, when compared with the referent group that was not exposed to single-dose nevirapine, those exposed from 1 month to 6 months postdelivery had an adjusted odds ratio (aOR) for failure of 1.9 (95% CI, 1.1-3.1), and those exposed from 7 months to 12 months postdelivery had an aOR of 1.6 (95% CI, 0.9-3.0). Adjusted odds of failure for the group of women initiating therapy more than 12 months after exposure were the same as those in the unexposed group. Similar findings were seen in an on-treatment analysis, and the authors' recommendation is that, for women likely to qualify for antiretroviral therapy within 1 year of delivery, prevention strategies other than single-dose nevirapine be considered.

A similar study was conducted to examine the response to treatment of HIV-infected children in Uganda (Abstract 583). HIV-infected children between 6 months and 12 years of age participating in perinatal trials in a hospital in Uganda who were eligible for antiretroviral therapy were enrolled between October, 2004, and May, 2006, and were observed for at least 48 weeks. Forty-four nevirapine-exposed children and 49 nonexposed children were enrolled. The nonexposed children were significantly older (mean age, 7.8 years) than the exposed children (mean age, 1.7 years; $P < .001$) and had a lower CD4+ cell percentage (8.5% compared with 14%; $P < .001$). They were otherwise similar in sex distribution, height, and weight for age, and WHO stage. Despite these differences, nevirapine-based regimens led to significant increases in CD4+ cell percentages and decreases in plasma HIV RNA levels at 48 weeks in both groups, and there was no statistically significant difference in achievement of

viral suppression (defined as HIV RNA level < 400 copies/mL) in nevirapine-exposed and -unexposed children.

Palombi and colleagues (Abstract 668) examined the effects of treatment interruption after mother-to-child-transmission (MTCT) prophylaxis with potent antiretroviral therapy during pregnancy within the Drug Resource Enhancement and Management (DREAM) Program in Mozambique. All 220 women had received zidovudine, lamivudine, and nevirapine for at least 1 month before and 6 months after delivery. The authors found that disease parameters at 12 months after treatment interruption did not differ significantly from baseline laboratory values. The CD4+ count was 496 cells/ μ L at baseline and 536 cells/ μ L at 12 months post-treatment interruption. Similar results were seen for median plasma HIV RNA level and concentrations of hemoglobin and alanine aminotransferase, supporting the safety of discontinuing potent antiretroviral therapy after delivery in women who do not meet criteria for treatment.

Selected Pediatric Clinical Trials and Outcome Studies

Prendergast and colleagues (Abstract 77LB) presented a randomized, controlled trial conducted in Durban, South Africa, of treatment strategies in HIV-infected infants. Sixty-three infants whose HIV was diagnosed by HIV polymerase chain reaction on days 1 or 28 of life underwent randomization to 1 of 3 arms: arm A, deferred therapy until CD4+ cell percentage was below 20%; arm B, immediate, continuous antiretroviral therapy from birth to 1 year; and arm C, immediate therapy with structured treatment interruptions when plasma HIV RNA level was below 50 copies/mL, with resumption when levels passed 5000 copies/mL for the first year of life, followed by treatment cessation.

Results in arm C were discouraging. Only 8 of 21 infants completed the entire structured treatment interruption protocol, and they required significantly more regimen switches for virologic failure (11 vs 2 each in arms A and B by

Table 2. Selected Studies on Antiretroviral Treatment Outcomes from Resource-limited Settings

| Abstract No. Study Description | Treatment Program; Location; Duration of follow up | Baseline Treatment Regimen(s) (No. Patients) | Baseline Age; Sex; Clinical Stage; Treatment Experience |
|--|---|--|--|
| Abstract 126. Long-term CD4+ response to potent antiretroviral therapy among treatment-naive patients in several low-income countries | ART-LINC Collaboration; 16 countries in Africa, Latin America, Asia; 5 y (most, 2004–current) | 2 nRTIs + 1 NNRTI, 92%; 2 nRTIs + 1 PI, 6% (n = 19,967) | Median age, 35 y; 60% female; 57% CDC Stage C or WHO Stage III/IV; antiretroviral therapy-naive |
| Abstract 127. Evaluation of clinical and immunologic outcomes from the National Antiretroviral Therapy Program in Rwanda, 2004 to 2005 | Rwandan National Treatment Program; Numerous sites throughout Rwanda; 1 y (2004–2005) | <i>Adults:</i> Nevirapine/lamivudine/stavudine or zidovudine, 78%; efavirenz/lamivudine/stavudine or zidovudine, 22% (n = 3194) | Median age, 37 y; 65% female; clinical stage, N.A.; antiretroviral therapy-naive |
| | | <i>Children:</i> Nevirapine/lamivudine/stavudine or zidovudine, 74%; efavirenz/lamivudine/stavudine or zidovudine, 26% (n = 288) | Median age, 7 y (71% 6–14y); 50% female; clinical stage, N.A.; antiretroviral therapy-naive |
| Abstract 816. Initial treatment outcomes from a rural-based antiretroviral therapy scale-up program in East Africa: the UARTO cohort | Uganda AIDS Rural Treatment Outcomes (UARTO); Mbarara, Uganda; 18 mo | nRTI + NNRTI (n = 816) | Median age, 35 y; 71% female; clinical stage, n.a.; antiretroviral therapy-naive |
| Abstract 822. 2-Year virologic outcomes of an alternative AIDS care model: evaluation of a peer health worker and nurse-staffed community-based program in Uganda | Reach Out Mbuya Parish HIV/AIDS Initiative; Kampala, Uganda; Oct 2003–Jan 2007 | <i>Active on Therapy:</i> Efavirenz/lamivudine/zidovudine, 41%; nevirapine/lamivudine/zidovudine, 28%; efavirenz/lamivudine/stavudine, 2%; nevirapine/lamivudine/stavudine, 30% (n = 258) | Median age range 25–44 y, 79%; 68% female, 71% WHO clinical stage III/IV; 81% antiretroviral therapy-naive |
| | | <i>No Longer on Therapy:</i> Efavirenz/lamivudine/zidovudine, 36%; nevirapine/lamivudine/zidovudine, 17%; efavirenz/lamivudine/stavudine, 10%; nevirapine/lamivudine/stavudine, 36% (n = 102) | Median age range 25–44 y, 77%; 62% female; 77% WHO clinical stage III/IV; 89% antiretroviral therapy-naive |
| Abstract 824. Predictors of clinical and immunologic outcomes among HIV-infected subjects on antiretroviral therapy in Tanzania | PEPFAR-funded HIV care program; Tanzania; 1 y (enrolled Nov 2004–Apr 2007) | Nevirapine/lamivudine/stavudine, 61%; efavirenz/lamivudine/stavudine, 14%; nevirapine/lamivudine/zidovudine, 10%; efavirenz/lamivudine/zidovudine, 4% (n = 6893) | Median age, 37 y; 71% women; clinical stage, N.A.; antiretroviral therapy-naive |
| Abstract 835. Probability and predictors of survival, drop-out, or switch to a WHO standard 2nd-line antiretroviral therapy regimen in resource-limited settings with viral load monitoring availability: the DREAM program | DREAM program; Mozambique, Malawi, Guinea; 4545 person-years (2002–2007) | Nevirapine/lamivudine/stavudine, 65%; nevirapine/lamivudine/zidovudine, 31% (n = 3749) | Median age, 24 y; 62% female; 37% WHO clinical stage III/IV; antiretroviral therapy-naive |

Abbreviations: ART-LINC indicates Antiretroviral Therapy in Lower Income Countries; nRTI, nucleoside analogue reverse transcriptase inhibitor; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor; y, year(s); CDC, US Centers for Disease Control and Prevention; WHO, World Health Organization; N.A., not available; mo, month(s); min, minute(s); Hb, hemoglobin; BMI, body mass index; wk, week(s)

| Baseline CD4+ Count (cells/ μ L); HIV-1 RNA/mL (\log_{10} copies/mL) | CD4+ Response (cells/ μ L) | Plasma HIV-1 RNA Response (copies/mL) | Mortality | Comments |
|---|---|---|---|---|
| 114 (median) (21% missing baseline); N.A. | Median at 1 y, +149; 5 y, +281 | N.A. | N.A. | CD4+ count increases among patients on antiretroviral therapy are sustained up to 5 y; baseline CD4+ count was the strongest predictor of CD4+ count trajectory |
| 141 (median); N.A. | Median at 6 mo, +98; 12 mo, +119 | N.A. | 6 mo, 3.6%; 12 mo, 4.6% | Lower baseline CD4+ count and CD4+ response in men; size of treatment site was inversely associated with retention in care and change in CD4+ count |
| N.A. N.A. | N.A. | N.A. | 6 mo, 2.4%; 12 mo, 2.6% | |
| 124 (median); 5.2 | Median at 6 mo, +99; 12 mo, +125; 18 mo, +182 | < 400 at 6 mo, 89%, at 12 mo, 83%, at 18 mo, 89% | 12 mo, 5.2% | Mortality was 15.1 times higher in the first 4 mo than the next 8 mo; relative hazard of death, 2.3 for every extra 30 min travel to clinic |
| 107 (median); N.A. | Median at average follow-up of 25 mo, +197 | < 400 at average follow-up of 25 mo, 86% | 6 mo, 13%; 12 mo, 16%; 24mo, 18% | Virologic failure was predicted by age < 25, prior antiretroviral therapy, and lack of CD4+ response; risk of not sustaining therapy and mortality higher in those with baseline CD4+ count < 100, WHO stage IV, and baseline stavudine/lamivudine/ efavirenz; high early mortality in first 6 mo |
| 81 (median); N.A. | N.A. | N.A. | | |
| 133 (median); N.A. | Median at 12 mo, +133 | N.A. | 12 mo, 12.1% | Women were less likely to die or be lost to follow-up; baseline CD4+ count < 100 and baseline Hb < 10 g/dL were associated with mortality |
| 206 (median); 4.6 (median) | N.A. | N.A. | 8.6 deaths/100 person-years (2.1 lost to follow-up/100 person-years) | Predictors of time to death: BMI, Hb, prescription pick-ups > 95% and age < 26 y (all inversely correlated); predictors of time to drop out of care: BMI, baseline CD4+ count, prescription pick-ups > 95%, attended visits > 95%; no significant predictors of time to switch to 2nd-line regimens |

(Continued on next page)

Table 2. Selected Studies on Antiretroviral Treatment Outcomes from Resource-limited Settings (cont'd)

| Abstract No. Study Description | Treatment Program; Location; Duration of follow up | Baseline Treatment Regimen(s) (No. Patients) | Baseline Age; Sex; Clinical Stage; Treatment Experience |
|---|---|---|---|
| Outcomes of 2nd-line Antiretroviral Therapy Regimens | | | |
| Abstract 831. Lopinavir/ritonavir + 2 nRTIs as 2nd-line antiretroviral therapy in PI-naïve adults in South Africa: outcomes and adverse effects | McCord Hospital; Durban, South Africa; Jul 2004– Feb 2007 | <i>Primary Regimen:</i> All NNRTI-based <i>Secondary Regimen:</i> Lopinavir/ritonavir + didanosine/zidovudine, 74%; lamivudine/zidovudine, 29%; lamivudine/stavudine, 15% (n = 155) | <i>At time of 2nd-line treatment initiation:</i> Median age, 38 y; 65% female; no. of prior regimens, 1, 59%; 2, 36% |
| Abstract 832. Immunologic response to ritonavir-boosted PI-containing 2nd-line antiretroviral therapy after switching for clinical/immunologic criteria is comparable to response to 1st-line in patients with low CD4+ counts in Africa | Development of Antiretroviral Therapy in Africa (DART) trial; Uganda, Zimbabwe; 48 wk | <i>Primary Regimen:</i> Lamivudine/zidovudine + tenofovir, 74%; nevirapine, 16%; abacavir, 9% <i>Secondary Regimen:</i> Lopinavir/ritonavir + NNRTI ± nRTIs, 87%; nRTIs, 12% (n = 477) | <i>At time of 2nd-line treatment initiation:</i> Median age, 38 y; 59% female; 96% WHO clinical stage III-IV |

Abbreviations: ART-LINC indicates Antiretroviral Therapy in Lower Income Countries; nRTI, nucleoside analogue reverse transcriptase inhibitor; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor; y, year(s); CDC, US Centers for Disease Control and Prevention; WHO, World Health Organization; N.A., not available; mo, month(s); min, minute(s); Hb, hemoglobin; BMI, body mass index; wk, week(s)

18 months; $P = .03$). When comparing arm A, which represents the current standard of care in Durban, with arm B, however, the investigators found that the percentage of infants meeting criteria to start antiretroviral therapy within 1 year after diagnosis (arm A) or treatment interruption (arm B) was significantly higher in arm A (85%) than B (43%; $P = .01$). Time to meeting criteria for medication restart in both arms B and C was correlated with CD4+ cell percentage at birth. Thus, providing infants continuous antiretroviral therapy for HIV diagnosed at birth for 1 year and then interrupting treatment, with or without guidance by baseline CD4+ cell percentage, may be an alternative to deferring treatment in HIV-seropositive infants.

Investigators in the United Kingdom and Uganda compared response to antiretroviral therapy in HIV-infected children in the Ugandan Mulago cohort with those in the Collaborative HIV Paediatric Study (CHIPS) cohort, which includes children treated at 54 hospi-

tals in the United Kingdom and Ireland (Abstract 584). They found that, at antiretroviral therapy initiation, Ugandan children were older (median, 7.6 years vs 5 years; $P < .0001$), had higher median plasma HIV RNA levels (5.54 vs 5.2 \log_{10} copies/mL; $P < .001$), had lower baseline CD4+ cell percentages (8% vs 14%; $P < .001$), and had significantly lower height- and weight-for-age z-scores (both $P < .001$). They also had more advanced HIV disease by US Centers for Disease Control and Prevention (CDC) and WHO clinical staging (62% WHO III/IV vs 56%; $P < .001$). Children in both cohorts had similar rates of virologic suppression, CD4+ cell percentage increases, and height response. In a multivariate logistic regression analysis adjusted for baseline differences between the cohorts, however, Ugandan children with lower baseline CD4+ cell percentages had a poorer immune response at 6 months (aOR, 0.69; 95% CI, 0.62-0.76) and a poorer weight response (aOR, 0.27; $P < .0001$). The odds of virologic

suppression decreased in adolescence for children in the CHIPS cohort but not for those in the Mulago cohort.

Thai investigators conducted an investigation of the safety and efficacy of a combination PI treatment with saquinavir, lopinavir, and ritonavir in children whose nRTI- or NNRTI-based regimens were failing (Abstract 586). The HIV-NAT 017 study enrolled 50 HIV-infected children in 2 sites in Thailand who were PI-naïve and whose nRTI- or NNRTI-based regimens were failing. Their median age was 9.3 years, 56% were female, 14% had CDC stage C disease, and 42% had received NNRTIs in the past. All children received lopinavir/ritonavir 230 mg/m²/57.5 mg/m² plus saquinavir 50 mg/kg twice daily, and median CD4+ cell percentage rise at 96 weeks was 14% (interquartile range, 7%-19%). The percentage of children for whom plasma HIV RNA levels fell below 50 copies/mL at 96 weeks differed between the 2 study sites: 90% in Bangkok and 63.3% in Khon Kaen. Antiretroviral therapy-related adverse drug

| Baseline CD4+ Count (cells/μL); HIV-1 RNA/mL (log ₁₀ copies/mL) | CD4+ Response (cells/μL) | Plasma HIV-1 RNA Response (copies/mL) | Mortality | Comments |
|---|---------------------------------------|---------------------------------------|--|---|
| 148 (median) 4.3 (median) | Median at 6 mo, +95 | < 50 at 6 mo, 82% | N.A. 5 patients who died in the first 3 mo of 2nd-line antiretroviral therapy were excluded | No difference in outcome at 6 mo between patients with recycled nRTI backbones and those with new; significant difference in virologic suppression at 6 mo by sex (88% in women, 70% in men) |
| At start of 1st-line, 39 (median); At start of 2nd-line, 46 (median) N.A. | Median at 24 wk, +153; 48 wk, +199 | N.A. | N.A. | Overall rate of switch to 2nd-line antiretroviral therapy was low, 7%–8%/y; of 15% of patients who had never achieved a CD4+ count increase of 50 cells/μL on 1st line, 87% had achieved this increase after 48 wk on 2nd-line antiretroviral therapy |

events of any kind were seen in 20% of participants, with the most common being diarrhea, vomiting, and elevated triglyceride levels. No progression of HIV disease was observed.

Treatment Strategies and Addressing Loss to Follow-up

When to initiate potent antiretroviral therapy. Walensky and colleagues (Abstract 812) developed a mathematical model that incorporates published data on the South African epidemic to determine the cost-effectiveness of early initiation of antiretroviral therapy at CD4+ counts below 350 cells/μL. They modeled 3 scenarios: no antiretroviral therapy, antiretroviral therapy initiated after the CD4+ count drops below 250 cells/μL, and therapy initiated once the CD4+ count drops below 350 cells/μL. They determined that the latter scenario, “early antiretroviral therapy,” reduced the occurrence of opportunistic disease and death and extended life expectancy by 0.8 years. They also found it to cost \$1200 per life-year saved, which, because its cost-effectiveness ratio was less than 1 times the South African gross do-

mestic product per capita (\$5400 in 2006), was defined by the authors as “very cost-effective.” A separate analysis, which modeled the availability of 3 lines of antiretroviral therapy and an initiation at CD4+ counts below 500 cells/μL, was also found to be very cost-effective, at \$1000 per life-year saved.

Loss to follow-up. Last year’s conference featured sobering news on death rates among patients lost to follow-up in resource-limited settings. This year, a poster discussion session featured 5 abstracts on loss to follow-up in Africa. The first, presented by Nash and colleagues (Abstract 838) reviewed rates of loss to follow-up in 108,056 patients and 173 programs supported by the International Center for AIDS Care and Treatment Programs (ICAP). The overall mean loss-to-follow-up rate was 140 per 1000 person-years on antiretroviral therapy. Programs that offered food support had significantly lower unadjusted and adjusted loss-to-follow-up rates than programs that did not (adjusted, 136 vs 241 per 1000 person-years on antiretroviral therapy; *P* < .0001).

Two abstracts highlighted issues regarding loss to follow-up in South Africa.

Bassett and colleagues presented data from McCord Hospital in Durban, South Africa, on patients eligible for antiretroviral treatment but lost to follow-up before initiation of therapy (Abstract 839). Of 501 patients eligible for antiretroviral drugs, 16.4% were lost before treatment initiation, and 32% of these were confirmed to have died. An average of 3.6 months passed between determination of antiretroviral drug eligibility and initiation of antiretroviral drug training, and those with CD4+ counts below 100 cells/μL had an aOR ratio of loss to follow-up of 1.9 (1.07-3.39; *P* < .05). The authors emphasized the need for linkage to care after diagnosis and prioritizing antiretroviral therapy for those with low CD4+ cell counts.

In an examination of factors associated with loss to follow-up in community clinics in South Africa, Wang and colleagues (Abstract 841) found that, over 4 sites and 1507 patients, mean time to loss to follow-up was 6 months, and 126 (8%) patients who initiated antiretroviral therapy were lost to follow-up at 6 months. Patients with lower baseline CD4+ counts (below 200 cells/μL) and pregnant women were statistically significantly

more likely to be lost to follow-up ($P = .0001$).

Two other abstracts highlighted the need for aggressive tracking of patients lost to follow-up. Muwanga and colleagues noted high rates of loss to follow-up in a large treatment center in Uganda (Abstract 840), where the loss-to-follow-up rate among those on antiretroviral therapy was 12.9% and among those not on therapy, 39.2%. The preliminary results from 36 home visits, conducted on a subset of the 50% of patients who were lost and not reachable by phone, found that 92% of the patients could be located and 58.3% had died. These deaths will significantly alter the overall clinic mortality rate, which authors plan to recalculate once home visits are completed for all patients lost to follow-up that cannot be reached by phone.

A second presentation from Geng and the East Africa IeDEA Consortium took a sampling approach to determining outcomes for patients lost to follow-up (Abstract 842). Of 3340 patients starting antiretroviral treatment in Mbarara, Uganda, after January, 2004, 728 were lost to follow-up at 3 years. A sample of 98 of those lost to follow-up was selected, and a health educator sought them out to determine their vital status, which was possible in 84% of the sample. Of those patients the health educator was able to speak with directly (47% of the total sample), 81% had resumed care in another clinic, and 50% cited difficulties with transportation as the main reason for their loss to follow-up. The authors then used mortality data among those lost to follow-up to adjust the cumulative clinic mortality rates using probability weighting. This calculation substantially increased previously reported clinic mortality rates: at 1 year, from 1.7% preadjustment to 5.4% postadjustment; at 2 years, 2.1% to 8.9%; and at 3 years, 2.6% to 10.2% overall mortality rate for the clinic.

Advances in Laboratory Monitoring

Many interesting presentations described new approaches to laboratory monitoring in RLS; selected abstracts are summarized here. Coutinho and colleagues presented an oral abstract

on the results of a randomized controlled trial completed within the rural Ugandan Home-Based AIDS program (Abstract 125). Participants initiating therapy within the program were randomized to 1 of 3 arms: arm A, weekly clinical monitoring by outreach workers, quarterly CD4+ cell counts and plasma HIV RNA levels; arm B, weekly clinical monitoring and quarterly CD4+ cell counts; and arm C, weekly clinical monitoring only. Of the 1116 participants randomized, 1094 initiated antiretroviral therapy, 39% of whom had WHO clinical stage III or IV disease. The median follow-up time was 3 years, and overall mortality rate was 11.2%, with 47% of deaths occurring within the first 3 months. Ninety percent of participants had an undetectable plasma HIV RNA level at 1 year. By a Cox proportional hazards model intention-to-treat analysis, the aOR for first morbidity or mortality was 1.88 (95% CI, 1.25-2.84; $P = .002$) for arm C compared with arm A. Of the 17 participants in arm C who switched regimens, 15 were switched based on clinical criteria but had undetectable plasma HIV RNA levels. Thus, the authors concluded that the monitoring regimens in arms A and B allowed for earlier detection of adherence challenges and should be adopted where feasible.

Investigators from the Academic Model of Prevention and Treatment of AIDS (AMPATH) clinic in Eldoret, Kenya, also examined the utility of plasma-HIV-RNA-level monitoring in RLS (Abstract 834). All adult patients attending the clinic who were adherent to the same regimen for more than 6 months but whose antiretroviral therapy was failing by CD4+ cell count criteria had their plasma HIV RNA levels tested. The authors defined treatment failure misclassification as a greater than or equal to 25% drop in CD4+ cell count with an undetectable plasma HIV RNA level. Of 112 patients who met criteria for treatment failure by decrease in CD4+ cell count, 66 had failure misclassification, with the likelihood of misclassification elevated in patients with higher CD4+ counts (OR, 2.68 per 100 cells/ μ L increase; 95% CI,

1.35-5.32; $P = .006$). The authors felt that these results strongly supported plasma-HIV-RNA-level monitoring and have implemented testing for all AMPATH patients for whom first-line antiretroviral therapy appeared to be failing.

Bassett and colleagues (Abstract 908) examined the performance of rapid point-of-care HIV testing in RLS with a high HIV prevalence by testing multiple rapid HIV-1 and -2 test kits in the outpatient department of McCord Hospital in Durban, South Africa. All patients testing seropositive were tested a second time and then referred for further determinations of plasma HIV RNA level; patients with seronegative or discordant test results were referred to the study. Of 705 patients who had seronegative rapid HIV test results, 11 (1.6%) were chronically HIV-infected on confirmatory testing. Of 13 patients with discordant rapid HIV test results, 61.5% were HIV-infected, and a total of 2.7% (95% CI, 1.7%-4.1%) of people with seronegative or discordant test results were chronically infected. The authors estimated the sensitivity of the rapid tests in this setting to be 98.8% (95% CI, 98.2%-99.5%), and the negative predictive value to be 98.4% (95% CI, 97.5%-99.4). They estimated that, based on the current rapid testing protocol and the rate of testing at the hospital, 2 HIV-infected people per week could be incorrectly told they are HIV-seronegative.

Resistance to Antiretroviral Therapy

Information on HIV drug resistance in RLS is critical for planning antiretroviral scale-up and assessing the need for second-line treatment regimens. This year's conference made several contributions to this emerging body of literature. Ayoub and colleagues (Abstract 899) presented data on drug resistance in recently infected, antiretroviral therapy-naïve patients in Burkina Faso, Cambodia, Cameroon, Thailand, and Vietnam. They collected a total of 280 samples from HIV-infected individuals, evenly distributed among the 5 countries, in antenatal clinics from women in their first pregnancy or with CD4+ counts above 500 cells/

μL, and in voluntary counseling and testing sites. Only 4 of the samples (1.4%, 95% CI, 0.6-3.6) had mutations that conferred resistance to 1 or more drugs by either the 2007 Stanford HIV database algorithm, the International AIDS Society-USA (IAS-USA) mutations list, or the French national AIDS trial group algorithm. Of these, all 4 had mutations that conferred resistance to NNRTIs. One sample also contained an M184V mutation, and another carried the M46I mutation.

Three abstracts presented novel data on HIV drug resistance after first-line therapy. Gupta and colleagues (Abstract 891), presented a meta-analysis of 18 clinical trials with HIV resistance data in patients for whom first-line therapy was failing in resource-rich settings, and for 2 African cohorts and 1 Thai study examining the same in RLS. The authors found that genotypic resistance to nRTIs and NNRTIs at up to 80 weeks of follow-up was more common in RLS, where first-line NNRTI-based antiretroviral regimens were used (cumulative, 7.61%, compared with 2.60% in resource-rich settings). They also noted that the prevalence of M184V, K65R, and resistance to a third agent was more common in patients initiating treatment with NNRTI-based regimens (4.09%) than in those initiating PI-based regimens (0.9%).

Kumarasamy and colleagues (Abstract 893) presented data on 93 patients in Chennai, India, whose NNRTI-based, first-line antiretroviral therapy was failing and who had HIV genotypic testing before initiating second-line treatment. Ninety percent of patients had 2 or more reverse transcriptase (RT) mutations that confer resistance to at least 1 antiretroviral medication, with M184V in 75% of patients and the NNRTI-related mutations K103N, Y181C, and G190A in 27%, 33%, and 26% of patients, respectively.

Chaplin and colleagues (Abstract 901) conducted a similar study among 304 Nigerian patients with documented virologic failure. In this sample, the prevalence of specific HIV drug-resistance-associated mutations (D67N, M41L, L210W, A98G, and V90I) varied by subtype. The TAM pathway that combines

mutations at K70R, K219QE, T215F, and D67N (TAM2) predominated in this sample dominated by HIV subtype G and CRF02_AG, as opposed to the TAM1 pathway (T215Y, M41L, L210W, and D67N), which is known to be more common in HIV subtype B viruses.

Three different groups presented data on HIV drug resistance after first-line antiretroviral failure in children. In South Africa, investigators followed 278 perinatally infected children from June, 2006, to January, 2008, of whom 25 (9%) had virologic failure with plasma HIV RNA levels greater than 1000 copies/mL (Abstract 587). The average duration of treatment before failure was 10 months (interquartile range, 6-17 months), and 88% of patients with failure had at least 1 significant mutation shown on HIV genotype testing. Sixty percent of patients had dual-class resistance, but none had 3-class resistance. The most common mutations were M184V (80%) and V106M (24%). A second abstract (589) describing HIV-genotype-testing results in 35 South African children whose first- or second-line therapy was failing had a similar mutational profile with respect to M184V and V106M, but 44% of these samples carried the K103N mutation. Of 7 patients on PI-based regimens, 3 carried virus with drug-resistance-associated mutations in the protease genome. In both South African studies, patients were infected predominantly with HIV subtype C virus.

Sungkanuparph and colleagues presented data from a cohort of HIV-infected children in Bangkok, Thailand, whose initial NNRTI-based regimen led to virologic failure between January, 2000, and December, 2007 (Abstract 588). After genotype testing, most patients were found to have at least 1 resistance-associated mutation to nRTIs (52%) and NNRTIs (43%), and patients infected with virus carrying the M184V mutation had a higher prevalence of NNRTI resistance mutations than did those without M184V/I (86% vs 21%; $P = .016$). Appropriate second-line therapy in 47% of children will require a PI, highlighting the need for increased access to second-line antiretroviral regimens in RLS.

Mother-to-Child Transmission

Several oral presentations of noteworthy studies reported rates of MTCT of HIV in RLS. Various regimens complemented or enhanced single-dose nevirapine for infants and mothers, demonstrating initiatives geared toward reduction of MTCT and resistance in some cases (Table 3).

Black and coauthors (Abstract 657) sought to identify risk factors for MTCT in women with advanced AIDS. They presented a retrospective analysis of women who had received care at the Antenatal Antiretroviral Clinic (ANC ARV) in South Africa between August, 2004, and February, 2007, looking for predictors of MTCT. They presented 6-week follow-up data on 302 mother-infant pairs and found that the rate of MTCT was 5% and that 2 features were associated with MTCT: shorter duration of antiretroviral treatment during pregnancy and lower CD4+ cell count. For each additional week of antiretroviral treatment, the odds of transmission were reduced by 27%, and the rate of transmission for patients who received more than 7 weeks of antiretroviral treatment was 0.3%.

Two studies reported MTCT in resource-rich settings. Townsend and colleagues (Abstract 653) confirmed the value of having an undetectable viral load in their presentation of data from the United Kingdom and Ireland National Study of HIV in Pregnancy and Childhood. The overall rate of MTCT in the United Kingdom and Ireland among infants born to HIV-infected women from 2000 to 2006 was 1.1% (61/5316 subjects). No statistically significant difference occurred in MTCT rates between women on antiretroviral therapy who underwent caesarean delivery (17/2337 subjects, or 0.7%), women on antiretroviral treatment who had a vaginal delivery (4/565 subjects, or 0.7%), and those who received prophylactic zidovudine along with a caesarean delivery (0/467 subjects, or 0%). Only 3 transmissions occurred among women on antiretroviral therapy whose viral load was below 50 copies/mL (3/2202 subjects, or 0.1%).

The second study (Abstract 654)

Table 3. Selected Studies in Mother-to-Child Transmission of HIV

| Abstract No. Study Description | Location; Treatment Program; Duration of Follow-up | Treatment for Mothers (No. Patients) | Treatment for Infants (No. Patients) | Breastfeeding Status |
|--|--|--|---|---|
| Abstract 43. Extended-dose nevirapine to 6 weeks of age for infants in Ethiopia, India, and Uganda: a randomized trial for prevention of HIV transmission through breastfeeding (See also abstracts 44, 635b) | Ethiopia, India, Uganda; Six Weeks of Extended Nevirapine (SWEN) Study Team; 6 mo follow-up of infants | Ethiopia: SD-NVP; India: SD-NVP or ZDV, or 3TC, or potent antiretroviral therapy; Uganda: SD-NVP | Randomized; placebo controlled; SD-NVP (n = 986) vs SD-NVP + extended NVP day 8–42 (n = 901) | Exclusive breastfeeding encouraged |
| Abstract 42LB. Extended infant postexposure prophylaxis with antiretroviral drugs significantly reduces postnatal HIV transmission: the PEPI Malawi study | Blantyre, Southern Malawi; The Post-Exposure Prophylaxis of Infants (PEPI) Malawi Study; 14 wk of infant treatment; 24 mo follow-up | Mothers received intrapartum NVP, if possible | Randomized; open-label; SD-NVP + 1 wk of ZDV (control arm, n = 1003) vs control + NVP days 8–98 (n = 1016) vs control + NVP/ZDV days 8–98; (n = 997); analysis excluded infants infected at birth | Exclusive breastfeeding until 6 mo then total wean; 98% breastfed at 14 wk; 20%–30% breastfed at 9 mo |
| Abstract 45b. The TEmAA ANRS 12109 phase II trial, Step 1: tolerance and viral resistance after single-dose nevirapine and short-course of tenofovir disoproxil fumarate and emtricitabine to prevent mother-to-child transmission of HIV-1 (See also Abstracts 47LB, 626) | Ivory Coast, Cambodia, South Africa; Tenofovir/Emtricitabine for PMTCT in Africa and Asia (TEmAA) Trial; 28–38 wk of gestation until 60-d postpartum follow-up | HIV-infected women 28–38 wks gestation received ZDV 300 mg bid; at start of labor, all women given SD-NVP and 2 tablets TDF/FTC, followed by TDF/FTC x 7 d postpartum (n = 38) | Open-label, phase II trial; SD-NVP and SD-TDF/FTC, followed by 7 d ZDV (n = 39) | Not reported |

Abbreviations: mo indicates month(s); SD, single-dose; NVP, nevirapine; ZDV, zidovudine; 3TC, lamivudine; wk, week(s); PMTCT, prevention of mother-to-child transmission; bid, twice daily; TDF, tenofovir; FTC, emtricitabine; d, day(s); y, year(s); h, hour(s); NFV, nelfinavir; MTCT, mother-to-child transmission; PI, protease inhibitor; RLS, resource-limited settings; TB, tuberculosis; LPV, lopinavir; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

reported rates of MTCT associated with amniocentesis in the French Perinatal HIV Cohort. Rates of amniocentesis increased from 1% before 2001 to 2.7% in the years 2001 to 2006 among HIV-infected women who delivered after 28 weeks of gestation (excluding multiples). Although a statistically nonsignificant trend toward higher rates of MTCT occurred among mothers who underwent amniocentesis, this trend was not found in women who underwent amniocentesis and were treated with antiretroviral drugs (0%). The authors pointed

out that any invasive prenatal testing is yet another indication to perform HIV testing.

Pharmacokinetics and Safety of Antiretroviral Drugs in Infants and Pregnant Women

Several presentations reported results of pharmacokinetic and safety studies of various antiretroviral drugs in infants and pregnant women. Such data were reported for tenofovir (Abstracts 47LB, 627a), emtricitabine (Abstracts 626, 629), atazanavir (Abstracts 624,

625), lopinavir/ritonavir (Abstracts 628-630), and enfuvirtide (Abstract 627b).

Tenofovir and emtricitabine were found to be safe and effective for pregnant women and infants. Hirt and colleagues (Abstracts 47LB, 626) looked at the pharmacokinetics of both drugs in 35 HIV-infected pregnant women and their infants. Women were given 2 tablets of tenofovir 300 mg/emtricitabine 200 mg at initiation of labor followed by 7 days of 1 tablet of tenofovir 300 mg/emtricitabine 200 mg. Pharmacokinetic samplings took place at delivery and at 1, 2, 3, 5, 8, 12, and 24

| Mother-to-Child Transmission | Infant Death | Resistance | Adverse Events | Comments |
|---|---|---|---|------------|
| 6 wk: SD-NVP, 5.27%; extended NVP, 2.53% (<i>P</i> = 0.009); 6 mo: SD-NVP, 8.98%; extended NVP, 6.91% (not statistically significant) | 6 wk: SD-NVP, 1.59%; extended NVP, 0.91% (not statistically significant); 6 mo: SD-NVP 3.61%; extended NVP, 1.12% (<i>P</i> = 0.016) | See note 1 | | |
| 9 mo: Control, 10.1%; extended NVP, 5.2%; extended NVP/ZDV, 6.4%; 24 mo: Control, 14.5%; extended NVP, 11.2%; extended NVP/ZDV, 12.3% | Probability of infant death: 9 mo: Control, 8.9%; extended NVP, 6.8%; extended NVP/ZDV, 6.3%; 24 mo: Control, 16.1%; extended NVP, 14%; extended NVP/ZDV, 13.4% | | | |
| Day 28 of life: 2/38 children (both in utero); no intrapartum infections reported | 4/39 infants | 0/37 mothers with resistance to NVP, FTC, or TDF; 0/2 infants with resistance to NVP, FTC, or TDF | Mothers: 9 serious adverse events (24%)— anemia, 3; neutropenia, 5; elevation of liver enzymes, 1 Infants: 9 serious adverse events (23%)— deaths 4; infectious events, 7; intestinal obstruction, 1; respiratory, 1; neurologic, 1; severe anemia, 2 | See note 2 |

Note 1. Abstract 44 highlights resistance analysis of Indian data. Among HIV-1 subtype C-infected infants (99), higher rates of NVP resistance were seen in infants treated with extended NVP (92%) than with SD-NVP (40%) in infants diagnosed in first 6 wk of life. Abstract 635b highlights resistance analysis from Uganda, where more genotypic resistance at 6 wk was found in extended-NVP (84%) than in SD-NVP arm (50%); phenotypic results were comparable. Resistance detected at 6 wk was more likely to persist at 6 mo in extended NVP group.

Note 2. Pharmacokinetic analysis of TDF in pregnant women and their infants (Abstract 47LB) showed that 1 dose TDF 600 mg in pregnant women at initiation of labor produced the same concentrations as 300-mg dose in other adults. Intrapartum, if delay between drug uptake and delivery is > 12 h, dose should be readministered. TDF placental transfer, ~60%. Infants should receive 11–13 mg/kg tenofovir disoproxil fumarate 1 h after birth to obtain similar drug levels as adults. Pharmacokinetic analysis of FTC (Abstract 626) showed good FTC placental transfer (~80%) and that 1 mg/kg within 6 h after birth and 2 mg/kg 12 h after birth are needed to achieve neonatal concentrations comparable to necessary adult concentrations.

[\(Continued on next page\)](#)

hours after emtricitabine, and before the second, third, and seventh doses of subsequent emtricitabine. Cord blood samples were taken at delivery, and infants were tested on days 1 and 2 of life. Plasma concentrations of both drugs were measured, and estimated neonatal concentration curves were derived. A dose of 600 mg of tenofovir

at birth in pregnant women achieved concentrations comparable to a 300-mg dose in nonpregnant adults, and placental transfer was approximately 60%. Infants required a 13-mg/kg dose of tenofovir 2 hours after birth to obtain the appropriate drug concentrations. Emtricitabine was also shown to have good placental transfer (~80%)

and required administration of 1 mg/kg within 6 hours of birth to maintain appropriate infant levels (see Table 3).

Data were also presented on the safety of tenofovir in pregnant women from the Frankfurt HIV Cohort in Europe (Abstract 627a). The authors analyzed the safety and tolerance of tenofovir in the 76 pregnant women

Table 3. Selected Studies in Mother-to-Child Transmission of HIV (cont'd)

| Abstract No. Study Description | Location; Treatment Program; Duration of Follow-up | Treatment for Mothers (No. Patients) | Treatment for Infants (No. Patients) | Breastfeeding Status |
|---|--|---|--|---|
| Abstract 45aLB. PMTCT of HIV-1 among breastfeeding mothers using potent antiretroviral therapy: the Kisumu Breastfeeding Study, Kisumu, Kenya, 2003–2007 (See also Abstracts 84LB, 640, 645, 646, 647) | Kisumu, Kenya; Kisumu Breastfeeding Study; treatment 24–36 wk gestation to 6 mo postpartum and follow-up 2 y postpartum | Phase IIb single-arm PMTCT trial; women 24–36 wk gestation given ZDV/3TC + NVP and treated until 6 mo postpartum (n = 296) Note: in January 2005 protocol was changed: women with CD4+ > 250cells/μL received ZDV/3TC + NFV instead (n = 201) | SD-NVP within 72 h of delivery (n = 497 live born) | Exclusive breastfeeding encouraged until 5.5 mo followed by a rapid 2-wk wean, resulting in complete wean by 6 mo. Note: despite a rigorous counseling program on benefits of exclusive breastfeeding until 6 mo followed by complete wean, 21% of women mixed-fed before 5 mo and 14% of women continued breastfeeding past 6 mo (Abstract 645) |
| Abstract 639. Decrease in HIV-1 mother-to-child transmission in women receiving postnatal potent antiretroviral therapy: 12-month follow-up data (See also Abstract 668, 835) | Mozambique; The Drug Resource Enhancement against AIDS and Malnutrition (DREAM) Program; Prospective cohort; 12-mo follow-up | All women enrolled in cohort began potent antiretroviral treatment at 15-wk gestation; all mothers of live-born infants (n = 341) continued until 6 mo postpartum (unless symptoms of AIDS/CD4+ count ≤ 200 cells/μL, then continued indefinitely); antiretroviral regimens include ZDV/d4T + 3TC + NVP and back-up with NFV or LPV/ritonavir | SD-NVP within 24 h of delivery, followed by short-course ZDV for first 4 d | Women counseled to exclusively breastfeed until 6 mo |

Abbreviations: mo indicates month(s); SD, single-dose; NVP, nevirapine; ZDV, zidovudine; 3TC, lamivudine; wk, week(s); PMTCT, prevention of mother-to-child transmission; bid, twice daily; TDF, tenofovir; FTC, emtricitabine; d, day(s); y, year(s); h, hour(s); NFV, nelfinavir; MTCT, mother-to-child transmission; PI, protease inhibitor; RLS, resource-limited settings; TB, tuberculosis; LPV, lopinavir; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

who received tenofovir as part of their regimen when first-line agents were not tolerated. The mean initiation of tenofovir was at 24 weeks' gestation. Two women stopped tenofovir, 1 because of rash and 1, nausea; no signs of tenofovir-related toxicity or birth malformations attributable to tenofovir were found in the 78 live-born infants. Pharmacokinetic data were reported (Abstract 629) on emtricitabine from the Pediatric AIDS Clinical Trials Group (PACTG) 1026 study, gathered from 18 women who took emtricitabine 200 mg daily throughout pregnancy and for 6 weeks to 12 weeks postpartum.

Steady-state profiles at 12 hours and 24 hours were calculated after obtaining maternal and umbilical cord samples. Emtricitabine exposure (as determined by AUC) was lower during pregnancy than postpartum. The magnitude was small, however, suggesting that dose adjustment may not be necessary during pregnancy.

Eley and colleagues (Abstract 624) reported on the safety and pharmacokinetic data for atazanavir 300 mg/ritonavir 100 mg daily in pregnancy. Data were analyzed after 12 women completed the third-trimester pharmacokinetic studies. Values for the

third-trimester atazanavir AUC and minimum plasma trough concentration (C_{\min}) were approximately 40% and 21% lower than in historical controls, respectively. The investigators suggested that this dosage level may be inadequate and plan to investigate a dose increase to atazanavir/ritonavir 400 mg/100 mg once daily in the third trimester. Otherwise, the study drugs were well tolerated. The bilirubin level reached grade 3 in 5 of 18 subjects. For the 10 subjects who reached delivery, plasma HIV RNA level was below 50 copies/mL, and all infants were HIV-seronegative. All infants had normal bili-

| Mother-to-Child Transmission | Infant Death | Resistance | Adverse Events | Comments |
|--|---|--------------|--|---|
| Cumulative rate of MTCT: 0-7 d, 2.4% 6 wk, 3.9% 3 mo, 4.1% 6 mo, 5.0% 9 mo, 5.5% 12 mo, 5.9% 18 mo, 6.7% | Not reported | See note 3 | See note 4 | Related Abstract 646 reports on the impact of implementation of a safe water system in 2005 on diarrhea rates in infants participating in the Kisumu Breastfeeding Study |
| 283/341 infants were available for follow-up at 12 mo; of these, MTCT rate was 2.8% (8/283) at 12 mo; 47 infants lost to follow-up | 11 infants known to have died by 12 mo, of which 4 had documented HIV status (1 seropositive) | Not reported | Abstract 668 presented follow-up data regarding treatment interruption of 220 women in DREAM Study. Median values of hemoglobin, CD4+ count, HIV RNA copies/mL, AST, and ALT were comparable at enrollment and 12 mo after antiretroviral treatment was discontinued. Resistance or mortality rates not reported | From original cohort, 54 infants did not have HIV diagnosis at 12 mo (47 lost to follow-up and 7 known deaths without clear HIV serostatus). Relative risk reduction of maternal antiretroviral treatment during pregnancy until at least 6 mo postpartum, assuming all infants were HIV seropositive, was 54%. Leaving them out of analysis results in 93% risk reduction, assuming an expected cumulative risk of perinatal HIV infection at 12 mo of 40% |

Note 3. Abstract 84LB analyzed resistance among infants who seroconverted and patterns of mutations based on timing of seroconversion and maternal regimen. 29/502 infants (5.8%) were HIV-infected. Infants underwent HIV testing on multiple study visits; resistance testing was done at time of initial HIV detection and at wk 14 or 24. 83% of the 29 HIV-infected infants were seropositive before 24 wk of life; 58% of HIV-infected infants had been born to women in NVP arm; 42% to women in NFV arm. Though 0/12 infants who were seropositive from birth to 2 wk were initially found to have resistance, by 6 mo 11/12 had evidence of resistance; drug resistance increased over time. At 6 mo 24 infants were seropositive, of whom 16 had genotypic resistance including 6/14 (43%) of mothers taking NVP and 10/10 (100%) of mothers taking NFV. Of infants exposed to NVP who developed resistance, 4 had nRTI resistance and 6 had NNRTI resistance including Y181C, K103N, G190A, and K101E. HIV-seropositive infants with prior exposure to NFV had no major PI mutations. In infants who were HIV-infected within first 6 wk of life, drug resistance was initially not detected until well into breastfeeding period, suggesting that resistant virus may have been transmitted by mother, likely through transfer of antiretrovirals in breast milk. Even though all children received SD-NVP, no case of NNRTI resistance was detected among infants whose mothers were treated with NFV.

Note 4. Abstract 640 highlights infant adverse fetal outcomes for this study among infants born to women with CD4+ \geq 250 cells/ μ L who initiated drug treatment from 34-wk gestation. Rates of low birth weight were similar in women taking NVP- vs NFV-based regimens; women taking NFV showed a trend toward decreased odds of preterm delivery. Rates of preterm delivery, low birth weight, and stillbirth in women in both drug groups were equal to or lower than WHO rates reported for RLS. Abstract 647 reports better tolerance of the NFV- than the NVP-based regimen. 440/522 enrolled women continued until 6 mo, including 62 who switched to another regimen. Of the 440 women, 263 began on NVP, of whom 41 (16%) switched to NFV or efavirenz for hepatotoxicity, rash, initiation of warfarin/TB therapy. ZDV also resulted in switches in 21/440 (5%) women, mainly because of anemia/neutropenia. No medication interruptions were made for NFV (177 women) or for 3TC-related intolerance.

rubin levels through day 14, and 1 had grade 3 at day 15.

Ferreira and colleagues (Abstract 625) further explored the effect of atazanavir exposure in utero on neonates and reported on their retrospective single-center cohort of 9 infants who were exposed to ritonavir-boosted atazanavir during pregnancy. Fetal unconjugated hyperbilirubinemia correlated to maternal bilirubin concentration at delivery, suggesting placental transfer of unconjugated bilirubin; however, neonatal levels of hyperbilirubinemia were not high enough to be harmful, and none of the 3 infants born with jaundice required phototherapy. Atazanavir levels found in the cord blood of the 9 infants were therapeutic, confirming previous reports of good placental transfer.

Three abstracts (628–630) focused on the question of whether standard dosing of lopinavir/ritonavir is adequate for pregnant women, particularly in the third trimester in PI-experienced women. Cressey and colleagues (Abstract 630) reported lopinavir/ritonavir pharmacokinetic data from the IMPAACT P1032 Trial, a randomized trial of short-course intrapartum and postpartum antiretroviral therapy in Thai women. Pharmacokinetic data were available for 16 women who initiated lopinavir/ritonavir treatment at standard doses during labor and achieved lopinavir exposure at 72 hours and 30 days postpartum similar to that seen in nonpregnant US adults, suggesting that standard doses for short-course therapy among Thai women may be adequate.

Abstracts 628 and 629 reported lopinavir/ritonavir pharmacokinetic data in non-Thai populations that suggest that, although standard doses of lopinavir/ritonavir at 400 mg/100 mg twice daily achieved an adequate minimal concentration for PI-naïve pregnant women, this dosage may not be adequate for PI-experienced women, particularly in the third trimester. Best and colleagues (Abstract 629) suggested a dose of lopinavir/ritonavir 600 mg/150 mg twice daily in the third trimester for all women and in the second trimester for PI-experienced women, followed by postpartum dose reduction to standard doses.

Haberl and colleagues (Abstract 627b) report on the use of enfuvirtide in 14 HIV-infected pregnant women. Indications for enfuvirtide included failure to suppress (7), late presenters (4), and cases of premature birth with incomplete transmission prophylaxis (3). All women were enfuvirtide-naïve, and 50% of women were antiretroviral therapy-naïve altogether. All women received enfuvirtide in addition to at least 3 other antiretroviral drugs. The mean baseline plasma HIV RNA level before receiving enfuvirtide was 75,120 copies/mL, and the mean period of exposure to enfuvirtide before caesarean delivery was 15 days, resulting in mean antenatal plasma levels of HIV RNA of 218 copies/mL. None of the 14 infants was HIV-infected, and no enfuvirtide-related adverse events were observed in mothers or infants. In infants for whom enfuvirtide concentrations were measured, the concentrations were below 200 ng/mL, revealing a lack of transplacental distribution.

Bell and coauthors (Abstract 656) presented data on the rate of reduction of plasma HIV RNA levels during the first 14 days of therapy in pregnant women, comparing nevirapine- and PI-based regimens (including 2 nRTIs) in women from 3 different centers. The authors measured plasma HIV RNA levels before treatment and at 14 days, as well as CD4+ cell counts, and found that the plasma half-life was shortest for women taking nevirapine, followed by those on lopinavir/ritonavir, then those on nelfinavir. They suggested that these data support the continued use of nevirapine in pregnant women who have a CD4+ count below 250 cells/ μ L.

Prevention of Mother-to-Child Transmission and Resistance

The development and transmission of resistance related to prevention of mother-to-child transmission (PMTCT) was addressed in numerous abstracts (Abstracts 44, 84LB, 631-634, 635a, 635b). Chi and colleagues reported on the reduction of NNRTI resistance mutations in women treated with a single dose of tenofovir 300 mg/emtricitabine 200 mg in addition to short-course zi-

dovudine and intrapartum nevirapine for PMTCT. Previously released data showed a significant risk reduction, but the investigators did not test for viral subpopulations and could not comment on viral subpopulations present at levels below 25%. The results of testing 122 specimens with the oligonucleotide ligation assay to detect resistance in minority subpopulations present as low as 5% were reported (Abstract 631). The investigators found a 69% reduction in NNRTI resistance at 2 weeks postpartum (2/15 subjects vs 10/23 subjects; relative risk [RR], 0.31; 95% CI, 0.08-1.21) and a 58% reduction in NNRTI resistance at 6 weeks postpartum (8/43 subjects vs 18/41 subjects; RR, 0.42; 95% CI, 0.21-0.87).

With regard to repeated use of single-dose nevirapine PMTCT, Eshleman and colleagues (Abstract 632) found that there was no difference in the proportion of nevirapine resistance, the types of mutations detected, or the frequency of K103N in women treated with single-dose nevirapine for the first time ($n = 57$) versus women who had been treated with single-dose nevirapine in a subsequent pregnancy ($n = 34$), nor did repeat exposure influence the emergence of resistance in HIV-infected infants.

Much inquiry has been made into the issue of NNRTI resistance fading after use of single-dose nevirapine for PMTCT. In HIV-infected women who received single-dose nevirapine for PMTCT, Wind-Rotolo and colleagues (Abstract 634) demonstrated that nevirapine-resistant virus in the plasma also persisted in the resting CD4+ T-cell latent reservoir. Not surprisingly, in some cases, nevirapine-resistant virus was identified in the latent reservoir but not identified as nevirapine resistance in the concurrent plasma sample.

Mutations associated with PI resistance were less common than NNRTI- or lamivudine resistance-associated mutations in virus in women treated with pregnancy-limited antiretroviral therapy (PLAT) in the US-based Women and Infants Study Group (WITS) cohort, according to Paredes and colleagues (Abstract 635a). Their analysis included HIV-infected pregnant women who received PLAT from 1998 to

2004 (n = 146). They note that overall, mutations were fairly common; they therefore recommend genotype resistance testing in women who have received PLAT.

Adverse Events

Several abstracts explored adverse events in pregnant women or infants exposed to antiretroviral drugs. Masaba and colleagues (Abstract 640) presented favorable data on low-birth-weight, stillbirth, and preterm babies among women treated with nevirapine-based antiretroviral therapy and infants treated with single-dose nevirapine from the Kisumu breastfeeding study (Table 3).

Ekouevi and colleagues (Abstract 641) presented data on pregnancy outcomes among HIV-infected women who were treated with potent antiretroviral therapy within the Ditrane Plus observational cohort in Abidjan, Cote D'Ivoire. Despite lower rates of MTCT in women with advanced AIDS who were treated with antiretroviral therapy than in women on short-course antiretroviral therapy (2.3% vs 16.1%), more low-birth-weight babies were born to women treated with nevirapine-based antiretroviral treatment (22.3%) than to those who received short-course antiretroviral therapy (12.4%). Fortunately, no difference in mortality rates was found for babies in the 2 groups in the first year of life.

Toro and colleagues found similar rates of antiretroviral-associated drug toxicities and substitutions in HIV-infected antiretroviral therapy-naïve pregnant women and in nonpregnant women and men participating in the MTCT-Plus Initiative (7.4, 5.8, and 4.6 toxicities per 100 patient-years, respectively; Abstract 787). Given these results, the authors suggested that antiretroviral therapy should not be delayed during pregnancy over concerns about medication side effects or toxicities.

Antiretroviral Concentrations in Breast Milk and Breastfeeding Infants

Corbett and colleagues (Abstract 648) looked at concentrations of antiretroviral drugs in the breast milk, mater-

nal plasma, and infant plasma of 20 women and infant pairs participating in the Malawi-based Breastfeeding Antiretroviral and Nutrition (BAN) study at the end of 12-hour dosing intervals at 6 weeks, 12 weeks, and 24 weeks postpartum. Participating women were treated with zidovudine or stavudine, lamivudine, and either nevirapine or nelfinavir. Zidovudine and stavudine concentrations were detectable in fewer than 20% of samples. Although lamivudine was present in higher concentrations in breast milk, the ratio that was actually present in infant plasma was low (1% of breast milk). Nevirapine concentrations in breast milk were approximately 70% of maternal plasma with low exposure in infants (20% infant plasma/breast milk). Nelfinavir exposure in breast milk was lower than in maternal plasma and undetectable in infants. Such findings suggest that there is a minimal risk of toxicity of these antiretroviral drugs to breastfeeding, HIV-seronegative infants. Of all of these drugs, nevirapine produced the highest levels in infants and may predispose infants who become infected to resistance.

Lehman and colleagues (Abstract 649) presented data on serial breast milk testing in 599 breast milk samples from women participating in antiretroviral treatment for PMTCT. Samples were tested for cellular DNA, HIV, and beta-actin DNA by real-time PCR. Although the investigators found cell-free and cell-associated HIV RNA levels suppressed in the presence of antiretroviral therapy, they also reported the presence of a large reservoir of latently infected cells that were not significantly affected by antiretroviral therapy, including short-course antiretroviral treatment.

Resistance

N348I

As previously reported at last year's conference, the N348I mutation confers dual resistance to both NNRTIs and nRTIs. Yap and colleagues (Abstract 79) further characterized the 2 related biochemical mechanisms by which this

mutation confers dual resistance. Using biochemical assays, they tested the zidovudine-monophosphate (MP) excision activity of wild-type and mutant HIV RT in the presence and absence of nevirapine. The N348I mutation decreases the ability of nevirapine to inhibit HIV RT, and the rate of RT RNase H cleavage, which provides RT with more time to efficiently excise the zidovudine-MP from an RNA-DNA template-primer. The ability of nevirapine to stimulate RNase H was significantly reduced in the presence of this mutation compared with the wild-type enzyme. The effect of zidovudine-triphosphate (TP) and nevirapine combined in RNA-dependent DNA polymerization reactions, along with the combined effects of N348I on nevirapine binding, RNase H activity, and zidovudine-MP excision, resulted in efficient enzyme replication. Mutations distal from the polymerase active site and NNRTI-binding pocket can confer drug resistance.

Ehteshami and coauthors (Abstract 81) explored the mechanism behind selective increases in zidovudine resistance in the presence of both TAMs and connection domain mutations N348I and A360V by comparing N348I, A360V, TAM, and TAM/N348I/A360V mutant enzymes. Mutations N348I and A360V mechanistically complemented each other to increase zidovudine resistance in a background of TAMs.

Q509L

Brehm and colleagues (Abstract 80) described the mechanism of action behind increased zidovudine resistance in the presence of TAMs and mutations at the connection (A371V) and the RNase H (Q509L) domains of the HIV RT. They determined zidovudine-MP excision and RNase H cleavage product and estimated single turnover zidovudine-MP excision. Compared with TAMs alone (D67N/K70R/T215F), TAM/A371V, TAM/Q509L, and TAM/A371V/Q509L increased zidovudine-MP excision 1.7-, 2.7-, and 2.9-fold, respectively, and decreased RNase H cleavage product formation 1.3-, 2.1-, and 2.1-fold. In the presence of TAMs, HIV RT muta-

tions Q509L and A371V/Q509L result in increased zidovudine-MP excision of RNA-DNA duplexes by reducing template degradation, and they increase the efficiency of excision on short RNA-DNA duplexes.

M184V

Selection of M184V in antiretroviral therapy-naïve and -experienced patients treated with entecavir for hepatitis B virus (HBV) in the setting of HIV and HBV coinfection was the subject of an important report. Audsley and colleagues reported on the emergence of the M184V mutation in both antiretroviral therapy-naïve and -experienced patients who received entecavir for HBV in the setting of HBV and HIV coinfection (Abstract 63). Entecavir, a guanosine nRTI that was approved by the US Food and Drug Administration in 2005 for HBV treatment, has recently received attention for its previously unreported anti-HIV activity *in vitro* and *in vivo*. The investigators for this study reviewed the effect of entecavir on plasma HIV RNA levels in an international, multicenter retrospective cohort of 17 HIV and HBV coinfecting patients who had received entecavir monotherapy. There were 17 patients, of whom 10 were antiretroviral-naïve and 7 were antiretroviral-experienced. Naïve patients experienced a median plasma HIV RNA level reduction of 1.0 log₁₀ copies/mL after a median 113 days on entecavir, whereas antiretroviral therapy-experienced patients had a 1.1 log₁₀ copies/mL drop in plasma HIV RNA level after a median of 96 days on the drug. Twelve of the patients with HIV polymerase sequencing revealed an M184V mutation in 3 antiretroviral-naïve and 3 -experienced patients. Of the 3 patients with antiretroviral drug experience, all had been exposed to lamivudine. Both reduction in HBV viral load and length of time on entecavir were statistically significantly associated with selection of the M184V mutation. The authors cautioned that entecavir monotherapy should not be used in HIV and HBV coinfecting patients given this selection for the M184V mutation, and they issued a reminder that

all HBV-seropositive patients should undergo HIV testing before initiation of HBV therapy.

Antiretroviral Therapy–Naïve Patients and Resistance

Several abstracts explored the impact of low-frequency minor drug-resistant variants or quasispecies on clinical outcome. Two (Abstracts 83, 879) examined clinical outcomes in antiretroviral treatment-naïve patients who were found to have low-frequency mutants despite sensitive conventional genotypes at baseline. Another report (Abstract 892) compared reported rates of primary drug resistance with clinical treatment outcomes in antiretroviral treatment-naïve patients who began standard antiretroviral therapy.

Minor Populations of Y181C

Paredes and colleagues (Abstract 83) reported additional results from the AIDS Clinical Trials Group A5095 case-cohort study (previously described as a randomized trial comparing the efficacy of 3 regimens consisting of zidovudine/lamivudine and abacavir or efavirenz or abacavir and efavirenz). The main study results revealed that triple-nRTI therapy was inferior to the efavirenz-based regimens and illustrated how baseline NNRTI resistance more than doubled the risk of virologic failure. In subjects without NNRTI resistance by bulk sequencing who met criteria for virologic failure (≥ 200 copies/mL at 16 weeks), blind assays by allele-specific PCR were performed to test for the presence of minor populations with K103N and/or Y181C. The authors then compared the prevalence of these minority NNRTI-resistant variants among virologic failures and nonfailures in the evaluable random cohort. The presence of preexisting minority Y181C mutants was associated with more than 3-fold increased risk of virologic failure to first-line efavirenz-based antiretroviral therapy, even among adherent subjects. The authors noted, however, that the mutants were present in very low levels, that their proportions overlapped in sub-

jects with and without virologic failure, and that some subjects with Y181C mutants still achieved long-term virologic suppression on efavirenz-based antiretroviral therapy. They did not detect an association between minority K103N mutants and increased risk of virologic failure.

Metzner and colleagues also explored the prevalence and clinical significance of minority quasispecies in 220 antiretroviral therapy-naïve patients in Germany (Abstract 879). Baseline samples were analyzed retrospectively in patients who had begun tenofovir/emtricitabine and either a ritonavir-boosted PI or an NNRTI. Minority variants were identified in 27 patients. The K65R, K103N, and M184V variants were detected by allele-specific, real-time PCR in 4 (1.8%), 10 (4.6%) and 17 (7.9%) patients, none of whom was identified using conventional genotyping (4 patients had 2 mutations). At 24 weeks of follow-up on antiretroviral therapy, 21 patients had a plasma HIV RNA level below 50 copies/mL, 4 were lost to follow-up, and 2 had HIV RNA levels that did not become undetectable, likely the result of nonadherence. Of those patients with K103N, only 2 had begun an NNRTI-based regimen, and they had undetectable plasma HIV RNA levels at follow-up. The authors concluded that those mutations present as quasispecies were not associated with virologic failure in patients initiating antiretroviral therapy.

Fessel and colleagues (Abstract 892) assessed all antiretroviral treatment-naïve patients with wild-type HIV by standard genotypic resistance testing and compared the rates of baseline resistance with rates of virologic failure. They identified 126 patients with wild-type HIV who had received at least 6 months of antiretroviral therapy. Six (4.8%) patients experienced virologic failure because of nonadherence, and 120 patients had undetectable plasma HIV RNA levels (< 75 copies/mL). Of the 111 regimens described, 41 were ritonavir-boosted PI-based regimens and 70 were NNRTI-based regimens. Using standard genotype testing, the investigators compared local rates of primary

drug resistance of 10% to 15% with the less than 5% of virologic failure found in patients with wild-type HIV who initiated antiretroviral therapy; they concluded that this type of analysis should continue to ensure that low-frequency mutations do not compromise the utility of standard genotyping.

Ritonavir-boosted Atazanavir Monotherapy Maintenance

McKinnon and colleagues (Abstract 890) reviewed the genotypic resistance results of 5 patients who experienced viral rebound during the ACTG 5201 study of atazanavir/ritonavir simplified maintenance therapy. Five subjects with plasma HIV RNA levels ranging from 508 copies/mL to 21,652 copies/mL, had no major PI resistance by standard genotyping or single genome sequencing. Minor mutations were detected; however, none was identified as likely to alter susceptibility to atazanavir per the Stanford drug resistance database. All patients had resuppression on another ritonavir-boosted PI regimen. The authors encouraged further investigation of this simplified low-risk maintenance therapy.

Protease Inhibitor Resistance and L76V

Norton and colleagues (Abstract 854) queried a commercial database (Monogram Biosciences, Inc) to identify isolates with at least 1 PI mutation with the objective of quantifying the frequency with which the L76V mutation occurred and its effect on susceptibility to other PIs either alone or with other PI-associated mutations. The L76V mutation was present in only 3.1% of the database isolates queried and was associated with a decreased susceptibility to lopinavir, darunavir, amprenavir, and indinavir. It notably did not affect susceptibility to other PIs including atazanavir, saquinavir, tipranavir, and nelfinavir. An atomic model was proposed to explain the meaning of the L76V mutation on the nearby S2 pocket, based on the known differential penetration of various PIs at that site. The presence of other PI mutations notably increased the susceptibility to

atazanavir and saquinavir. This mutation was seen in a higher incidence at the time of failure to lopinavir/ritonavir monotherapy.

De Meyer and colleagues (Abstract 874) presented detailed resistance characterization of patients who experienced virologic failure in the darunavir/ritonavir arm of the randomized, controlled TITAN trial comparing lopinavir/ritonavir with darunavir/ritonavir in a treatment-experienced population that was naive to both darunavir/ritonavir and lopinavir/ritonavir. Ten percent of patients in the darunavir/ritonavir arm experienced virologic failure, compared with 22% of patients in the lopinavir/ritonavir arm. The following primary PI mutations developed in the darunavir/ritonavir failures: V32I in 3 patients, I47V and V76V in 2 patients, and I54L in 1 patient. Fewer virologic failures arose in the darunavir/ritonavir arm than in the lopinavir/ritonavir arm that lost susceptibility to any other PI based on phenotypic analysis and confirmatory genotypic interpretation.

Enfuvirtide and Resistance

Several abstracts focused on resistance mutations developing during treatment with the fusion inhibitor enfuvirtide. Poveda and colleagues (Abstract 850) presented the details of clonal analysis of a total of 23 plasma samples from 10 patients who experienced virologic failure on enfuvirtide. They performed clonal analysis and analyzed the Rev response element and the gp41 open-reading frame. The high-affinity Rev binding site was highly conserved and was not modified after the selection of enfuvirtide-associated resistance mutations. Mutations V38A and V38E statistically significantly altered the secondary structure of the high-affinity Rev binding site; this alteration in the critical region of the Rev response element could potentially interfere with HIV-1 replication. The authors hypothesized that such impairment could confer virologic and immunologic benefits in the setting of incomplete viral suppression on enfuvirtide.

Svicher and colleagues (Abstract 851) analyzed 181 sequences of HIV-1

gp41 and observed 88 enfuvirtide-treated patients clinically from baseline to week 48. They identified 3 Rev mutations, of which 2 (E57A and N86S) were statistically significantly correlated with known enfuvirtide-resistance mutations (Q40H and L45M in gp41; bootstrap, 0.78; $P < .05$). The E57A Rev mutation in particular was associated with increased viremia ($P = .006$) and a loss of CD4+ cells ($P = .04$) from baseline to week 48. The Rev N86S mutation at baseline was predictive of on-treatment development of enfuvirtide mutations Q40H + L45M ($P = .01$). Consequently, the question raised was whether Rev mutations may be driving the evolution of enfuvirtide resistance.

CCR5 Antagonists

In vivo evidence of evolution of CXCR4 tropic virus from CCR5-tropic virus.

HIV coreceptor switching and emergence occurs in approximately 50% of treatment-experienced patients. Patel and colleagues (Abstract 245) characterized *env* genes to understand the evolutionary pathway from CCR5 to CXCR4 usage, utilizing phylogenetic and phenotypic analysis of *env* gene. They found patterns that were consistent with accumulations of mutations over time, with evolution occurring from CCR5- to mixed-tropic to CXCR4-tropic *Env*.

Enhanced Sensitivity Tropism Assay

Hunt and colleagues (Abstract 864) reported on the improved detection of preexisting minority CXCR4 mutants using a modified assay with enhanced sensitivity for CXCR4-using variants. HIV-infected patients ($n = 57$) with drug-resistant viremia (> 1000 copies/mL) on a non-CCR5-inhibitor-based regimen were tested by the standard tropism assay and a new modified, more sensitive assay every 4 months. The standard assay, which picks up as little as 10% minority X4 populations, found 70% R5, 26% dual-mixed, and 4% X4 virus at baseline. At 1 year, 15% of those originally identified by standard assay as R5 were reclassified as dual-mixed tropic by the standard assay. Of the viruses that were reclassified at 1

year, 60% were persistently identified as dual-mixed via the enhanced sensitivity assay (which detects 0.1%-0.3% X4 populations). The more sensitive assay was also associated with reclassification of viruses at 1 year; however, reclassification took place in only 15% of those with R5-tropic virus at baseline. Further correlation of these findings with clinical outcomes is needed.

Changes in the V3 loop sequence were found to be associated with maraviroc treatment failure in patients enrolled in the MOTIVATE 1 and 2 trials. Clonal analysis of V3 loop sequences at baseline was compared with that at week 24 in 35 patients who experienced virologic failure on maraviroc as the result of a change in tropism or phenotypic resistance (Abstract 871). All cases of phenotypic resistance of the CCR5-tropic virus to maraviroc were associated with mutations in the V3 loop.

Two abstracts presented conflicting results regarding a recently developed assay for identification of CXCR4- versus CCR5-tropic viruses (Abstracts 919 and 920a). One assay (SensiTROP, Pathway Diagnostics) was reported by its developers to have good ability to detect and quantify the amount of both CXCR4-tropic and CCR5-tropic HIV virus (Abstract 919). The assay uses heteroduplex tracking technology to detect CXCR4-tropic virus with numerous mutations in the V3 loop by forming heteroduplexes with the CCR5 V3 probes. This process was then modified to allow separation, detection, and quantitation of the CCR5-CCR5 homoduplex DNA hybrids and CXCR4-CCR5 heteroduplex DNA hybrids. Using this assay, the authors reported the ability to quantify X4-R5 DNA mixtures down to a level of 5% (interassay coefficient, 1.8%-16.9%), to determine X4:R5 ratios when the plasma HIV RNA level is more than 1000 copies/mL, and to accurately detect CXCR4-tropic HIV when present at only 1% of the amount of CCR5-tropic virus.

In contrast, Tressler and colleagues (Abstract 920a), presented a less favorable assessment of the same assay (SensiTROP) compared with another assay (Trofile, Monogram Biosciences, Inc). They calculated values for the sen-

sitivity and specificity of the SensiTROP assay relative to the Trofile by retesting stored samples in a blinded manner from 100 HIV-infected, treatment-experienced patients who had participated in the maraviroc Expanded Access program with the SensiTROP assay. To determine the sensitivity, specificity, positive predictive value, and negative predictive value, the authors considered samples that tested as R5 at baseline and screening to be true positives ($n = 40$) and samples that tested dual-mixed or X4 at baseline to be non-R5 ($n = 39$) per their Trofile assay results. The SensiTROP assay identified only 19 of 39 non-R5 viruses; the authors determined a non-R5 detection sensitivity of 42.4% and a specificity of 92.5% for this test. The utility of this assay was questioned given its failure to identify dual-mixed or X4 virus in more than 50% of samples.

Integrase Inhibitors

Hackett and colleagues (Abstract 872) explored integrase inhibitor polymorphisms with the objective of understanding pathways to resistance, potential group subtype effects, and the prevalence of resistance-associated mutations. Analysis included phylogenetic analysis of 1265 integrase inhibitor-naïve subjects from diverse continents, of which 1200 were identified as group M, 100 as group O, and 4 as group N strains. Of 288 amino acids, 42% were polymorphic at a level of 1% or greater. They noted that the catalytic regions were highly conserved and that residues 148 and 155 were associated with primary resistance. Some known resistance mutations were identified as naturally occurring polymorphisms including V72I (55%), L74M (5% of group M), T97A (5%), T112I (11% of group M and 35% of group O), V151I (2%), K156N (1%), E157Q (4%), V165 (5%), and I203M (3%).

In terms of resistance testing for the integrase inhibitors, Abstracts 881 and 882 presented data on novel resistance testing methods from 2 manufacturers. Smith and colleagues presented data on integrase genotypic reagents for analysis of 81 diverse HIV-

1 strains including subtypes A, B, C, D, F, G, CRF01, and CRF02 (Abstract 881) from diverse nations. Using the “Celera” prototype HIV-1 integrase genotyping reagents, they amplified the catalytic core domain of the integrase in 83 of 84 samples (98%). Although they found many polymorphisms in this key domain, no polymorphisms were located in resistance-associated codons. Henry and colleagues (Abstract 882) presented their data on a novel phenotypic drug susceptibility assay based on the generation of recombinant HIV-1 using yeast recombinant cloning technology.

Etravirine and Resistance

Several abstracts presented analyses of cohorts with heavy NNRTI exposure for prevalence of mutations and eligibility for etravirine as second-line therapy (Abstracts 865-868). Sungkanuparph and colleagues (Abstract 865) analyzed the mutational patterns in a cohort of 158 HIV-infected patients in Thailand for whom treatment with NNRTI-based regimens had failed (84.2% nevirapine, 15.8% efavirenz). Etravirine-associated mutations were found in 82.9% of patients, including 59.5% Y181C/I/V, 33.5% G190A/S, 8.4% V179D/F, 4.4% V106I, 0.8% V90I, 0.8% A98G, 0.8% L100I, and 0.8% K101E/P. Of 131 patients with etravirine-associated mutations, 92 (70.2%) had fewer than 3. The majority of these 92 etravirine-eligible patients also had at least 2 active nRTIs available to them based on genotype results (69 subjects, or 75%). Such findings beg routine use of genotype testing to assist with second-line therapy selection in resource-poor settings and suggest that etravirine-based therapy is a hopeful option for second-line therapy despite NNRTI-based treatment exposure in such settings.

Likewise, Picchio and colleagues (Abstract 866) presented an analysis of HIV genotypic data to determine the preponderance of isolates that would be eligible for etravirine (fewer than 3 etravirine-associated resistance mutations). The investigators reviewed a large clinical database (Virco Lab, Inc) of samples submitted from 1999 until

2007 and found 89,113 samples that met the definition for NNRTI resistance based on the IAS-USA mutation list. Of these, 40% had no etravirine associated mutations, 36.7%, 16%, and 7.3% harbored 1, 2, and 3 or more etravirine-associated resistance mutations, respectively. The 4 most frequently occurring etravirine-associated mutations, in descending order of frequency, were Y181C, G190A, K101E, and L100I. Overall, only 7.3% of clinical isolates with known NNRTI resistance harbored 3 or more etravirine-associated mutations. The authors did not comment on any knowledge of whether samples were collected on or off therapy or whether patients with multiple resistance-test results with different NNRTI mutations were pooled in any way. They also noted that 95,019 samples met the criteria for NNRTI resistance based on the commercial biologic cutoff values that yielded similar results, which were not presented.

In a Nigerian cohort (Abstract 867) of patients with predominantly non-subtype-B HIV (CRF02, 43%; G, 43%; A, 5%; CRF06, 4%; recombinant, 3%; other, 2%), 214 patients with virologic failure on an NNRTI-based regimen had genotypic analysis. In 32% of samples, there were no etravirine-associated mutations. There were 1, 2, and 3 or more mutations in 35%, 23%, and 10%, respectively, and the presence of etravirine mutations was found to be statistically significantly associated with length of time on NNRTI-based therapy. The 4 most frequently identified etravirine-associated mutations in the cohort were Y181C, G190A, A98G, and K101E.

Llibre and colleagues (Abstract 868) also found that a high degree of etravirine resistance was rare in their analysis of 1586 Spanish Resistance Laboratory samples with at least 1 NNRTI-associated resistance mutation based on the IAS-USA list. Only 1.14% of samples had more than 3 etravirine-associated resistance mutations, and 8.2% of samples had more than 2 such mutations.

Winters and colleagues presented virtual phenotype (a genotype interpretation) predictions of etravirine drug susceptibility and clinical (Virco Lab,

Inc) cutoff values (Abstract 873). They based their analysis on clinical isolates with drug-susceptibility phenotypes, viral genotypes, and a clinical regression model developed from data from the DUET trials. Ultimately, they defined 2 clinical cutoff levels, corresponding to predicted fold-change values associated with 20% or 80% loss of the response of subjects infected with HIV-1 wild-type strains. The virtual phenotype predicting etravirine resistance ranged from a 0.9 fold-change for wild-type isolates to a 200-fold change. Based on their analysis, they found a 20% and 80% loss of etravirine response in patients with 1.6 and 27.6 etravirine fold-changes in susceptibility, respectively. Patients receiving etravirine with an etravirine fold-change of less than 20% ($n = 355$), 20% to 80% ($n = 413$), and more than 80% ($n = 85$) had median reductions in plasma HIV RNA levels of $-2.6 \log_{10}$, $-2.3 \log_{10}$, and $-1.3 \log_{10}$ copies/mL, and 38%, 24%, and 15%, respectively, had plasma HIV RNA levels below 50 copies/mL at 8 weeks. By week 24, these same patients, defined by their baseline clinical cutoff category, had plasma HIV RNA levels below 50 copies/mL in 55%, 37%, and 26%, respectively.

Adherence and Resistance by Antiretroviral Class

Gardner and colleagues (Abstract 777) presented an adherence analysis by class of antiretroviral therapy from the FIRST study, a prospective, randomized, antiretroviral-therapy-strategy trial for 903 antiretroviral therapy-naïve patients, of which 446 were on an NNRTI-based regimen and 457 were on a PI-based regimen. Adherence was assessed at 7 days, 1 month, 4 months, and then every 4 months thereafter. Genotypic testing was also performed at virologic failure (plasma HIV RNA levels above 1000 copies/mL). Patients were observed for a median of 5 years, and the mean baseline CD4+ count was 211 cells/ μ L.

Increased NNRTI resistance was associated with decreased adherence in the NNRTI arm but not the PI-regimen arm. Hazard ratios for resistance in the NNRTI arm based on level of reported

adherence were 2.3 (range, 1.4-3.7) for people with 80% to 99% adherence, and 6.5 (range, 2.9-10.7) in the 80% adherent group compared with the 100% adherent people. The median time to virologic failure, however, was 1.2 years on the PI-based regimen as opposed to 3.0 years on the NNRTI-based regimen. Though both arms had similar rates of overall resistance at virologic failure (28%, NNRTI arm; 30%, PI arm), only 8% of patients in the PI-based arm had PI resistance, whereas 25% of patients had NNRTI resistance in the NNRTI-based treatment arm. The bulk of resistance identified in patients on the PI strategy was nRTI-associated. Although the study confirms the association between adherence, NNRTI-based regimens, and resistance, the authors acknowledged that the study failed to obtain information on differential adherence, which could explain some of the findings.

Cozzi-Lepri and colleagues (Abstract 894) also reviewed the incidence of resistance by class in their large United Kingdom cohort of antiretroviral therapy-naïve patients who had initiated continuous antiretroviral therapy consisting of 2 nRTIs plus either an NNRTI ($n = 5080$) or a ritonavir-boosted PI ($n = 929$) between 1998 and 2005. Of the 1016 patients who experienced the first virologic failure, 564 (56%) had genotypic results recorded. At 7 years, the rate of resistance was 19% for at least 1 nRTI mutation, 17% for at least 1 NNRTI mutation, and 3% for at least 1 major PI mutation. Detection of class-specific mutations was less likely in patients who initiated PI-based regimens than in those on NNRTI-based regimens. No difference was found in the rate of nRTI mutations associated with PI- versus NNRTI-based regimens.

Treatment Interruption and Resistance

Danel and colleagues (Abstract 778) analyzed data from the Trivacan Trial, a fixed-cycle trial of 2-months-off, 4-months-on antiretroviral therapy in patients with high pretreatment CD4+ cell counts in West Africa. Originally, a 3-arm trial comparing continuous therapy

with CD4+ cell count–guided therapy and a cycle of antiretroviral treatment of 2 months off then 4 months on, the CD4+ cell count–guided arm was terminated because of high rates of morbidity. Results of the remaining 2 arms were analyzed comparing mortality, severe HIV-related morbidity, and percentage of patients with a CD4+ count greater than 350 cells/ μ L at 24 months.

Of the 435 patients who underwent randomization to continuous versus 2-months-off, 4-months-on therapy with zidovudine/lamivudine/efavirenz, the incidence of mortality was 0.45 per 100 person-years in the continuous group versus 0.45 per 100 person-years in the 2-months-off, 4-months-on treatment group, and the incidence of severe HIV-associated morbidity was 6.8 per 100 person-years in the continuous therapy arm and 9.1 per 100 person-years in the fixed-cycle therapy arm. At 24 months, 94% of patients in the continuous therapy arm reached a CD4+ count of 350 cells/ μ L or greater, as did 85% of patients in the 2-months-off, 4-months-on treatment group.

The authors noted important secondary analyses. Short-term cost was lower in the 2-months-off, 4-months-on treatment group ($P < .001$); however, this cost savings came in exchange for increased resistance in the 2-months-off, 4-months-on antiretroviral therapy group (21% vs 9% of patients with at least 1 resistance mutation; $P = .007$). Of resistance mutations, 62% were NNRTI- and 23% were lamivudine/emtricitabine-associated. Although clinically noninferior, the 2-months-off, 4-months-on therapy regimen led to unacceptable resistance rates.

Treatment Interruption and Minority Drug-Resistant Viral Populations

Wang and colleagues (Abstract 877) analyzed 14,779 viral genomes from plasma samples taken at several time points after treatment interruption of up to 59 weeks from 3 patients using the parallel allele-specific sequencing assay. Low-level virus replication during nonsuppressive antiretroviral therapy was different from that found in vi-

ruses during high levels of replication. After treatment interruption, minority drug-resistant viruses increased in the high-level viral replication grouping and persisted for more than 9 weeks before being replaced by single-drug-resistant viruses and finally by wild-type viruses.

PI Probability Estimations and Resistance Testing in Heavily Treatment-experienced Patients

King and colleagues (Abstract 773) presented a small proof-of-concept study of probability estimations for PI resistance to aid in the selection of antiretroviral regimens in treatment-experienced patients as an alternative to exclusive use of phenotypic testing. Twenty-three subjects with PI resistance (median, 34-fold change) underwent randomization to either a regimen chosen based on phenotypic analysis alone or a regimen chosen using the probability-estimations approach. The authors defined the probability-estimations method as an integration of expected drug exposure with susceptibility testing to estimate each patient's probability of achieving trough concentrations above the protein-binding IC_{50} level. They observed patients serially after randomization and found that changes in plasma HIV RNA levels at weeks 4, 8, and 15 were not statistically different between the 2 arms.

Nonsubtype-B HIV-1 Infections

Several abstracts highlighted resistance issues in nonsubtype-B viruses. Differences in polymorphisms resulted in substantial structural changes in CRF01_AE compared with subtype B virus (Abstract 900). Using crystallographic techniques, the protease p1-p6 substrate structure of CRF01_AE was compared with that of nonsubtype-B virus. The CRF01_AE subtype showed a significant change in the flap-hinge region of protease and revealed a unique interaction at key sites that was not seen in the subtype B structure. Such sequence polymorphisms in the CRF01_AE subtype confer substantial structural changes within protease compared with the subtype B protease structure.

Chaplin and colleagues (Abstract 901) presented subtype, genotype, and resistance patterns from a Nigerian panel of 304 patients with virologic failure after more than 6 months of antiretroviral therapy. Based on *pol* sequencing in 214 patients, the following subtypes were identified: 43% CRF02, 43% subtype G, 5% subtype A, 4% CRF06, and 5% other. Substantial differences in TAM development were found in these subtypes that differed from the pattern seen most frequently in subtype B virus. Subtype B virus develops TAMs via the “TAM1” pathway (T215Y, M41L, L210W, D67N, confers more cross resistance to didanosine and tenofovir and occurs more frequently) or the “TAM2” pathway (K70R, K219QE, T215F, D67N, which confers less cross resistance). In contrast, investigators found that TAM2 mutations were twice as common as TAM1 in subtype G and that M41L and L210W were quite uncommon in the panel overall and particularly low in subtype CRF02 than in other subtypes.

Investigators from the Aquitaine cohort presented an analysis of the relationship between recent seroconversion, HIV-1 subtype, and transmission of resistance among patients identified in their southwestern French cohort between 1996 and 2006 (Abstract 902). Reverse transcriptase and protease sequences as well as phylogenetic analysis were obtained. The authors identified 263 patients as recent seroconverters within 18 months, of which 84.4% clustered with subtype B and 15.6% clustered with nonsubtype-B virus. Twenty-four clusters of transmission were identified, of which 22 were subtype B and only 1 nonsubtype B. The frequency of segregation into clusters was higher within the B sequences than within the nonsubtype-B sequences (35.1% vs 4.9%; $P < .0002$). Three clusters with resistant isolates were identified, and the prevalence of resistance in clustering viruses was 12.5% versus 14.7% in nonclustering isolates. The high frequency of segregation into clusters suggested forward transmission events in subtype-B-infected patients and suggested that such a pat-

tern could result in high transmission rates of drug-resistant strains.

HIV-2 and Resistance

Rodes and colleagues (Abstract 885) reported on resistance outcomes in 22 HIV-2-infected patients who started antiretroviral therapy and were observed for 12 months. Notably, 15 of 22 patients received triple-nRTI therapy (zidovudine/lamivudine/abacavir), and the others received nevirapine/zidovudine/lamivudine and indinavir/abacavir/danosine regimens. At 12 months, 19 of 22 (86%) patients experienced treatment failure of these regimens. Of failures, 84% developed M184V mutations, 3 had virus that developed K65R in the absence of tenofovir exposure, and there were no Q151M mutations. The authors noted how quickly and differently RT mutations form in HIV-2 compared with HIV-1, and they urged caution and careful selection of drug-treatment combinations and treatment strategies in HIV-2-infected patients.

Roquebert and colleagues (Abstract 886) examined the *in vitro* susceptibility of HIV-2 to the integrase inhibitors raltegravir and the investigational agent elvitegravir using the ANRS trial assay method in 50 patients enrolled in the French HIV-2 cohort. Despite 40% heterogeneity between HIV-1 and HIV-2 integrase genes, phenotypic susceptibility to the integrase inhibitor was similar in both viruses, suggesting that these integrase inhibitors could be useful therapeutic options in HIV-2-infected people.

Resistance Testing from Dried Blood Samples

Youngpairoj and colleagues presented promising findings regarding the use of dried blood samples stored for 1 year at 4°C (Abstract 927). Previously, the group showed that resistance genotypes generated from dried blood samples were highly concordant with those obtained from plasma. Realizing that storage of samples below –20°C is often not feasible in RLS, the authors tested the hypothesis that dried blood samples could be genotyped efficiently

after storage at 4°C for 1 year.

The investigators described their method of storage for 40 dried blood samples analyzed from HIV-1 subtype-B-infected people. A small quantity of blood from each specimen was stored onto 903 filter paper cards, which were dried overnight at room temperature and stored in a sealed plastic bag with desiccant. At 1 year, resistance testing was done, and a real-time PCR assay was performed to amplify a smaller *pol* fragment; a nested PCR step was used. Only 23 of 40 specimens could be successfully genotyped using standard resistance testing, however, when the specimens were tested using the in-house reverse transcriptase-nested PCR assay, 38 of the 40 specimens were successfully genotyped. They attributed this improvement in genotyping to their in-house nested PCR protocol with quality-controlled reagents to overcome possible losses in the HIV-1 RNA integrity. Such methods could prove very useful in RLS.

Acute HIV Infection

Treatment of Acute HIV Infection

Methods of treatment in acute HIV infection were reported in several presentations. Most data were drawn from cohorts of patients with acute HIV infection and were therefore somewhat limited by selection bias. Results were conflicting; some presentations concluded that there was a lack of benefit in terms of CD4+ cell count (Abstracts 694, 697) and viral load (Abstracts 693, 697). In contrast, Abstracts 695, 696, and 698b highlighted favorable CD4+ or viral load outcomes associated with early initiation of antiretroviral treatment.

Studies Showing Early Treatment Is Not Beneficial

Setpoint or viral load. Recent nonrandomized trials of treatment of acute and recent HIV seroconversion have failed to show a clinical benefit. Given the known differences in the immunologic picture of acute versus recent HIV, there may be a treatment benefit associated with viral suppression

on antiretroviral therapy in very early, acute HIV seroconversions.

Volberding and colleagues (Abstract 693) reviewed the results of ACTG 371 and compared the degree of viral suppression after treatment with a PI-based regimen among subjects acutely infected with HIV-1 (estimated infection within 14 days) with that of subjects who have been infected recently (estimated infection in the prior 14 to 180 days). Patients were treated until their plasma HIV RNA level was undetectable for at least 52 weeks, at which point treatment was interrupted until either the HIV RNA level was greater than 5000 copies/mL on 3 or more occasions or more than 50,000 copies/mL on more than 2 occasions followed by reinitiation of treatment until the HIV RNA level was again undetectable for at least 52 weeks. Of the 73 patients (28 acute infections, 45 recent infections) who entered treatment interruption, 40% overall sustained a plasma HIV RNA level below 5000 copies/mL after 24 weeks of treatment interruption. However, no statistically significant difference in outcome was seen when the authors compared those who began in the setting of acute infection with those who began treatment in the setting of recent infection.

CD4+ decline. Desquilbet and colleagues reported data from the French ANRS PRIMO cohort of subjects acutely infected with HIV-1 (within 2 months of infection). The cohort included 73 patients who received antiretroviral therapy for 6 months to 24 months after enrollment and 149 patients who remained untreated for 3 months or more (Abstract 694). Because the analysis was nonrandomized, the authors created a propensity score to correct for selection bias. They reported the time to CD4+ count decline below 350 cells/μL from baseline and generated Kaplan-Meier curves. Sixty-three patients in each group were matched by propensity score. The proportion of individuals who maintained a CD4+ count greater than 350 cells/μL 36 months after baseline did not differ between the 2 groups. It was concluded, therefore, that relatively short-course

antiretroviral therapy did not confer a statistically significant benefit in preventing or delaying a CD4+ count decline to below 350 cells/ μ L.

Pantazis and colleagues (Abstract 697) reported a lack of beneficial effect on both CD4+ cell count and viral load set point in their analysis of 348 patients who received transient early antiretroviral treatment within 6 months of seroconversion compared with 675 patients who deferred treatment in the Concerted Action on SeroConversion to AIDS and Death in Europe (CASCADE) cohort. Both viral load set points ($P = .43$) and AIDS rates were similar between the early and deferred groups at follow-up.

Immune Modulator in Addition to Antiretroviral Therapy During Acute HIV

Markowitz and colleagues shared the results of a multicenter, 48-week, open-label, randomized phase II study of 4 weeks of cyclosporine A in addition to PI-based antiretroviral therapy in patients with acute or recent HIV infection. Fifty-six patients underwent randomization 2:1 to cyclosporine plus antiretroviral treatment versus antiretroviral treatment alone. There were no statistically significant differences in mean time to a plasma HIV RNA level below 50 copies/mL, CD4+ cell count at weeks 12, 24, and 48, or change from baseline CD4+ cell count. Thus, 4 weeks of cyclosporine A in addition to antiretroviral therapy did not add any immunologic or virologic benefit in acutely or recently HIV-infected patients.

Studies Showing Early Treatment of Acute HIV Is Beneficial

CD4+ count and viral load. From their observational multicenter cohort, Prazuck and colleagues presented favorable long-term effects on CD4+ count and viral load in acutely infected patients who began antiretroviral treatment very early after seroconversion (Abstract 695). All patients were enrolled within 10 weeks of estimated seroconversion and “self-decided” to initiate antiretroviral therapy. Twenty

patients were in the treatment group (treated for 1-7 years; median, 2.3 years) and 18 patients in the untreated group. The CD4+ counts and plasma HIV RNA levels at serial intervals were compared. Untreated patients experienced a median monthly loss in CD4+ cells that was twice as high as in the treated group following cessation. Statistically significant differences were found between the proportions of treated and untreated patients whose HIV RNA levels remained below 400 copies/mL at weeks 48 (42.1% vs 56%), 96 (36% vs 0%), and 144 (31% vs 0%), with $P < .001$ after treatment cessation. The HIV RNA levels of 25% of treated patients were able to stay below 50 copies/mL at 144 weeks after treatment cessation compared with none in the untreated group. Steingrover and coauthors (Abstract 698b) also found lower HIV RNA levels 36 weeks after treatment interruption in patients with acute HIV who underwent early antiretroviral treatment for 24 or 60 weeks ($n = 37$; HIV RNA level, 4.0 \log_{10} copies/mL) than in untreated patients ($n = 11$; HIV RNA level, 4.9 \log_{10} copies/mL; $P < .005$). Statistically significantly higher CD4+ counts were seen in treated patients at 36 weeks after treatment cessation than in untreated patients (581 vs 349 cells/ μ L; $P < .05$).

Coinfection with GB Virus C Slows HIV

Many studies have suggested that GB virus C (GBV-C) has a beneficial effect on HIV pathogenesis. Giret and colleagues (Abstract 273) demonstrated the association between GBV-C viremia and lower T-cell activation in their cohort of recently infected patients. Of the 40 patients enrolled in the Sero-logic Testing Algorithm for Recent HIV Seroconversion (STARHS), 24 were GBV-C infected. Two known markers of T-cell activation, CD38+ CD8+ T cells and CCR5+ CD8+ T cells ($r = 0.65$; $P < .01$), were highly correlated. The authors further demonstrated that GBV-C-infected subjects had a lower percentage of all of these T-cell activation markers. This mechanism may

help explain the observed protection against progression to immunodeficiency by this virus.

Race, Ethnicity, and Sex as Predictors of Virologic Outcomes and Mortality

Palella and colleagues (Abstract 530) analyzed mortality risk in 2383 patients from the HIV Outpatient Study (HOPS) in 7 US cities from 1999 to 2005. Participants had a mean follow-up time of 5.9 years. They noted increased death rates among people with public compared with nonpublic insurance: 4.0 vs 1.3 deaths/100 person-years, respectively. Non-Hispanic blacks also had higher death rates (3.3 deaths/100 person-years) than those of nonblacks or Hispanics (1.9 deaths/100 person-years). In a multivariate analysis that controlled for other known HIV-related mortality risks, having public insurance, being of non-Hispanic black ethnicity, being of older age, and having a lower CD4+ cell count at antiretroviral therapy initiation were all associated with increased mortality risk.

The virologic outcomes of African Americans (AAs) versus European Americans (EAs) initiating therapy between 1996 and 2004 were examined in 1794 participants (900 AA; 894 EA) in the TriService AIDS Clinical Consortium HIV Natural History Study, a longitudinal US military cohort launched in 1987 (Abstract 809). Though most baseline parameters were similar, AAs had lower CD4+ counts at diagnosis than did EAs (mean, 478 vs 552 cells/ μ L, respectively; $P < .0001$) and lower CD4+ counts at initiation of antiretroviral therapy (mean, 333 vs 367 cells/ μ L; $P = .004$). The authors completed a multivariate logistic regression analysis and found the odds of having a plasma HIV RNA level below 400 copies/mL at 6 months after antiretroviral initiation to be 0.5 for AAs compared with EAs (95% CI, 0.4-0.7; $P < .001$), after adjustment for age, sex, military rank, baseline plasma HIV RNA level and CD4+ count, prior AIDS events, prior antiretroviral use, antiretroviral regimen, hepatitis B coinfection, he-

moglobin level, and year of antiretroviral initiation.

Lemly and colleagues (Abstract 810) used a retrospective cohort of people receiving HIV care at a center in Nashville, Tennessee, to establish race, ethnicity, and sex differences in antiretroviral therapy use and mortality within the cohort. Unadjusted all-cause mortality rates did not differ significantly by sex but did differ between blacks and nonblacks (49 vs 31 deaths/1000 person-years; $P < .001$.) After adjusting for baseline clinical and demographic characteristics, death was associated with female sex, black race, and having injection drug use as an HIV risk factor. Both women and blacks were also less likely to be receiving antiretroviral therapy, even among persons with a baseline CD4+ count below 200 cells/ μ L.

In the Netherlands, ATHENA Cohort investigators took a slightly different approach (Abstract 817) by selecting patients initiating antiretroviral therapy between January, 1996, and May, 2005, and stratifying participants' CD4+ cell count restoration by region of origin. Of 4348 eligible patients, 2970 (68%) were from Western Europe or North America, 751 (17%) from sub-Saharan Africa, 157 (4%) from Southeast Asia, and 470 (11%) from Latin America or the Caribbean. The median increase in CD4+ cell count after 5 years of antiretroviral therapy was higher in patients from Western Europe or North America (360 cells/ μ L) than in patients from sub-Saharan Africa (320 cells/ μ L; P value for difference, .004.) There were no significant differences in patients from other regions. The estimated mean increases in CD4+ count were also higher in women than in men (an additional 27 cells/ μ L/year from 0-6 months; $P = .04$; and 11 cells/ μ L/year from 6-36 months; $P = .008$.)

Outcome Data from Large Randomized Control Trials and Longitudinal Cohort Studies

Riddler and colleagues (Abstract 776) examined the effect of baseline demographic and clinical parameters on treatment outcomes among par-

ticipants in the Adult ACTG A5142 trial. This trial randomized 753 treatment-naive, HIV-infected people to the class-sparing regimens of efavirenz plus 2 nRTIs, lopinavir/ritonavir plus 2 nRTIs, or efavirenz plus lopinavir/ritonavir. In a multivariate hazards analysis, a shorter time to virologic failure was inversely associated with age (HR, 0.81 per 10-year increase; 95% CI, 0.69-0.94; $P = .005$), female sex (HR, 0.73 for men vs women; 95% CI, 0.53-0.99; $P = .046$), baseline CD4+ count (HR, 0.88; 95% CI, 0.79-0.99; $P = .03$), and race (HR, 0.64 nonblack vs black as referent; 95% CI, 0.48-0.85; $P = .002$). For women, the risk of virologic failure was lowest and the time to treatment-limiting toxicity was longest in the lopinavir plus efavirenz arm.

Carr and Amin (Abstract 782) presented a meta-analysis of all randomized control trials and prospective cohorts conducted for more than 28 weeks and published or presented after January, 1996. They extracted data from 143 studies on 23,067 patients and defined their primary endpoint as undetectable HIV RNA levels by intention-to-treat analysis. The mean intention-to-treat success, defined as percentage of people with HIV RNA levels below 50 copies/mL, was 59% at the mean follow-up time of 14.3 months. Factors independently associated with higher rates of undetectable HIV RNA levels were nonwhite race, antiretroviral regimens for which dosage was assigned regardless of food intake, third-drug class (most favorable were ritonavir-boosted PI regimens), and nRTI backbone (most favorable were didanosine/lamivudine or didanosine/emtricitabine). The authors noted that these findings differ from results of some other large studies, in that success was correlated with older age and lower CD4+ cell count, and that prior injection drug use or AIDS diagnosis were not inversely associated with success.

A similar tactic was used by investigators from the ACTG and Antiretroviral Therapy Cohort Collaboration (ART-CC), who compared the outcomes of abacavir- and efavirenz-based antiretroviral therapy in the A5095 trial with those seen in ART-CC patients (Ab-

stract 783). Efavirenz was used more commonly in men, and median CD4+ counts were lower for patients initiating efavirenz versus abacavir (209 vs 251 cells/ μ L, respectively). The authors used findings from A5095 as a surrogate for efficacy and from the ART-CC as surrogate for effectiveness. As such, they determined that efficacy and effectiveness of efavirenz at 24 weeks was similar in the 2 groups (OR, 0.78 for A5095 vs ART-CC; 95% CI, 0.54-1.13), but effectiveness was significantly lower for abacavir (OR, 0.45 for A5095 vs ART-CC; 95% CI, 0.32-0.64). The percentage of participants reaching a 48-week AIDS or death endpoint also differed significantly: 3.1% in A5095 and 6.9% in the ART-CC ($P < .01$).

Lau and colleagues (Abstract 785) compiled data from the Johns Hopkins HIV Clinical Cohort to develop a prediction model for AIDS-defining illnesses or death after initiation of antiretroviral therapy. Their analysis included data from 2961 participants in the cohort who initiated antiretroviral therapy between 1996 and 2004, among which there were 772 AIDS-defining illnesses and 463 deaths over 10,728 person-years of follow-up. Variables predictive of shorter time to AIDS-defining illness or death were age, history of injection drug use, cocaine use, anxiety, depression, *Pneumocystis jirovecii* pneumonia prophylaxis, prior AIDS-defining illness, CD4+ count, HIV RNA level, total lymphocyte count, hemoglobin level, and albumin level. The model was compared with a published model derived from the EuroSIDA cohort and was found to have slightly better discrimination at 6 months (0.73 area-under-the-receiver-operator curve compared with 0.65 for EuroSIDA).

Predictors of Response to Second-line Antiretroviral Therapy

Moore presented an analysis of response to second-line therapy from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), which includes data from 22 cohorts from the United States and

Canada (Abstract 41). The authors included data from 5057 cohort participants who had initiated antiretroviral therapy between 1996 and 2005, had virologic failure of their first regimen, changed antiretroviral regimens, and had documented virologic failure of their second regimen. They defined virologic failure as having an HIV RNA level above 1000 copies/mL 6 months after initiating a second-line regimen or any time after they had obtained a level below 400 copies/mL on the second-line regimen.

The authors found a steady decrease in both the incidence and the adjusted relative risk of second-line failure over time, with an incidence of 113.6 failures per 100 person-years between 1996 and 1997, decreasing to 15.1 per 100 person-years between 2004 and 2005. Median survival post-virologic failure of the second-line regimen was 7.1 years (95% CI, 6.5-7.8), and CD4+ cell count, HIV RNA level, and a history of AIDS at initiation of second-line treatment were all significantly associated with mortality. These 3 factors were predictive of mortality in an analysis limited to the 1276 patients who were antiretroviral-naïve at the start of their first potent antiretroviral regimen.

Cozzi-Lepri and colleagues (Abstract 797) undertook a similar analysis of participants for whom second-line therapy failed in the EuroSIDA Study, which began enrolling in 1994 and now has 72 participating sites throughout Europe. Forty-five percent of patients who initiated second-line therapy experienced virologic failure, with a definition similar to the NA-ACCORD study; median time from start of a second-line regimen to virologic failure was 39 months. Factors associated with a relative hazard of virologic failure of second-line antiretroviral therapy were viral load at the start of the second regimen (adjusted relative hazard [aRH], 1.20 per log₁₀ copies/mL higher; 95% CI, 1.04-1.40) and the use of nevirapine (aRH, 2.19; 95% CI, 1.38-3.50) or nelfinavir (aRH, 1.80; 95% CI, 1.13-2.87) as opposed to efavirenz in the second-line regimen. A substantial limitation to this study was that patients who changed antiretrovi-

ral therapy for reasons other than failure, like medication-associated toxicity or temporary suspension of treatment, were not excluded from the analysis.

Data from 982 participants in the Johns Hopkins and University of North Carolina prospective cohorts with virologic failure on their initial antiretroviral regimens were combined to determine the consequences of delay in antiretroviral regimen modification after confirmed virologic failure (Abstract 798). Delay in modification of the first antiretroviral regimen was associated with different HRs for death by regimen type: failing regimens containing PIs had an HR of 0.93 (95% CI, 0.87-0.99; $P < .03$) for each additional delay of 3 months (ie, patients who had a delay in switching antiretroviral therapy had a lower risk of death than those who switched immediately). However, patients experiencing failure of non-PI regimens, most of which contained NNRTIs, had an HR of 1.23 (95% CI, 1.08-1.40; $P = .002$) for each additional delay of 3 months compared with switching immediately. Delay in modification of first-line therapy was also associated with an increased HR for the combined endpoint of immunologic failure or death for those on non-PI regimens but not for subjects experiencing failure of a PI-based regimen or of second-line treatment regardless of regimen. Globally, a majority of patients initiate antiretroviral therapy with an NNRTI-based regimen, and efforts should be made to minimize the length of time spent on a virologically failing NNRTI regimen.

Wilkin and colleagues, reported findings from a meta-analysis of recent clinical trials involving CCR5 inhibitors (Abstract 800). They included 16 clinical trials with 37 total treatment arms and found that factors associated with CD4+ count gain were virologic suppression (estimated 12-cell/ μ L increase per 10% higher proportion of HIV RNA level below 50 copies/mL; $P < .0001$), baseline HIV RNA level (43-cell/ μ L increase per log₁₀ copies/mL increase; $P = .003$), and use of a CCR5 inhibitor (32-cell/ μ L increase; $P < .0001$). The fact that the use of a CCR5 inhibitor was associated with CD4+ count in-

creases, even after controlling for degree of virologic suppression, warrants further exploration of the role of CCR5 inhibitors in enhancement of the immune response.

Pharmacokinetic Considerations

CCR5 Antagonists

Maraviroc in the genital tract. Dumond and colleagues presented data on the levels of maraviroc, a CCR5 antagonist, in the female genital tract (Abstract 135LB). Cervicovaginal levels of maraviroc exceeded that of plasma throughout the dosing cycle. The AUC was approximately 4 times higher in the genital tract than in the plasma. The authors also performed vaginal biopsies and found levels that were generally higher than that found in the plasma, suggesting that maraviroc may be a useful agent for preexposure prophylaxis.

Nucleoside Analogue Reverse Transcriptase Inhibitors

Tenofovir concentration in cerebrospinal fluid. Best and colleagues presented data on the concentration of tenofovir in cerebrospinal fluid (CSF) (Abstract 131). They analyzed paired plasma and CSF samples from 63 subjects and found that tenofovir levels in the CSF were 4% of those in plasma. The CSF levels were below the IC₅₀ for wild-type HIV. The authors asserted that this would put subjects at risk for viral replication in the central nervous system, but clinical confirmation of this concern is needed.

Nonnucleoside Analogue Reverse Transcriptase Inhibitors

Pharmacodynamics of etravirine. Kakuda and colleagues presented combined data from 2 phase III studies of etravirine (Abstract 762). They did not find a relationship between the AUC or C_{min} and the probability of achieving a plasma HIV RNA level below 50 copies/mL. They did not find any subgroups that required dosing adjustment to improve outcomes.

Protease Inhibitors

Lopinavir/ritonavir formulations. Best and colleagues compared the pharmacokinetics of once-daily administration of lopinavir in liquid, soft-gel, and tablet formulations (Abstract 766a). The tablet formulation resulted in significantly higher trough concentrations than did the liquid or soft-gel formulations (3.7 µg/mL vs 1.1 and 1.6, respectively; $P < .05$).

Antimalarial drugs and lopinavir/ritonavir. Artemisinin-based regimens are being used increasingly for treatment of malaria throughout the world. German and colleagues investigated the interactions of lopinavir/ritonavir (inhibitor of CYP3A4) with fixed-dose combination of artemisinin/lumefantrine (substrate of CYP3A4) (Abstract 132). The addition of lopinavir/ritonavir significantly increased the levels of lumefantrine. The AUC increased 298%, and the maximum plasma concentration (C_{max}) increased 82%. The changes were highly variable among subjects. The levels of lopinavir and ritonavir were not affected significantly. The authors concluded that these drugs could be coadministered despite the interaction based on the excellent safety record for lumefantrine.

Rifampin and atazanavir/ritonavir. Haas and colleagues have previously presented data on the interaction of rifampin and atazanavir/ritonavir. They updated this trial with information from 3 subjects out of a planned sample size of 14 who received atazanavir 300 mg and ritonavir 100 mg twice daily in addition to rifampin 600 mg daily started 7 days before the atazanavir/ritonavir (Abstract 766b). All 3 participants experienced nausea and vomiting and had increased levels of hepatic transaminase. This prompted discontinuation of the study. The authors theorized that preinduction of

CYP3A4 by rifampin led to creation of a toxic metabolite of ritonavir or that inhibition of CYP3A4 by ritonavir blocked clearance of a rifampin metabolite, leading to toxicity.

Switch from atazanavir/ritonavir to unboosted atazanavir. Rodriguez-Novoa and colleagues presented data from a single-arm, open-label trial of 56 patients who changed from atazanavir/ritonavir to unboosted atazanavir after having adverse events from atazanavir/ritonavir such as jaundice or gastrointestinal distress. The average C_{min} value dropped from 880 ng/mL to 283 ng/mL after switching to unboosted atazanavir. Four subjects (7%) had a C_{min} value below the desired trough concentration of 150 ng/mL, 3 of whom were receiving tenofovir. The proportion of subjects with grade 3 or 4 bilirubin dropped from 29 (52%) to 7 (12%) after the switch. Virologic failure developed in 1 subject after a mean follow-up time of 10 months.

Conclusion

The 15th Conference on Retroviruses and Opportunistic Infections in Boston maintained the tradition of being the preeminent conference for the presentation of the latest data on antiretroviral therapeutics. This year's meeting was characterized by a balance of new discoveries and consolidation of existing knowledge. The field remains dynamic and, although progress in both the developed and developing worlds has been impressive, major challenges remain if we are to deliver and sustain the benefits of antiretroviral therapy to the global population in need.

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A list of all cited abstracts appears on page 69-77.

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Update of the Drug Resistance Mutations in HIV-1: Spring 2008

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This Spring 2008 version of the International AIDS Society–USA (IAS-USA) Drug Resistance Mutations Figures updates the figures published in this journal in August/September 2007.¹ The authors comprise the IAS-USA Drug Resistance Mutations Group, an independent, volunteer panel of experts charged with the goal of delivering accurate, unbiased, and evidence-based information on these mutations to HIV clinical practitioners. As for all IAS-USA panels, a rotation procedure is in place whereby 1 or 2 panel members periodically step down from panel participation and new members join. These rotations are designed to ensure that all IAS-USA expert panels remain diverse in member affiliations and areas of expertise.

The figures are designed for practitioners to use in identifying key mutations associated with viral resistance to antiretroviral drugs and in making therapeutic decisions. Updates are posted periodically at www.iasusa.org. Care should be taken if using this list of mutations in surveillance or epidemiologic studies of transmission of drug-resistant virus. Some amino acid substitutions, particularly minor mutations, represent polymorphisms that in isolation may not reflect prior drug selective pressure or reduced drug susceptibility.

The mutations listed have been identified by 1 or more of the following criteria: (1) *in vitro* passage experiments or validation of contribution to resistance by using site-directed mutagenesis; (2) susceptibility testing of laboratory or clinical isolates; (3) genetic sequencing

of viruses from patients in whom the drug is failing; (4) correlation studies between genotype at baseline and virologic response in patients exposed to the drug. The group reviews data that have been published or have been presented at a scientific conference.

Drugs that have been approved by the US Food and Drug Administration (FDA) as well as any drugs available in expanded access programs are included. They are listed in alphabetic order by drug class. User notes provide additional information as necessary. Although the Drug Resistance Mutations Group works to maintain a complete and current list of these mutations, it cannot be assumed that the list presented here is exhaustive. Readers are encouraged to consult the literature and experts in the field for clarification or more information about specific mutations and their clinical impact.

In the context of making clinical decisions regarding antiretroviral therapy, evaluating the results of HIV genotypic testing includes: (1) assessing whether the pattern or absence of a pattern in the mutations is consistent with the patient's antiretroviral therapy history; (2) recognizing that in the absence of drug (selection pressure), resistant strains may be present at levels below the limit of detection of the test (analyzing stored samples, collected under selection pressure, could be useful in this setting); and (3) recognizing that virologic failure of the first regimen typically involves HIV-1 isolates with resistance to only 1 or 2 of the drugs in the regimen (in this setting, resis-

tance most commonly develops to lamivudine or the nonnucleoside analogue reverse transcriptase inhibitors [NNRTIs]). The absence of detectable viral resistance after treatment failure may result from any combination of the following factors: the presence of drug-resistant minority viral populations, nonadherence to medications, laboratory error, drug-drug interactions leading to subtherapeutic drug levels, and possibly compartmental issues, indicating that drugs may not reach optimal levels in specific cellular or tissue reservoirs.

Revisions to the Figures for the Spring 2008 Update

In addition to minor formatting and color alterations, revisions to the figures include removal of the “expanded access” indication for etravirine because the drug was approved by the US FDA in early 2008. A new etravirine mutation, V179T, has been added to the figure bar, and user note 13 has been revised to reflect new information concerning etravirine mutations. Also, the expanded access indication for raltegravir has been removed because the drug was approved by the US FDA in late 2007.

Comments?

The IAS-USA Drug Resistance Mutations Group welcomes comments on the mutations figures and user notes.

(continued, page 67)

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MUTATIONS IN THE REVERSE TRANSCRIPTASE GENE ASSOCIATED WITH RESISTANCE TO REVERSE TRANSCRIPTASE INHIBITORS

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (nRTIs)¹

Multi-nRTI Resistance: 69 Insertion Complex² (affects all nRTIs currently approved by the US FDA)

| | | | | | | | | |
|-----------|-----------|--------------|--|--|--|--------------------|---|---|
| M | A | ▼ K | | | | L | T | K |
| 41 | 62 | 69 70 | | | | 210 215 219 | | |
| L | V | Insert R | | | | W | Y | Q |
| | | | | | | F | E | |

Multi-nRTI Resistance: 151 Complex³ (affects all nRTIs currently approved by the US FDA except tenofovir)

| | | | | | | | | |
|--|-----------|---|--------------|---|------------|------------|--|--|
| | A | V | F | F | Q | | | |
| | 62 | | 75 77 | | 116 | 151 | | |
| | V | I | L | Y | M | | | |

Multi-nRTI Resistance: Thymidine Analogue-associated Mutations^{4,5} (TAMs; affect all nRTIs currently approved by the US FDA)

| | | | | | | | | |
|-----------|-----------|-----------|--|--|--|--------------------|---|---|
| M | D | K | | | | L | T | K |
| 41 | 67 | 70 | | | | 210 215 219 | | |
| L | N | R | | | | W | Y | Q |
| | | | | | | F | E | |

| | | | | | | | | |
|-----------------------|-----------|---|-----------|------------|------------|--|--|--|
| Abacavir ⁶ | | K | L | Y | M | | | |
| | 65 | | 74 | 115 | 184 | | | |
| | R | V | | F | V | | | |

| | | | | | | | | |
|---------------------------|-----------|---|-----------|--|--|--|--|--|
| Didanosine ^{7,8} | | K | L | | | | | |
| | 65 | | 74 | | | | | |
| | R | V | | | | | | |

| | | | | | | | | |
|---------------|-----------|---|--|--|------------|--|--|--|
| Emtricitabine | | K | | | M | | | |
| | 65 | | | | 184 | | | |
| | R | | | | V | | | |
| | | | | | I | | | |

| | | | | | | | | |
|------------|-----------|---|--|--|------------|--|--|--|
| Lamivudine | | K | | | M | | | |
| | 65 | | | | 184 | | | |
| | R | | | | V | | | |
| | | | | | I | | | |

| | | | | | | | | |
|-------------------------------|-----------|-----------|-----------|--|--|--------------------|---|---|
| Stavudine ^{4,5,9,10} | M | D | K | | | L | T | K |
| | 41 | 67 | 70 | | | 210 215 219 | | |
| | L | N | R | | | W | Y | Q |
| | | | | | | F | E | |

| | | | | | | | | |
|-------------------------|-----------|---|-----------|--|--|--|--|--|
| Tenofovir ¹¹ | | K | K | | | | | |
| | 65 | | 70 | | | | | |
| | R | E | | | | | | |

| | | | | | | | | |
|--------------------------------|-----------|-----------|-----------|--|--|--------------------|---|---|
| Zidovudine ^{4,5,9,10} | M | D | K | | | L | T | K |
| | 41 | 67 | 70 | | | 210 215 219 | | |
| | L | N | R | | | W | Y | Q |
| | | | | | | F | E | |

Nonnucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)^{1,12}

| | | | | | | | | | | |
|-----------|------------|------------|------------|------------|---|---|------------|------------|------------|------------|
| Efavirenz | | | L | K | V | V | Y | Y | G | P |
| | 100 | 103 | 106 | 108 | | | 181 | 188 | 190 | 225 |
| | | I | N | M | I | | C | L | S | H |
| | | | | | | | I | A | | |

| | | | | | | | | | | |
|--------------------------|--|----|----|-----|-----|-----|-----|-----|-----|--|
| Etravirine ¹³ | | V | A | L | K | V | V | Y | G | |
| | | 90 | 98 | 100 | 101 | 106 | 179 | 181 | 190 | |
| | | I | G | I | E | I | D | C | S | |
| | | | | | P | | F | I | A | |
| | | | | | | | T | V | | |

| | | | | | | | | | |
|------------|------------|------------|------------|------------|---|------------|------------|------------|--|
| Nevirapine | | L | K | V | V | Y | Y | G | |
| | 100 | 103 | 106 | 108 | | 181 | 188 | 190 | |
| | | I | N | A | I | C | C | A | |
| | | | | M | | I | L | | |
| | | | | | | | H | | |

The International AIDS Society–USA (IAS–USA) Drug Resistance Mutations Group reviews new data on HIV drug resistance to maintain a current list of mutations associated with clinical resistance to HIV. This list includes mutations that may contribute to a reduced virologic response to a drug.

The mutations listed have been identified by 1 or more of the following criteria: (1) in vitro passage experiments or validation of contribution to resistance by using site-directed mutagenesis; (2) susceptibility testing of laboratory or clinical isolates; (3) genetic sequencing of viruses from patients in whom the drug is failing; (4) correlation studies between genotype at baseline and virologic response in patients exposed to the drug. In addition, the group reviews only data that have been published or have been presented at a scientific conference. Drugs that have been approved by the US Food and Drug Administration (US FDA) as well as any drugs available in expanded access programs are included (listed in alphabetical order by drug class). User notes provide additional information as necessary. Although the Drug Resistance Mutations Group works to maintain a complete and current list of these mutations, it cannot be assumed that the list presented here is exhaustive. Readers are encouraged to consult the literature and experts in the field for clarification or more information about specific mutations and their clinical impact.

User Notes

1. Numerous nucleoside (or nucleotide) analogue reverse transcriptase inhibitor (nRTI) mutations, such as the M41L, L210W, and T215Y mutations, may lead to viral hypersusceptibility to the nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs) in nRTI-treated individuals. The presence of these mutations may improve subsequent virologic response to NNRTI-containing regimens in NNRTI treatment-naïve individuals (Shulman et al, *AIDS*, 2004; Demeter et al, 11th CROI, 2004; Haubrich et al, *AIDS*, 2002; Tozzi, *J Infect Dis*, 2004; Katzenstein et al, *AIDS*, 2003). NNRTI hypersusceptibility can be conferred by 2 distinct phenotypes: increased enzyme susceptibility to NNRTI (eg, V118I/T215Y) or decreased virion-associated levels of reverse transcriptase (eg, H208Y/T215Y and V118I/H208Y/T215Y). The viruses that contained less reverse transcriptase replicated less efficiently than those with wild-type levels of reverse transcriptase. (Clark et al, *Antivir Ther*, 2006). The clinical relevance of all these mutations has not been assessed.

2. The 69 insertion complex consists of a substitution at codon 69 (typically T69S) and an insertion of 2 or more amino acids (S-S, S-A, S-G, or others). The 69 insertion complex is associated with resistance to all nRTIs currently approved by the US FDA when present with 1 or more thymidine analogue-associated mutations (TAMs) at codons 41, 210, or 215 (Miller et al, *J Infect Dis*, 2004). Some other amino acid changes from the wild-type T at codon 69 without the insertion may also be associated with broad nRTI resistance.

3. Tenofovir retains activity against the Q151M complex of mutations (Miller et al, *J Infect Dis*, 2004).

4. Multi-nRTI resistance mutations, also known as nucleoside analogue-associated mutations (NAMs), are associated with resistance to numerous nRTIs. The M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E are known as TAMs. TAMs are a subset of NAMs that are selected by the thymidine analogues zidovudine and stavudine and are associated with cross-resistance to all nRTIs currently approved by the US FDA (Larder et al, *Science*, 1989; Kellam et al, *Proc Natl Acad Sci USA*, 1992; Calvez et al, *Antivir Ther*, 2002; Kuritzkes et al, *J Acquir Immune Defic Syndr*, 2004). Mutations at the C-terminal reverse transcriptase domains (amino acids 293–560) outside of regions depicted on the figure bars may prove to be important for HIV drug resistance. Mutations in the connection (A371V) and RNase H (Q509L) domains of reverse transcriptase are coselected on the same genome as TAMs and increase significantly zidovudine resistance when combined with TAMs. They also increase, although to a much lesser extent, cross-resistance to lamivudine, abacavir, and tenofovir but not to stavudine or didanosine (Brehm et al, *Antivir Ther*, 2006). When the polymerase domain contains TAMs, mutations in the connection domain (E312Q, G335C/D, N348I, A360I/V, V365I, and A376S) increase resistance to zidovudine from 11-fold to as much as 536-fold over wild-type reverse transcriptase (Nikolenko et al, *Proc Natl Acad Sci USA*, 2007). Three mutations (N348I, T369I, and E399D) in the reverse transcriptase C-terminus are associated with the increased resistance to zidovudine and to NNRTIs. Mutations at this level could modulate NNRTI resistance by affecting dimerization of p66/p51 heterodimers (Gupta et al, *Antivir Ther*, 2006). Since the clinical relevance of these mutations has

not been demonstrated, they are not depicted on the figure bars.

5. The E44D and the V118I mutations increase the level of resistance to zidovudine and stavudine in the setting of TAMs, and correspondingly increase cross-resistance to the other nRTIs. The significance of E44D or V118I when each occurs in isolation is unknown (Romano et al, *J Infect Dis*, 2002; Walter et al, *Antimicrob Agents Chemother*, 2002; Girouard et al, *Antivir Ther*, 2002).

6. The M184V mutation alone does not appear to be associated with a reduced virologic response to abacavir in vivo (Harrigan et al, *J Infect Dis*, 2000; Lanier et al, *Antivir Ther*, 2004). When present with 2 or 3 TAMs, M184V contributes to reduced susceptibility to abacavir and is associated with impaired virologic response in vivo (Lanier et al, *Antivir Ther*, 2004). The M184V plus 4 or more TAMs resulted in no virologic response to abacavir in vivo (Lanier et al, *Antivir Ther*, 2004).

7. The K65R mutation may be selected by didanosine and is associated in vitro with decreased susceptibility to the drug (Winters et al, *Antimicrob Agents Chemother*, 1997). The impact of the K65R mutation in vivo is unclear.

8. The presence of 3 of the following—M41L, D67N, L210W, T215Y/F, and K219Q/E—has been associated with resistance to didanosine (Marcelin et al, *Antimicrob Agents Chemother*, 2005). The K70R and M184V mutations are not associated with a decreased virologic response to didanosine in vivo (Molina et al, *J Infect Dis*, 2005).

9. The presence of the M184V mutation appears to delay or prevent emergence of TAMs (Kuritzkes et al, *AIDS*, 1996). This effect may be overcome by an accumulation of TAMs or other mutations. The clinical significance of this effect of M184V is not known.

10. The T215A/C/D/E/G/H/I/L/N/S/V substitutions are revertant mutations at codon 215, conferring increased risk of virologic failure of zidovudine or stavudine in antiretroviral-naïve patients (Riva et al, *Antivir Ther*, 2002; Chappey et al, *Antivir Ther*, 2003; Violin et al, *AIDS*, 2004). In vitro studies and preliminary clinical studies suggest that the T215Y mutant may emerge quickly from one of these mutations in the presence of zidovudine or stavudine (Garcia-Lerma et al, *J Virol*, 2004; Lanier et al, *Antivir Ther*, 2002; Riva et al, *Antivir Ther*, 2002).

11. The K65R mutation is associated with a reduced virologic response to tenofovir

in vivo (Miller et al, *J Infect Dis*, 2004). A reduced response occurs in the presence of 3 or more TAMs inclusive of either M41L or L210W (Miller et al, *J Infect Dis*, 2004). Slightly increased treatment responses to tenofovir in vivo were observed if M184V was present (Miller et al, *J Infect Dis*, 2004).

12. The long-term virologic response to sequential NNRTI use is poor, particularly when 2 or more mutations are present (Antinori et al, *AIDS Res Hum Retroviruses*, 2002; Lecossier et al, *J Acquir Immune Defic Syndr*, 2005). The K103N or Y188L mutation alone prevents the clinical utility of efavirenz and nevirapine (Antinori et al, *AIDS Res Human Retroviruses*, 2002). The V106M mutation is more common in HIV-1 subtype C than in subtype B, and confers cross-resistance to all currently approved NNRTIs (Brenner et al, *AIDS*, 2003; Cane et al, *J Clin Microbiol*, 2001).

13. Virologic response was seen in clinical trials despite the presence of single mutations. The impact of most mutations depends on the simultaneous presence of Y181C; Y181C has impact only when present with 1 or more of these mutations (Vingerhoets et al, *Antivir Ther*, 2007). The presence of V179D/F/T, Y181V, or G190S at study baseline was associated with a decreased virologic response to efavirenz (efavirenz package insert). The presence of 3 or more baseline mutations (V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, G190A/S) resulted in a reduced virologic response to efavirenz that was similar to placebo (Picchio et al, *CROI*, 2008). However, the presence of K103N does not affect efavirenz response (efavirenz package insert). Correlations between detection of efavirenz mutations and subsequent virologic response will likely undergo revision with the accumulation of more phenotypic susceptibility data and genotypic results in treatment-experienced individuals.

14. The same mutations usually emerge whether or not PIs are boosted with low-dose ritonavir, although the relative frequency of mutations may differ. Data on the selection of mutations in antiretroviral-naïve patients in whom a boosted PI is failing are very limited. Numerous mutations are often necessary to significantly impact virologic response to a boosted PI. Although numbers vary for the different drugs, 3 or more mutations are often required.

15. Resistance mutations in the protease gene are classified as either “major” or “minor,” if data are available.

Major mutations in the protease gene are defined in general either as those selected first in the presence of the drug; or those shown at the biochemical or virologic level to lead to an alteration in drug binding or an inhibition of viral activity or viral replication. Major mutations have an effect on drug susceptibility phenotype. In general, these mutations tend to be the primary contact residues for drug binding.

Minor mutations generally emerge later than major mutations and by themselves do not have a significant effect on phenotype. In some cases, their effect may be to improve replicative fitness of the virus containing major mutations. However, some minor mutations are present as common polymorphic changes in HIV-1 nonsubtype B clades, such as K201/R and M36I in protease.

16. Ritonavir is not listed separately as it is currently used at therapeutic doses as a pharmacologic booster of other PIs. At higher doses tested previously in humans, ritonavir administered as monotherapy produces mutations similar to those produced by indinavir (Molla, *Nature Med*, 1996).

17. HIV-1 Gag cleavage site changes can cause PI resistance in vitro. It has been observed that mutations in the N-terminal part of *gag* (MA: E40K; L75R; K113E and CA: M200I; A224A/V), outside the cleavage site, contribute directly to PI resistance by enhancing the overall Gag processing by wild-type protease (Nijhuis et al, *PLoS Med*, 2007). The clinical relevance of these mutations has not been assessed.

18. In most patients in whom an atazanavir/ritonavir-containing regimen was failing virologically, accumulations of the following 13 mutations were found (L10F/I/V, G16E, L33F/I/V, M46I/L, I54L/V/M/T, D60E, I62V, A711/T/L, V82A/T, I84V, I85V, L90M, and I93L). Seven mutations were retained in an atazanavir score (L10F/I/V, G16E, L33F/I/V, M46I/L, D60E, I84V, I85V); the presence of 3 or more of these mutations predicts a reduced virologic response at 3 months, particularly when L90M was present (Vora et al, *AIDS*, 2006; <http://www.hivfrenchresistance.org/2006/tab2.html>). A different report (Bertoli et al, *Antivir Ther*, 2006) found that the presence of 0, 1, 2, or greater than or equal to 3 of the following mutations was associated with 92%, 93%, 75%, and 0% virologic response to atazanavir/ritonavir: L10C/I/V, V32I, E34Q, M46I/L, F53L, I54A/M/V, V82A/F/I/T,

I84V; presence of I15E/G/L/V, H69K/M/N/Q/R/T/Y, and I72M/T/V improved the chances of response. For unboosted atazanavir, the presence of 0, 1, 2, or greater than or equal to 3 of the following mutations was associated with 83%, 67%, 6%, and 0% response rates: G16E, V32I, K201/M/R/T/V, L33F/I/V, F53L/Y, I64L/M/V, A711/T/V, I85V, I93L/M.

19. Darunavir (formerly TMC-114), boosted with ritonavir, was approved by the US FDA in June 2006. Resistance data are therefore still preliminary and limited. HIV RNA response to boosted darunavir correlated with baseline susceptibility and the presence of multiple specific PI mutations. Reductions in response were associated with increasing numbers of the mutations indicated in the bar. Some of these mutations appear to have a greater effect on susceptibility than others (eg, I50V versus V11I). Further study and analysis in other populations are required to refine and validate these findings.

20. The mutations depicted on the chart bar cannot be considered to be comprehensive since little relevant research has been reported in recent years to update the resistance and cross-resistance patterns for this drug.

21. In PI-experienced patients, the accumulation of 6 or more of the mutations indicated on the bar is associated with a reduced virologic response to lopinavir/ritonavir (Masquelier et al, *Antimicrob Agents Chemother*, 2002; Kempf et al, *J Virol*, 2001). The product information states that accumulation of 7 or 8 mutations confers resistance to the drug. In contrast, in those in whom lopinavir/ritonavir is their first PI used, resistance to this drug at the time of virologic rebound is rare. However, there is emerging evidence that specific mutations, most notably I47A (and possibly I47V) and V32I are associated with high-level resistance (Mo et al, *J Virol*, 2005; Friend et al, *AIDS*, 2004; Kagan et al, *Protein Sci*, 2005).

22. In some nonsubtype-B HIV-1, D30N is selected less frequently than other PI mutations (Gonzalez et al, *Antivir Ther*, 2004).

23. Accumulation of more than 2 mutations at positions 33, 82, 84, and 90 correlates with reduced virologic response to tipranavir/ritonavir, although an independent role for L90M was not found. Detailed analyses of data from phase II and III trials in PI-experienced patients identified mutations associated with reduced susceptibility or virologic response. These include: L10V, I13V, K20M/R, L33F, E35G, M36I, K43T, M46L,

I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D, and I84V. Accumulation of these mutations is associated with reduced response. Subsequent genotype-phenotype and genotype-virologic response analyses determined some mutations have a greater effect than others (eg, I84V versus I54M). Refinement and clinical validation of these findings are pending (Baxter et al, *J Virol*, 2006; Mayers et al, *Antivir Ther*, 2004; Hall et al, *Antivir Ther*, 2003; McCallister et al, *Antivir Ther*, 2003; Parkin et al, *CROI*, 2006; Bachelier et al, European HIV Drug Resistance Workshop, 2006).

24. Although resistance to enfuvirtide is associated primarily with mutations in the first heptad repeat (HR1) region of the gp41 envelope gene, viruses that are wild type in the depicted HR1 region vary 500-fold in susceptibility. Such pretreatment susceptibility differences were not associated with differences in clinical responses (Labrosse et al, *J Virol*, 2003). Furthermore, mutations or polymorphisms in other regions in the envelope (eg, the HR2 region or those yet to be identified) as well as coreceptor usage and density may affect susceptibility to enfuvirtide (Reeves et al, *Proc Natl Acad Sci USA*, 2002; Reeves et al, *J Virol*, 2004; Xu et al, *Antimicrob Agents Chemother*, 2005). Thus, testing to detect only the depicted HR1 mutations may not be adequate for clinical management of suspected failure (Reeves et al, *J Virol*, 2004; Menzo et al, *Antimicrob Agents Chemother*, 2004; Poveda et al, *J Med Virol*, 2004; Sista et al, *AIDS*, 2004; Su, *Antivir Ther*, 2004).

25. Maraviroc activity is limited to patients with only CCR5 (R5)-using virus detectable; CXCR4 (X4)-CCR5 mixed tropic viruses and X4-using viruses do not respond to maraviroc treatment. Some cases of virologic failure during maraviroc therapy are associated with outgrowth of X4 virus that pre-exists as a minority population below the level of assay detection. Mutations in the HIV-1 gp120 molecule that allow the virus to bind to R5 receptors in the presence of drug have been described in viruses from some patients whose virus remained R5 at the time of virologic failure. A number of such mutations have been identified, and the phenotypic manifestation of this drug resistance is a reduction in the maximal percentage inhibition (MPI) rather than the increase in the 50% inhibitory concentration (IC_{50} ; defined by fold increase) that is characteristic of resistance to other classes of antiretrovirals. The resistance profile for maraviroc is too complex to be depicted on the figures. The frequency and rate at which maraviroc resis-

tance mutations emerge are not yet known.

26. Raltegravir failure was associated with integrase mutations in 2 distinct genetic pathways defined by 2 or more mutations including: (1) a signature (major) mutation at either Q148H/K/R or N155H; and (2) 1 or more minor mutations unique to each pathway. Minor mutations described in the Q148H/K/R pathway include L74M + E138A, E138K, or G140S. The most common mutation pattern in this pathway is Q148H + G140S; this Q148H + G140S pattern exhibits the greatest loss of drug susceptibility. Mutations described in the N155H pathway include this primary mutation plus either L74M, E92Q, T97A, E92Q + T97A, Y143H, G163K/R, V151I, or D232N (Hazuda et al, *Antivir Ther*, 2007).

(continued from page 62)

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- 18.** Patterns of CD8+ Immunodominance May Influence the Ability of *Mamu-B*08+* Macaques to Naturally Control SIV_{mac259} Replication. John Loffredo, A Bean, D Beal, E Leon, S Piaskowski, S Musani, E Rakasz, N Wilson, D Allison, and D Watkins.
- 22.** Functionality of HIV-1-specific CD8+ T Cells Is Dependent on Antigen Load and Sequence Diversification. Hendrik Streeck, Z Brumme, M Anastario, K Cohen, J Jolin, G Alter, A Meier, T Allen, B Walker, and M Altfeld.
- 26.** Comprehensive Pre-clinical Assessment of Microbicide Safety Using In Vitro and Murine Models. Pedro Mesquita, S Wilson, N Cheshenko, M Keller, B Galen, and B Herold.
- 28LB.** Trial of Male Circumcision: Prevention of HSV-2 in Men and Vaginal Infections in Female Partners, Rakai, Uganda. Aaron Tobian, D Serwadda, T Quinn, G Kigozi, S Reynolds, F Makumbi, T Suntoke, S Watya, M Wawer, and R Gray.
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- 33LB.** Trial of Male Circumcision in HIV+ Men, Rakai, Uganda: Effects in HIV+ Men and in Women Partners. Maria Wawer, G Kigozi, D Serwadda, F Makumbi, F Nalugoda, S Watya, D Buwembo, V Ssempijja, L Moulton, and R Gray.
- 35.** A Prospective, Randomized, Controlled, Open-label Trial Evaluating the Effect of Therapeutic Drug Monitoring and Protease Inhibitor Dose Escalation on Viral Load Responses in Antiretroviral-experienced, HIV-infected Patients with a Normalized Inhibitory Quotient Lisa Demeter, H Jiang, L Mukherjee, G Morse, R DiFrancesco, K Klingman, L Bachelier, R DiCenzo, A Rinehart, M Albrecht, and the A5146 Study Team.
- 36.** Re-initiation of ART in the CD4-guided ART Interruption Group in the SMART Study Lowers Risk of Opportunistic Disease or Death. Wafaa El-Sadr and SMART Study Group.
- 37.** Efficacy and Safety of Once-daily Atazanavir/Ritonavir Compared to Twice-daily Lopinavir/Ritonavir, Each in Combination with Tenofovir and Emtricitabine in ARV-naive HIV-1-infected Subjects: The CASTLE Study, 48-week Results. Jean-Michel Molina, J Andrade-Villanueva, J Echevarria, P Chetchotisakd, J Corral, N David, M Mancini, L Percival, A Thiry, and D McGrath.
- 38.** Safety and Activity of SCH532706, a Small Molecule Chemokine Receptor 5 Antagonist in HIV-1-infected Individuals. Sarah Pett, S Emery, K MacRae, R Norris, M McCarthy, A Tendlokar, J Tseng, K Williams, and D Cooper.
- 39LB.** Vicriviroc, a Next Generation CCR5 Antagonist, Exhibits Potent, Sustained Suppression of Viral Replication in Treatment-experienced Adults: VICTOR-E1 48-week Results. Barry Zingman, J Suleiman, E DeJesus, J Slim, M McCarthy, E Lee, N Case, C Mak, and L Dunkle.
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- 41.** Trends in Second Virologic Failure and Predictors of Subsequent Mortality among ART-experienced Patients: North American Experience. Stephen Deeks and North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of the IeDEA.
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- 46.** Duration and Pattern of Breastfeeding and Postnatal Transmission of HIV: Pooled Analysis of Individual Data from a West and South African Cohort Study. Renaud Becquet, R Bland, V Leroy, N Rollins, D Ekouevi, A Coutoudis, F Dabis, H Coovadia, R Salamon, and M L Newell.
- 47LB.** Population Pharmacokinetics of Tenofovir in HIV-1-infected Pregnant Women and Their Neonates: TEMAA ANRS 12109. Deborah Hirt, S Urien, E Rey, D Ekouevi, S Blanche, G Gray, P Coffie, K Leang Sim, F Dabis, and J M Treluyer.
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- 55.** Prevention for Positives. Simon Rosser.
- 56.** Addressing Substance Abuse. David Vlahov.
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- 66.** Natural Enhancers and Inhibitors of HIV Infection. J Munch, L Standker, W G Forssmann, and Frank Kirchhoff.
- 67.** Reducing the Prevalence of Primary HIV Brain Pathology by Antiretrovirals. Ian Everall, F Vada, S Letendre, D Lazzaretto, B Gelman, S Morgello, E Singer, R Ellis, E Maslah, I Grant, and National NeuroAIDS Tissue Consortium and the UCSD HIV Neurobehavioral Research Center.
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James Hoxie, A Jordan, B Haggarty, J Romano, M Piatak, J Lifson, D Montefiori, M Marsh, and P Fultz.

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- 743.** Ritonavir-, Lopinavir-, and Efavirenz-containing Nanoparticles: *in vitro* Release of ART. Chris Destache, T Belgum, G Elsasser, K Christensen, and A Shibata.
- 760.** Pharmacokinetics of Nevirapine and Rifampicin in TB/HIV Co-infected Patients in Burkina Faso. Alberto Matteelli, N Saleri, M Regazzi, P Villani, V Bonkougou, J Simpo, A Carvalho, M Cusato, G Carosi, and M Dembele.
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- 787.** Single Antiretroviral Switches for Pregnant Women Compared to Non-pregnant Women and Men Who Initiated HAART in the MTCT-Plus Initiative. Patricia Toro, M Katyal, D Nash, and R Carter.
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- 799.** Outcomes of Patients Switched from Enfuvirtide to Raltegravir within a Virologically Suppressive Regimen. Marianne Harris, G Larsen, and J Montaner.
- 800.** The Relationship of CCR5 Inhibitors to CD4 Cell Count Changes: A Meta-analysis of Recent Clinical Trials in Treatment-experienced Subjects. Timothy Wilkin, H Ribaldo, and R Gulick.
- 809.** Disparate Virologic Response to HAART between Ethnicities. Amy Weintrob, G Grandits, B Agan, A Ganesan, N Crum-Cianflone, S Fraser, S Patel, G Wortmann, S Wegner, and V Marconi.
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