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Topics in HIV Medicine™

A publication of the International AIDS Society–USA

Highlights of the 9th Conference on Retroviruses and Opportunistic Infections

Perspectives

Special Contribution

About This Issue

This issue begins the 10th volume of *Topics in HIV Medicine* and also marks the 10th year of the International AIDS Society–USA. The issue contains our annual summary of research presented at the Conference on Retroviruses and Opportunistic Infections, held this year in Seattle, Wash, from February 24 to February 28. Our authors—Drs Mario Stevenson, Judith S. Currier, Diane V. Havlir, Timothy J. Wilkin, C. Mhorag Hay, Christine M. Hogan, and Scott M. Hammer—review approximately 200 abstracts, plenary lectures, and symposia presentations, focusing on new research in basic science, complications of HIV disease and therapy, and a broad spectrum of issues in the management of antiretroviral therapy. A list of conference abstracts cited in the text is included at the back of the issue, and the full text of all abstracts is available online at www.retroconference.org. The next issue of *Topics in HIV Medicine* will include a review by R. Paul Johnson, MD, of new research presented at the Retrovirus Conference on HIV pathogenesis and vaccine candidates.

Also included in this issue are summaries of lectures from recent International AIDS Society–USA educational programs: Marshall J. Glesby, MD, PhD, reviewed mitochondrial toxicity in HIV infection at an IAS–USA course in New York in October, and Daniel R. Kuritzkes, MD, discussed issues in antiretroviral failure at an IAS–USA symposium at the Interscience Conference on Antimicrobial Agents and Chemotherapy in Chicago in December.

The final article is a special contribution, a review of studies conducted in the past 3 years on the effect of switching antiretroviral regimens on metabolic complications such as insulin resistance, lipid abnormalities, and changes in body fat distribution. The review was conducted by the IAS–USA Metabolic Complications Guidelines Panel as part of the process of developing guidelines for the management of these complications. The panel recently submitted its guidelines for publication.

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Correction

In "Update on Drug Resistance Mutations in HIV-1" in the December 2001 issue (2001;9 [6]:21-23), Robert M. Grant, MD, MPH, of the Gladstone Institute of Virology and Immunology in San Francisco, California, should have been included in the list of members of the Drug Resistance Mutations Group.

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Highlights of the 9th Retrovirus Conference

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Special Contribution

Highlights of Basic Science Research

Mario Stevenson, PhD

The 9th Conference on Retroviruses and Opportunistic Infections arguably enjoyed its strongest showing in basic research. Some of the highlights included the identification of novel cellular factors that are essential for efficient HIV assembly and the identification of cellular ligands that may mediate the inhibitory action of the accessory protein Vif. Several presentations on the accessory proteins Nef and Vpr provided more insight into the possible mechanism of action of these enigmatic viral proteins. A general consensus has emerged regarding the important relationship between T-cell activation and susceptibility of the host cell to viral infection and replication. Several studies have begun to identify minimal states of T-cell cycle status that are sufficient for viral replication. Studies with dendritic cells have further pointed to the possible existence of a novel type of reservoir for HIV that surprisingly may not require the involvement of a proviral (ie, integrated) intermediate within the infected cell.

Virology

Following the transport of structural viral precursor proteins to the plasma membrane of the infected cell, virion proteins form immature assembly complexes that eventually detach from the cell. Proteolytic processing of structural virion proteins occurs predominantly after virus budding, leading to formation of the mature and infectious virion. Pioneering work by Carter and Wills has previously shown that the assembly and attachment of immature particles from the cell surface require sequences within the Gag polyprotein, otherwise known as late or L-domains. In HIV-1, the p6 domain of Gag contains the L-domain that facilitates virus particle budding. Previous studies using genetic screens have demonstrated that the p6 domain binds to a cellular protein called Tsg101. Studies presented at the conference have now provided definitive evidence that this cellular protein is essential for the final stages of particle budding and thus is an essential cofactor for viral replication.

Martin-Serrano and colleagues (Abstract 51) demonstrated that the Gag protein of HIV-1 and the matrix protein of Ebola virus bind Tsg101 in a 2-hybrid assay. Using a panel of HIV Gag p6 mutants, they demonstrated that infectious virion production was absolutely dependent upon the ability of p6 to bind Tsg101. A 4-amino acid (PTAP) motif was specifically required for interaction with Tsg101 and virion production. A similar motif was identified in the matrix protein of an Ebola virus. Importantly, in absence of the PTAP motif, the recruitment of Tsg101 to sites of viral assembly independent of Gag was sufficient to restore particle formation.

Demirov and colleagues (Abstract 52) extended this story by demonstrating that overexpressing a specific domain within Tsg101 potently inhibited virus particle production. The general requirement for this protein in retrovirus assembly was evidenced by its ability to impair the release of murine leukemia virus and Mason-Pfizer monkey virus particle production. The significance of this observation is that Tsg101 analogues represent potential specific inhibitors that target HIV particle production.

These studies complement published studies by Sundquist and colleagues (Garrus et al, *Cell*, 2001; Jenkins et al, J *Virol*, 2001) underscoring an essential role for Tsg101 in the assembly and production of HIV particles. The Sundquist group made use of a new technique in which specific RNAs can be targeted for degradation in the presence of small interfering RNAs. Sundquist and colleagues demonstrated that specific degradation of Tsg101 RNA within the cell by Tsg101-specific small interfering RNA rendered that cell incapable of manufacturing HIV virions. Collectively, these studies point to an exciting new target for antiretroviral intervention. These studies should spark efforts to identify dominant negative Tsg101 derivatives or nonfunctional mimetics that could target late stages in the viral life cycle.

Within the virus particle, viral nucleic acids are contained within a conical core comprised predominantly of the viral capsid protein. This core protects nucleic acids while in transit from the virus-producing cell to the new target cell. Upon infection of a new target cell, the viral core must be disassembled in order for viral nucleic acids to access cytoplasm of the target cell. Studies presented by Forshey and colleagues (Abstract 53) have identified mutations within the capsid that do not appear have any gross effects on the characteristic conical morphology of the core, but nevertheless markedly impair the ability of viral nucleic acids to undergo reverse transcription in the target cell. The investigators propose that these mutations affect the stability of the core and consequently may impair the function of the reverse transcription complex upon core disassociation. Thus, the capsid appears to control a crucial postentry step that influences the efficiency of viral DNA synthesis in target cells. Agents that affect core stability may have a utility in blocking establishment of infection in the cell.

The theme of host-virus interactions that are essential for the function of viral proteins was illustrated in a number of presentations. Bushman (Abstract S1) discussed host cell factors that influence viral integration, and how the host cell deals with the presence of viral complementary DNA (cDNA). The Bushman group previously demonstrated that linear unintegrated HIV-1 cDNA promotes apoptosis. It is well established that some linear HIV cDNA molecules undergo circularization, and this process is thought to minimize induction of apop-

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tosis by linear cDNA molecules. Bushman and colleagues characterized preintegration complexes in which viral cDNA synthesis occurs and demonstrated that they contain the Ku protein that is involved in host cell nonhomologous DNA end-joining. These investigators have further demonstrated that this end-joining pathway is required for circularization of viral cDNA. Together, these studies demonstrate that the nonhomologous DNA end-joining pathway is exploited by HIV in order to circularize viral cDNAs that would otherwise induce host cell apoptosis. By circularizing cDNA molecules, the virus avoids inducing host cell apoptosis, thereby preserving the host cell to maximize virus output.

Kalpana and colleagues (Abstract S3) have identified a cellular protein that interacts with HIV-1 integrase and is known as integrase interactor-1 (Ini-1). This cellular protein, previously identified in yeast, is a chromatin remodeling protein that regulates transcription by repositioning nucleosomes. Studies in the Kalpana laboratory have demonstrated that Ini-1 is important for HIV assembly and particle production, in that expression of a fragment of Ini-1 carrying a minimal integrase interaction domain inhibits HIV particle production *in trans*. The Kalpana laboratory further demonstrated that Ini-1 carries a nuclear export signal that is masked in the context of the native protein and unmasked when downstream sequences are deleted. These investigators propose that the nuclear export activity is important for the ability of Ini-1 to regulate viral assembly, for example, through incorporation into virus particles.

Gomez and Hope presented evidence for differential interaction between actin, a cellular cytoskeletal protein, and the HIV Gag and matrix protein (Abstract 154-M). Within the virus-producing cell, matrix exists in the form of a Gag polyprotein that is processed after virus budding. Gomez and Hope demonstrated that actin exhibits a differential interaction with matrix and Gag, in that a mature matrix protein interacted with actin whereas matrix in the context of unprocessed Gag did not interact within actin. Although the significance of this observation is unclear, the investigators propose that the ability of matrix to interact with actin may be important for the ability of matrix to regulate early events in viral infection, ie, following initial entry into the new target cell. Presumably, such interactions would not be required in a virus-producing cell, which would explain the lack of an interaction between the Gag precursor and actin.

Accessory Genes

All members of the HIV-1/simian immunodeficiency virus$_{cpz}$ (SIV$_{cpz}$) lineage contain a *vpu* gene. However, *vpu* is absent from the genomes of HIV-2 and SIV that infect nonhuman African primates (SIV$_{sm}$, SIV$_{agm}$, SIV$_{syk}$, SIV$_{lhoest}$, and SIV$_{col}$). Courgnaud and colleagues (Abstract LB1) described molecular characterization of a novel SIV (SIV$_{gsn}$) from Cameroon, which contains a *vpu* gene, and which represents the first demonstration of a *vpu* homologue within a virus of the HIV-2/SIV lineage. Although HIV-2 and SIV lack a distinct *vpu* gene, they nevertheless contain Vpu-like activities in their envelope glycoproteins. Although Courgnaud and colleagues presented no evidence to suggest that their *vpu* homologue was functional with regard to certain Vpu activities (eg, CD4 down-regulation), it will be interesting to determine whether their novel SIV$_{gsn}$ variant contains duplicate Vpu-like activities (ie, within Vpu itself and within envelope).

> Highlights of basic research included identification of novel cellular factors essential for efficient HIV assembly and of cellular ligands that may mediate inhibitory action of Vif

The accessory protein, Vif, is essential for viral replication in primary cells and certain cell lines and is present in the genomes of all primate lentiviruses except equine infectious anemia virus. Certain cell lines, commonly referred to as permissive cells, have been identified that are permissive to infection by Vif-negative viruses. Studies examining the phenotype of heterokaryons among permissive and nonpermissive cells have demonstrated that nonpermissive cells (ie, those that will only replicate Vif-positive virus) contain an as yet unidentified cellular factor that inhibits the production of infectious virions. The current consensus is that lentiviruses have evolved a Vif protein to counteract this negative cellular factor, thereby preventing it from interfering with virus replication. Given the essential requirement for Vif in virus replication, there has been an intensive search for the negative cellular factor since it profoundly modulates viral infectivity.

Studies presented by Madan and colleagues (Abstract S2) pointed to one potential negative cellular factor that is targeted by Vif. Using a yeast 2-hybrid system, Madan and colleagues identified a nuclear body protein (Sp140) as a binding partner of Vif. Sp140 exists in multiple isoforms. The expression of Sp140 correlated with the Vif permissivity phenotype in that permissive cells that do not require Vif did not express Sp140, but nonpermissive cells that do require Vif for virus replication did express Sp140. Mutations that inactivate the biologic activity of Vif were also shown to impair the association of Vif with Sp140. HIV infection caused redistribution of Sp140 from nuclear bodies to the cytosol. Interestingly, Sp140 is related to the progressive multifocal leukoencephalopathy (PML)-associated nuclear body protein Sp100, and since PML has previously been implicated in defenses against unrelated viruses, this may represent a general antiviral defense mechanism of the cell. Madan and colleagues proposed that Sp140 or one of its isoforms may potently inhibit HIV and that Vif counteracts this inhibitory activity, thereby facilitating viral replication in primary cells.

Additional candidate Vif-interacting proteins were described by Sheehy and Malim (Abstract 55). Those investigators

took an approach very different from that of Madan and colleagues in that they identified 2 T-cell lines that, although genetically similar, were permissive and nonpermissive with respect to Vif function. Using a polymerase chain reaction (PCR)-based cDNA subtraction technique, Sheehy and Malim identified approximately 20 cDNAs that are expressed primarily in nonpermissive cells. Two of these cDNAs exhibited a suppressive effect on HIV replication when expressed in T-cell lines. At present, it is unclear whether either of these cDNAs are targeted by Vif. Nevertheless, this provides intriguing evidence for an intrinsic host defense mechanism against viruses such as HIV that may be exploited in order to reduce the susceptibility of the host cell to viral infection and replication.

Klein and Lingappa (Abstract 54) identified a Vif-associated protein (HP68) that appears to participate in viral capsid formation. HP68 was originally identified as a cellular factor that associates with HIV-1 Gag polyproteins, and dominant-negative variants of HP68 were found to interfere with posttranslational events in capsid formation. Subsequent studies by Klein and Lingappa demonstrated that HP68 also interacts with Vif. The significance of this interaction to Vif function is at present unclear.

All HIV-1 and HIV-2 variants and some strains of SIV contain a *vpr* gene within the so-called central viral region, which is a genomic region overlapping the *vif* and *tat* open reading frames. Members of HIV-2/SIV_{sm} lineage also contain a *vpx* gene. Three activities associated with HIV-1 *vpr (*induction of cell-cycle arrest, promotion of nuclear import of viral reverse transcription complexes, and association with the DNA repair enzyme uracil DNA glycosylase [UDG]), are segregated between the *vpr* and *vpx* genes of HIV-2/SIV_{sm}. That is, import activity is associated with SIV *vpx* whereas cell-cycle arrest and UDG association are activities exhibited by SIV *vpr*.

Goh and colleagues (Abstract 57) provided detailed information on the mechanism through which Vpr affects G_2 arrest. Goh and colleagues demonstrated a specific association of HIV-1 Vpr with the cellular phosphatase Cdc25C, which is an important regulator of cell cycle progression. The interaction of Vpr with Cdc25C specifically impaired the ability of this phosphatase to dephosphorylate p34Cdc2, which is normally necessary for progression into mitosis. These studies elucidate the mechanism of cell-cycle arrest by Vpr.

Evidence that cell-cycle arrest occurs within infected cells in vivo was presented by Sherman and colleagues (Abstract 58). These investigators used an intracellular p24 staining protocol to identify infected peripheral blood mononuclear cells from patients with primary HIV infection and high viral loads. They demonstrated that a large percentage of p24-positive, activated T cells obtained from infected individuals were arrested or paused at the G_2/M phase of the cell cycle, while p24-negative cells from the same patients had a normal cell-cycle profile. This study provides formal in vivo evidence that HIV infection of the host cell interferes with its cell cycle progression, and although it is not possible to confirm that this is strictly Vpr-dependent, this delayed cell-cycle progression is most likely of consequence of *vpr* expression.

Vpr is a virion protein, a feature that supports the notion that Vpr acts at an early stage in viral infection (ie, prior to de novo synthesis of viral proteins) to regulate viral replication. The paradox is that Vpr is also a nuclear protein, and an unresolved issue is why the nuclear localization of Vpr does not interfere with its virion incorporation. Studies described by Elder and colleagues (Abstract 140-M) suggest that Vpr localization is strongly affected by the presence of other genes previously shown to interact with Vpr. Elder and colleagues have been studying Vpr activity in the fission-yeast model system. As discussed previously, Vpr binds to the DNA repair enzyme UDG. In work by the Elder laboratory, overexpression of UDG redirected Vpr from the nuclear envelope into the nucleus or to the mitochondria, depending on which form of UDG was over-expressed.

Vpr has previously been shown to interact with *14-3-3* proteins, which are involved in cell-cycle regulation. Overexpression of RAD25, which is a yeast homologue of human 14-3-3 genes, redirected Vpr from nuclear envelope to the cytoplasm. Recently, Green and colleagues (de Noronha et al, *Science*, 2001) described how expression of Vpr can cause blebbing of the nuclear envelope, a property that may facilitate nuclear uptake of viral reverse transcription complexes. Interestingly, Vpr also induced nuclear blebbing in fission-yeast. Elder and colleagues propose that Vpr localization may depend upon coordinated interaction with cellular proteins that alter the subcellular distribution of Vpr, thereby allowing it to participate in multiple steps in the viral replication cycle.

Tsopanomichalou and colleagues (Abstract 141-M) used a yeast 2-hybrid system to identify cellular proteins that interact with Vpr. They identified isoforms of 14-3-3 as being able to interact with Vpr. Vpr and 14-3-3 could be coimmunoprecipitated from cell extracts. Since 14-3-3 proteins are involved in cell-cycle regulation, the authors propose that interaction between these proteins may interfere with the function of Cdc25C, thereby affecting G_2/M arrest in the infected cell.

Other potential mechanisms through which HIV-1 Vpr affects cell-cycle arrest were described. Sawaya and colleagues (Abstract 144-M) described the interaction of Vpr with p21, a cellular protein implicated in cell-cycle arrest. The investigators demonstrated that Vpr interacts directly with p21 and that overexpression of Vpr impaired p21-mediated cell-cycle arrest. Roshal and colleagues (Abstract 145-M) described the interaction of Vpr with ATR, a member of the PI3 kinase family. Inhibition of ATR function led to reduction in Vpr-induced cell-cycle arrest.

Two studies addressed the biologic significance of natural polymorphisms in Vpr alleles obtained from infected individuals. Tungaturthi and colleagues (Abstract 143-M) examined the impact of naturally occurring mutations, identified in Vpr alleles from diverse clades, on various aspects of Vpr function. Polymorphisms, particularly within turn regions of Vpr, markedly compromised Vpr stability, and some polymorphisms redistributed Vpr from the nucleus to the cytoplasm. The significance of these polymorphisms in terms of viral fitness are as yet unclear.

Lum and colleagues (Abstract 146-M) described experiments that draw a

provocative link between the Vpr and host-cell cytopathicity. They examined the in vitro properties of Vpr proteins obtained from HIV-1-infected patients who are long-term nonprogressors (LTNPs) with normal coreceptor alleles. Interestingly, they observed that peptide derivatives of Vpr alleles from LTNPs inefficiently induced host-cell apoptosis compared with wild-type peptides. The investigators identified an R77Q mutation in Vpr that was present at high frequency in the LTNP cohort. In vitro, Vpr peptides containing the R77Q polymorphism induced lower levels of apoptosis and caspase activation than peptides derived from a wild-type Vpr. The investigators propose that polymorphisms within Vpr that impact its apoptotic activity may contribute to the LTNP phenotype.

Many activities have been described for the accessory protein Nef, including down-regulation of cell surface receptors CD4 and class I major histocompatibility complex (MHC), modulation of host cell activation pathways, activation of chemokine genes in macrophages, and increase in susceptibility of suboptimally activated T cells to viral infection. Pillai and colleagues (Abstract 60) examined whether Nef alleles obtained from 2 different anatomical compartments, namely the plasma and central nervous system, would vary with regard to class I MHC down-regulation. It has been proposed that down-regulation of class I MHC by Nef suppresses recognition of the infected cell by cytotoxic T lymphocytes (CTLs). The investigators reasoned that there may be less pressure to maintain such a function in the central nervous system, where there is less CTL surveillance. Nef alleles were obtained from cerebrospinal fluid in plasma by reverse transcriptase PCR and multiple Nef alleles were examined for their ability to down-regulate class I MHC. The authors observed clustering of cerebrospinal fluid and plasma Nef sequences, but this was not due to differences in ability to down-regulate class I MHC. It is unclear whether these cerebrospinal fluid and plasma Nef alleles exhibit differences in other Nef-associated activities.

Saksela (Abstract S4) examined the impact of Nef on host-cell activation status. Until recently, scientists thought that permissiveness to productive HIV infection required T cells beyond the G_1b phase of the cell cycle. A number of studies have shown that the cycling T cells provide a more efficient environment for reverse transcription and nuclear translocation of viral cDNA. Therefore, much activity has focused on the potential role of Nef in augmenting T-cell activation status, thereby improving conditions for viral replication. Studies by Saksela and colleagues have focused on the mechanism through which Nef activates T-cell signal transduction. The investigators described an interaction between Nef and the p21-activated kinase-2 (PAK-2). There is extensive biochemical evidence that Nef activates PAK-2, but formal evidence that this interaction directly promotes host-cell activation is still pending.

Viral Replication Cycle

All lentiviruses and retroviruses encapsidate 2 copies of genomic viral RNA within each virus particle. Although there is detailed mechanistic information on the mechanism of RNA packaging specificity in retroviral systems, features governing specific packaging of HIV-1 genomic RNA are less clear. Studies presented by Russell and colleagues (Abstract 163-M) investigated the contribution of the so-called dimerization initiation site (DIS) to packaging of HIV-1 genomic RNA. Previous studies have indicated that this sequence promotes dimerization of genomic viral RNA prior to encapsidation. Russell and colleagues demonstrated that viruses carrying mutations at the DIS still retained significant levels of dimerized RNA. In contrast, viruses carrying deletions within the poly (A) and U5-PBS motifs at the 5' end of the viral genome exhibited reduced levels of dimeric RNA and severely delayed replication kinetics. These studies shed new light on the complex nature of HIV RNA dimerization and encapsidation.

In an extension of these studies, Whitney and colleagues (Abstract 162-M) examined the contribution of sequences in *gag* and in the DIS to dimerization and packaging of SIV genomic RNA. Mutations within stem-loop 1, a sequence containing the DIS, abrogated RNA dimerization, while the stability as well as incorporation of dimers was affected by sequences within *gag*.

Several groups have exploited genomic approaches to identify genes that are regulated after HIV infection. Ottones and colleagues (Abstract 166-M) examined the expression levels of genes upon HIV infection of macrophages. Interestingly, some genes previously shown to be implicated in host resistance to viral infection were up-regulated by HIV infection. For example, the *MxA* and *MxB* genes, which have been shown to interfere with the trafficking and transcriptional activity of viral ribonucleoprotein protein complexes, were up-regulated by HIV infection. Similarly, expression of the *NOD2* gene (the macrophage-specific homologue of *NOD1* that regulates apoptosis and NF-κB activation pathways) was up-regulated by HIV infection. These studies suggest an intriguing activation of host-cell defense mechanisms against viruses by the process of viral infection itself. It will be interesting to identify the mechanism through which HIV triggers increased expression of these antiretroviral gene products.

Van't Wout and colleagues (Abstract 168-M) examined genes that were up-regulated upon HIV infection of a human T-cell line. The investigators used a pseudo-type virus, which would bypass any potential signaling upon HIV binding to CD4 and coreceptor molecules. The investigators reported an up-regulation of several genes involved in sterol synthesis. Studies by the Hildreth group (Liao et al, *AIDS Res Hum Retroviruses*, 2001) have previously demonstrated that cholesterol present within lipid rafts promotes viral infectivity, most likely by influencing the fluidity of the viral membrane. Van't Wout and colleagues proposed that stimulation of sterol synthesis may lead to increased levels of cholesterol in the cell membrane and ultimately promote the infectiousness of viral particles emerging from that cell.

Several groups examined the potential impact of HIV infection on cellular signaling pathways. Previous studies have suggested that HIV interaction with CCR5 and CXCR4 initiates a signaling cascade, which may increase the susceptibility of the cell to infection. On the other hand, signaling itself is not

required for HIV entry since signaling-defective coreceptor molecules still permit efficient HIV entry. Francois and Klotman (Abstract 171-M) described the activation of the phosphatidylinositol 3-kinase (PI3-kinase) pathway both by soluble HIV gp120 and by virion-associated gp120. Signaling was observed both with the R5 and X4 gp120 molecules. Interestingly, those investigators presented evidence that activation of PI3-kinase signaling enhanced infection, in that treatment of macrophages and T cells with a PI3-kinase-specific inhibitor suppressed viral infection. The basis of this effect is unclear.

Del Corno and colleagues (Abstract 186-M) examined the consequences of gp120 signaling through CCR5 and CXCR4 on macrophages. Macrophages express both CCR5 and CXCR4, but infection of those cells through CXCR4 is very inefficient. Those investigators have shown previously that gp120 activates several signaling molecules through CCR5 and CXCR4 on macrophages. They have now extended those observations to examine the ability of virion-associated envelope to initiate signaling in macrophages. Evidence was presented that soluble gp120 activates the tyrosine kinase Pyk2 and several MAP kinases. By comparison, whole virions elicited Pyk2 phosphorylation approximately 300-fold more efficiently than monomeric gp120. Since MAP kinases have been shown to regulate the activity of chemokine genes, Del Corno and colleagues propose that this signaling cascade may activate leukocytes and promote leukocyte migration processes that may be operative in HIV-mediated neuropathogenesis.

Vasudevan and colleagues (Abstract 85) presented intriguing evidence that gp120 signaling through CCR5 may significantly impact the ability of resting cells to support HIV infection. As discussed previously, truly resting T cells are refractory to HIV infection in vitro. Nevertheless, observations in acutely infected monkeys and humans and experiments conducted with tonsilar histocultures suggest that under certain conditions, HIV can infect cells of a minimally activated phenotype. Vasudevan and colleagues established resting memory T cells from normal donors and challenged these T cells with R5 HIV or X4 HIV. Those cells were then activated with the chemokine MIP-1β or with R5 or X4 virions. The investigators demonstrated that resting memory T cells were infected by R5 HIV but not X4 HIV. Infection by R5 HIV correlated with activation of the protein tyrosine kinase, Pyk2. Importantly, a wild-type but not signaling-defective CCR5 molecule was able to promote susceptibility of resting memory T cells to HIV infection. Collectively, these data suggest that HIV binding to CCR5 generates a signal that increases a threshold for infection in resting memory T cells. The physiologic changes that occur in these T cells that allow them to support HIV infection await characterization. Previous work by Spina and colleagues (*J Virol*,1995) similarly established that resting T cells could be infected but not produce virions unless they were subsequently activated.

Host-Virus Interactions

An important task in basic HIV research is the identification of the mechanism of HIV latency and its contribution to maintaining viral persistence in the face of highly active antiretroviral therapy. Several presentations pointed to the existence of a potential new form of latency, one that may present a significant obstacle to long-term control of HIV infection. Richman (Abstract S21) discussed the possible existence of a long-lived reservoir of HIV virions on follicular dendritic cells (FDCs). He discussed recent studies by Smith and colleagues (*J Immunol*, 2001) that examined the stability of viral particles in a non-permissive murine model. Those investigators demonstrated that HIV virions were stable for upwards of 9 months when trapped on murine FDCs in vivo.

The mechanism by which virion integrity is preserved in association with FDCs is unclear, although some insight was provided in a talk by Pope (Abstract L2). She examined distribution of virions in pulsed, mature, and immature dendritic cells, and demonstrated that virions exhibit a vacuolar distribution in mature dendritic cells, but tend to accumulate at the plasma membrane in immature dendritic cells. The nature of this vacuolar reservoir is unclear. Clearly, it does not represent an endosome since the pH of these endosomes would rapidly inactivate viral infectivity. These studies have important implications for antiretroviral therapy. The half-life of virions in association with dendritic cells or FDCs is unclear. However, since these virions do not necessarily require a proviral intermediate, the establishment of these vacuolar reservoirs may be insensitive to current antiretroviral agents and could significantly hamper efforts to eradicate reservoirs of infectious HIV in infected individuals.

Current models of viral latency suggest that resting T cells harbor integrated viral genomes that are transcriptionally silent. Studies presented by Chun and colleagues (Abstract 493-M) suggest that latently infected T cells may not be as virally inactive as previously thought. They examined whether the latent viral reservoir is actually capable of manufacturing HIV virions in patients on potent antiretroviral therapy. Resting CD4+ T cells were isolated from 6 viremic and 7 aviremic patients. In the absence of activating stimuli, resting T cells from all viremic patients produced readily detectable levels of viral particles. Cultures from a small number of aviremic patients on therapy were also capable of shedding viral particles. These studies challenge the prevailing view that HIV latency involves an inactive proviral state. These studies further underscore the notion that full cell-cycle progression is not required either for HIV infection or for virion production.

HIV Envelope and Receptors

The envelope glycoproteins on the surface of HIV virions interact sequentially with CD4 and a 7-transmembrane coreceptor on the surface of cells. These events trigger fusion of cell and viral membranes, allowing entry of the virus core into the cytoplasm of the cell. The mechanisms and intermediate structures involved in this process are becoming better understood. Several therapeutic strategies that target these entry events are currently being developed.

Wyatt (Abstract L4) gave an overview and update on the gp120 structure. He has studied the cavity or hollow into which the N-terminus of CD4 binds. The

aromatic ring on the F43 of CD4 fills a second, smaller cavity close by on gp120. The site around the F43 cavity is highly conserved. The first hollow appears to allow in the IgG-like N-terminal domain of CD4 but is too small for most dimeric antibodies. IgGB12 is an antibody that does seem to be able to get into the hollow, although the mechanism is not known. Wyatt and colleagues measured entropy and enthalpy during CD4 binding. Results indicate that there are substantial rearrangements in the gp120 core when CD4 binds. These experiments included gp120 without V1, V2, and V3 and indicate that rearrangements do not just involve movement of the variable loops to expose a coreceptor binding site. The gp120 is floppy before CD4 is bound, and some mutations that partially push gp120 into the activated state were described (375S/W). A glycosylation site at the base of V3 (N301R) severely influences sensitivity to neutralizing antibodies. When this site is mutated, YU2 becomes more sensitive to F105, 15e (CD4bs monoclonal antibodies), and 39F (V3 loop monoclonal antibody), but not to 2F5 (gp41). The former three do not usually neutralize YU2. These monoclonal antibodies bind equally to YU2wt and YU2 with the N301R mutation. The mechanism of neutralization is therefore unclear.

Hoxie and colleagues (Abstract 81) reported a frameshift mutation in the cytoplasmic tail of HIV-1, which results in a stop codon. Amazingly, this results in exposure of CD4-induced epitopes on gp120. The implications of these results are unclear, but they show that there is "communication" between gp120 outside and gp41 domains inside the particle or cell.

Richman and colleagues (Abstract LB5) followed neutralizing antibody response over time in 14 infected individuals. Reporter viruses were used that carried envelopes PCR-amplified from plasma RNA at different times. Most patients generated strong neutralizing responses to autologous virus; however, the rate of viral escape was remarkable. Envelopes were resistant to neutralization by concurrent serum samples but were sensitive to serum samples taken at later time points. The data presented were very clear and it is strange that such lucid observations have not been made previously. The new observations were made possible by the new entry assay utilizing envelope amplified from plasma RNA. Previous assays of neutralizing antibody have been hampered by the difficulty of isolating, propagating, and titering multiple virus isolates.

All HIV and SIV strains bind CD4, and it is therefore hoped that reagents that inhibit this interaction will be active against divergent viruses. Colonno and colleagues (Abstract 9) reported that BMS-806 (molecular weight, ~400) blocks infection by a panel of HIV-1 isolates including subtypes A, B, C, and D; however, subtypes E, F, G, and O are resistant. BMS-806 binds gp120 and competes with CD4 for binding. Virus variants selected for resistance to BMS-806 carried mutations around the CD4-binding site consistent with this gp120 site as the target for BMS-806. It is hoped that BMS-806 will eventually lead to derivatives that block more diverse HIV isolates.

There is a proliferation of development of small molecules that target coreceptors. Some are now in phase 1 and 2 clinical trials. Reynes and colleagues (Abstract 1) reported that SCH-C, an investigational CCR5 inhibitor, was safe and well tolerated in 12 HIV-seropositive adults who took the drug orally every 12 hours for 10 days. Ten of 12 subjects showed at least a 0.5-$\log_{10}$ reduction in plasma HIV-1 RNA level, with 4 achieving a reduction of more than 1 $\log_{10}$. There was a prolonged effect on plasma HIV-1 RNA level before a rebound following cessation of treatment. In vitro inhibition experiments showed that a large range of R5 viruses of different subtypes are sensitive to SCH-C, but 1 Russian strain was largely resistant despite apparently using CCR5 only as a coreceptor.

Schols and colleagues (Abstract 2) described dose-escalating treatment of 40 HIV-seropositive individuals with AMD3100, a CXCR4 inhibitor, administered over 10 days by continuous infusion (AMD3100 is not bioavailable). One patient who carried X4 virus at the start and finish of the treatment benefited from nearly a 1-$\log_{10}$ reduction in plasma HIV-1 RNA level. Other patients who carried R5 as well as X4 or R5/X4 envelopes at the start had only R5 envelopes at the end of treatment. Other small-molecule inhibitors specific for CCR5 were described in the poster session on entry inhibitors, including spirodiketopiperazine derivatives and SCH-D, a more potent version of SCH-C (Abstracts 396, 402, and 404). These compounds hold great promise for therapy.

Steffens and colleagues (Abstract 84) looked at the location and mobility of CD4 and CCR5 on HOS cells. CD4 was located on actin-dependent structures (eg, microvilli on projections) and restricted to small spots. CCR5 was expressed slightly differently on the leading edges of cells and where membrane activity was occurring. This group then used fluorescence recovery after photobleaching to look at the mobility of receptors on the cell surface. A fluorescent area on the cell surface was photobleached to darkness and then the recovery of fluorescence due to fluorescent receptors moving back into the dark area was measured. CCR5 was highly mobile and fluorescence was completely restored in 20 seconds. Recovery was completely blocked if cholesterol was depleted. CD4 recovered much more slowly over 5 minutes.

HIV Origins

The 3 HIV-1 groups (M, N, and O) were derived from 3 individual zoonoses from a naturally infected primate reservoir. Closely related SIV_{cpz} strains harbored in chimpanzees are the most likely origin of HIV-1. However, very few SIV-seropositive chimpanzees have been identified, with most belonging to the *Pan troglodytes troglodytes* subspecies. These viruses cluster with HIV-1 subgroup N rather than with M, the cause of the HIV-1 global epidemic. Hahn (Abstract L1) described how noninvasive techniques are being used to survey SIV-specific antibodies and viral sequences in chimpanzee urine and fecal samples collected in the field. Hahn's group has now surveyed 2 more of the 4 chimpanzee subspecies, including *P troglodytes verus* in Cote d'Ivoire and *P troglodytes schweinfurthii* in Gombe Park, Tanzania, at the eastern end of their habitat. Of 58 chimpanzees, only 1 *P troglodytes schweinfurthii* from Gombe was SIV-seropositive, although a second seropositive chimpanzee was subsequently identified from a more focused

survey at Gombe. Sequences from these 2 animals clustered with the single previous *P troglodytes schweinfurthii* SIV and not with the *P troglodytes troglodytes* SIV or with HIV-1. SIV_{cpz} in *P troglodytes troglodytes* is therefore still the main candidate as the source of HIV-1. However, the seroprevalence of SIV_{cpz} in chimpanzees is remarkably low, and the possibility of an alternative primate species harboring the progenitor of HIV-1 is still open. Hahn also reported a survey of SIV in primate bushmeat sold at African markets and supermarkets. Meat from 13 of 16 different primate species was seropositive for SIV. Five new SIV lineages were discovered and 4 new species were identified as harboring SIV. Clearly, the potential for further zoonoses remains.

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Additional Suggested Reading

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Complications of HIV Disease and Therapy

Judith S. Currier, MD, and Diane V. Havlir, MD

Metabolic Complications

As in past years, there was a great deal of new information on metabolic complications at the 9th Conference on Retroviruses and Opportunistic Infections. In contrast to prior years, there were no plenary lectures or symposia; instead, the data this year were concentrated in the posters, late breakers, and a slide session. In this review, the new information is summarized by topic, with an emphasis on data that may have direct clinical application.

Diabetes

What is the risk of diabetes in HIV infection? Several presentations addressed the incidence of and risk factors for the development of diabetes in patients with HIV infection. Yoon and colleagues conducted a matched case-control study to examine risk factors for diabetes in a group of age-, sex-, and race-matched HIV-infected patients (Abstract 678-T). Although protease inhibitor use and hepatitis C virus (HCV) coinfection appeared to contribute to the risk of diabetes, only body mass index, family history, and alanine aminotransferase level were associated with diabetes mellitus in a multivariate model. Using the MediCal claims database, Currier and colleagues examined age- and sex-specific rates of diabetes in HIV-seropositive adults compared with HIV-uninfected adults (Abstract 677-T). They reported an overall incidence rate of 10.68 per 100 person-years of observation for those with HIV infection compared with 2.91 per 100 person-years of observation for the HIV-uninfected group, yielding a relative risk of 3.32. This increased risk of diabetes was seen in both men and women and in all age groups. No information about the effect of HIV therapy on diabetes rates was included in this analysis.

Mehta and colleagues (Abstract 679-T) examined the effect of highly active antiretroviral therapy (HAART) and HCV infection on the development of diabetes among patients on a first HAART regimen at the Hopkins Moore Clinic (Table 1). Although diabetes was more common among the HCV-coinfected patients, the presence of HCV did not appear to increase the risk of incident diabetes among those receiving HAART. In a multivariate analysis, the development of diabetes was associated with older age, African-American ethnicity, and failure to gain weight during HAART.

How should patients with HIV infection be screened for diabetes? Falutz and Gardiner (Abstract 676-T) examined this issue in a prospective assessment of several screening tests for diabetes in 32 HAART-treated patients. They compared the oral glucose tolerance test to measurements of fasting insulin and glucose, with calculation of the homeostasis model assessment (HOMA) score (fasting insulin × fasting glucose/22.5). Overall, 9 (28%) of 32 patients had impaired glucose tolerance as measured by the oral glucose tolerance test. Of these 9 patients, only 3 had impaired fasting glucose, 5 had elevated fasting insulin, and 5 had an elevated HOMA score. A total of 8 of the 32 patients had a HOMA score above 4.0, and 6 of those 8 had abnormal oral glucose tolerance test results. The results of this study confirm prior observations demonstrating that fasting glucose measurements alone will miss cases of diabetes. At the current time, oral glucose tolerance testing remains the best option for screening for diabetes in this population. The optimal frequency for use of this test in clinical practice remains to be determined.

Lipid Abnormalities

To date, most of the data comparing lipid profiles among patients receiving currently available antiretroviral agents have been generated in cross-sectional studies. It was encouraging to see more prospective data emerge this year. Gatell and colleagues (Abstracts LB17 and 699-T) reported the results of a Spanish switch study. Patients with viral suppression on a protease inhibitor-based regimen were randomized to substitute the protease inhibitor component with abacavir, nevirapine, or efavirenz, allowing the first head-to-head comparison of the lipid effects within the same trial. After 48 weeks of follow-up, the proportion of patients with triglyceride levels above 400 mg/dL was lowest in the abacavir arm compared with the efavirenz or nevirapine arms. In addition, while mean total cholesterol levels were lowest in the abacavir arm, high-density lipoprotein (HDL) cholesterol values rose only in the nevirapine and efavirenz arms. The results of this study suggest that abacavir has less of an impact on triglyceride and total cholesterol levels than nevirapine or efavirenz, but that the elevations in total cholesterol levels seen in the nonnucleoside reverse transcriptase inhibitor arms are offset by an increase in HDL cholesterol level not observed for abacavir.

Kumar and colleagues (Abstract 33) presented the results of a prospective study comparing the lipid effects of 3 regimens in treatment-naive patients. The study arms were lamivudine/zidovudine (fixed dosage) and abacavir, lamivudine/zidovudine (fixed dosage) and nelfinavir, and stavudine/lamivudine/nelfinavir. The primary endpoint of this trial was change in lipid parameters at 48 weeks. Importantly, this 258-patient study included a diverse patient population (50% women, 36% African Americans, and 40% Hispanics). After 48 weeks of follow-up, the increases in total cholesterol, LDL cholesterol, and

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Table **1.** Overlapping Incidence Rates for Diabetes Among Patients on Their First Antiretroviral Therapy Regimen

Group	Incidence of Diabetes per 100 Person-Years of Observation (95% CI)
Overall	4.0 (2.8-5.6)
Protease inhibitor users	4.7 (3.2-6.8)
NNRTI users	2.6 (0.9-8.2)
HCV-seronegative	4.1 (2.4-6.1)
HCV-seropositive	4.6 (2.8-7.5)

CI indicates confidence interval; HCV, hepatitis C virus; NNRTI, nonnucleoside reverse transcriptase inhibitor. Adapted from Mehta et al (Abstract 679-T).

triglyceride levels were greater in the nelfinavir-containing arms than in the triple nucleoside reverse transcriptase inhibitor (nRTI) arm. In addition, within the nelfinavir-containing arms, those who received stavudine were more likely to experience increases in triglyceride and total cholesterol levels than those who received zidovudine. Interestingly, this increase in triglyceride and cholesterol levels was driven by increases seen in the men and not the women in this study.

Additional prospective data on the lipid profiles of patients receiving the investigational protease inhibitor atazanavir or nelfinavir were reported from 2 ongoing prospective trials (Abstract 706-T). The median percent increase from baseline for triglycerides was 2% to 7% among atazanavir recipients compared with increases of 42% to 50% for nelfinavir recipients. Increases in total cholesterol levels ranged from 5% to 7% for atazanavir, which were also lower than the 25% to 28% increases seen with nelfinavir.

The limited data that exist on the efficacy of statins and fibrates for managing hyperlipidemia in the setting of HIV therapy have been disappointing. Niacin has not been extensively studied because of concerns that this drug may worsen insulin resistance. Fessel and Follansbee examined the impact of niacin (median dose, 3000 mg/d) in a group of protease inhibitor-treated patients with hyperlipidemia and central fat accumulation (Abstract 703-T). After an average of 1 year of niacin therapy, intra-abdominal fat as measured by single-slice computed tomography (CT) was reduced in 13 patients (81%), with an average loss of 26% intra-abdominal fat. The percentage decrease in intra-abdominal fat was associated with an increase in HDL level and a decrease in the total cholesterol/HDL ratio. No data on insulin resistance was reported. These preliminary results suggest a possible role for niacin for the management of hyperlipidemia in HIV infection. Confirmation of the impact on intra-abdominal fat and more information about insulin resistance is needed from larger studies.

Cardiovascular Disease

Several presentations this year addressed the ongoing concern regarding risk of cardiovascular disease in patients with HIV infection. Dubé and colleagues (Abstract LB10) demonstrated changes in endothelial function (reduced flow mediated dilatation in the femoral artery) among HIV-uninfected patients receiving short-term indinavir therapy. The long-term consequences of these changes are unknown.

Klein and Hurley updated previously reported data on rates of hospitalization for men enrolled in the Kaiser Permanente insurance program (Abstract 696-T). As in the past, overall myocardial infarction (MI) rates were higher in the HIV-seropositive group than in the HIV-seronegative group, but no differences between protease inhibitor recipients and non-protease inhibitor recipients could be demonstrated. The distribution of cardiovascular risk factors was compared by HIV serostatus and the most notable finding was the higher rate of smoking in the HIV-infected group than in the non-HIV-infected group.

HIV Outpatient Study (HOPS) investigators also looked at MI rates within their HIV-seropositive cohort (Abstract 698-T). The MI rate for protease inhibitor recipients was 1.2 per 1000 person-years of observation, which was statistically significantly higher than the rate in patients not treated with protease inhibitors (0.5 per 1000 person-years of observation). This difference persisted after control for age, sex, smoking, and diabetes. It should be noted that the overall MI rate in this study was low and that most of the 15 patients who had events had other risk factors for cardiovascular disease.

The final word on this topic at this year's conference came from Bozzette's late-breaker presentation of rates of cardiovascular and cerebrovascular disease among 36,766 HIV-infected US veterans (Abstract LB9). Use of antiretroviral therapy (defined by class of agents) and rates of admission or death attributable to cerebrovascular and cardiovascular disease were analyzed from January 1993 through June 2001. There were several striking findings. Most importantly, all-cause mortality fell from 18 per 100 person-years of observation to 5 per 100 person-years of observation during this time frame (presumably because of the use of antiretrovirals). In addition, rates of cerebrovascular and cardiovascular disease remained stable or declined along with the introduction of HAART. Although there was no available comparison with HIV-uninfected, matched patients from the Veterans Affairs medical system, these results provide some reassurance that at least over the short term, there does not appear to be an increase in the risk of cardiovascular or cerebrovascular events in the Veterans Affairs patient population.

Collectively, further follow-up of all of these cohorts will be needed to determine the longer-term cardiovascular risks of HIV infection and the metabolic changes associated with current treatments. Until these data are available, clinicians should continue to weigh the

uncertain metabolic risks against the known benefits of HIV therapy.

Lipodystrophy

Proposed Case Definition. Carr presented the preliminary results from a multisite international lipodystrophy case definition study (Abstract 31). In this study, 1081 consecutive patients at 32 sites were evaluated by a physician and were questioned regarding the presence of 1 or more signs of lipodystrophy. The patient and physician assessed each body site and rated whether fat accumulation or atrophy was absent, mild, moderate, or severe. If the physician and patient agreed that the patient had 1 or more moderate or severe features of lipodystrophy, the patient was considered to be a case. When the patient and physician could not agree, the patient was considered non-assigned. All patients were prospectively evaluated with dual-energy x-ray absorptiometry (DEXA) scans and blood samples in addition to detailed case histories.

Of the 1081 patients enrolled, 417 were characterized as cases, 371 as controls, and 288 were non-assigned. The analysis then identified factors that distinguished cases from controls and a point system was developed to help characterize patients. A model was developed to calculate a lipodystrophy score that had a sensitivity of 79% and a specificity of 80%. The variables included in this model are both demographic characteristics (eg, age, sex, duration of HIV infection) and clinical features. The authors plan to make this model available on a Web site to allow clinicians to calculate a lipodystrophy score in clinical settings (A. Carr, personal communication).

Although it is very encouraging to see progress in the development of a method to characterize patients, the inclusion of both subjective and objective measures in the proposed case definition does not answer the question of what constitutes lipodystrophy. Studies that include an age-matched, HIV-infected control group will help to further define the clinical features that are specific for a diagnosis of lipodystrophy. Objective measures of the component physical findings (lipoatrophy and fat accumulation) as measured by DEXA and CT are required to characterize patients in prospective studies, especially those studies that are evaluating interventions for the treatment or prevention of these problems.

Role of Adipocyte Hormones in Pathogenesis. The adipocyte hormones leptin and adiponectin are thought to help regulate fat deposition. Prior studies have yielded conflicting results about the levels of these hormones and their possible role in the development of lipodystrophy. Kosmiski and colleagues (Abstract 40) examined the relationship between plasma levels of leptin and adiponectin in patients with or without lipodystrophy. In addition to assessing body composition using DEXA and CT, insulin sensitivity was measured using a dynamic test, the frequently sampled intravenous glucose tolerance test. Leptin levels were significantly higher and adiponectin levels significantly lower in subjects with lipodystrophy than in controls. Leptin levels correlated with measures of body fat, and adiponectin levels correlated with the presence of insulin resistance. The cross-sectional nature of this study makes it difficult to determine the causal relationship between adiponectin deficiency and the development of insulin resistance. Prospective studies, using the same types of methods employed in this well-designed study, are needed to further these observations and determine the role of adipocyte hormones in the pathogenesis of lipodystrophy.

Distinguishing Lipodystrophy From Wasting Associated With Tuberculosis. How do the body shape changes associated with lipodystrophy compare with what occurs during acute opportunistic infections? Paton and colleagues from Singapore (Abstract 687-T) examined this issue by comparing appendicular (limb) and trunk fat and lean mass as measured by whole-body DEXA in HIV-infected patients with active tuberculosis (TB; n=11) or with lipodystrophy (n=12) and in clinically stable patients with no lipodystrophy or opportunistic infections (n=24). Appendicular fat mass was lower in the patients with lipodystrophy and TB than in the stable HIV group, but trunk fat was lower among those with TB and unchanged in the lipodystrophy group compared with controls. The ratio of appendicular fat to total body fat increased in the TB group (0.58) and decreased in the lipodystrophy group (0.39) compared with the HIV controls (0.50). The ratio of appendicular lean mass to total body lean mass was decreased in the TB arm (0.38) and unchanged in the lipodystrophy arm (0.42) and HIV controls (0.41). These results demonstrate the utility of whole body DEXA in distinguishing patients who may have peripheral lipoatrophy due to wasting from those with lipodystrophy. In addition, these findings suggest a role for DEXA scanning in determining a definition for lipodystrophy.

Stage of Disease and Risk. Lichtenstein and colleagues reported further analysis of the HOPS cohort at this year's meeting (Abstract 684a-T). They limited the analysis to examining the incidence and risk factors for the development of moderate to severe lipoatrophy. The incidence of lipoatrophy was highest among patients who had a prior CD4+ count of less than 100 cells/µL. The prevalence of moderate to severe atrophy was 30.8% among subjects with minimum and maximum CD4+ counts below 200 cells/µL, compared with 3.8% for those with minimum and maximum values all greater than 350 cells/µL. These differences persisted after controlling for time on antiretroviral therapy. These results suggest (as prior analyses from this group have suggested) that stage of HIV infection may play a role in the pathogenesis of lipoatrophy. Prospective observations of patients who have initiated therapy at higher and lower CD4+ cell counts are needed to confirm these findings. If confirmed, these results have implications for the "when to start therapy" debate.

Interventions. A current paradigm that has emerged to explain the association between HIV therapy and fat accumulation and fat atrophy includes a role for both protease inhibitors and for nRTIs. It has been shown that protease inhibitors induce insulin resistance in vitro and in vivo, which in turn might lead to fat accumulation. In addition, it has been proposed that mitochondrial toxicity induced by nRTIs leads to fat wasting

and when protease inhibitors and nRTIs are combined, this is accelerated, possibly because of fat cell apoptosis. Studies have been designed to try to test these hypotheses, and preliminary data from several studies were presented.

Three different approaches to examine the risks and benefits of switching out the nRTI component of a triple-drug regimen were reported this year. In the MITOX study led by Carr, patients with clinically apparent lipoatrophy and viral suppression on a protease inhibitor-containing regimen with either zidovudine or stavudine were randomized to substitute the nRTI with abacavir or remain in the same triple-drug arm (Abstract 32). At 24 weeks, a small (10%) but statistically significant increase in arm fat was seen in those who made the switch. This increase in limb fat was not detectable by the physicians in the study and did not impact quality of life. Among those who switched, 10% developed abacavir hypersensitivity. Further follow-up of the group is planned to see if longer time is needed to observe clinically significant improvements.

In the TARHEEL study led by McComsey (Abstract 701-T), stavudine recipients who were experiencing either lipoatrophy, symptoms of hyperlactatemia, or lactate levels above 3.2 mmol/L substituted stavudine with either abacavir (if zidovudine-experienced) or zidovudine and lamivudine (if zidovudine-naive). All 118 subjects underwent prospective evaluations of lactate and DEXA measurements for body composition. After 24 weeks of follow-up, median increases in arm (25%), leg (6%), and trunk (9%) fat were reported that were also noticeable by patient self-report. The absolute increase in arm fat in this study was similar to what was observed in the study by Carr and colleagues. No statistical analysis of these changes was reported.

Mallal reported the results from a smaller study (n=40) in which patients with viral suppression on a stavudine-containing regimen were randomized to switch to the triple nRTI regimen of zidovudine, lamivudine, and abacavir or remain on the original therapy (Abstract 700-T). At 48 weeks of follow-up, statistically significant increases in limb fat by DEXA were more apparent for the arms than the legs and were again on the same order of magnitude (ie, small) as the other switch studies. Collectively, these studies are very important in that they demonstrate that lipoatrophy may be reversible (albeit slowly) and that nRTI therapy alone may not be the sole cause of lipoatrophy (as evidenced by the Mallal study, where patients who switched off the protease inhibitor and stavudine appeared to have greater benefit). Long-term results from these studies are eagerly awaited.

Agents that improve insulin sensitivity are currently under intensive investigation to probe the pathophysiology of fat accumulation and lipoatrophy. The 2 agents that top the list of candidates are metformin and rosiglitazone. Sutinen presented the first randomized prospective data evaluating rosiglitazone for treatment of lipodystrophy (Abstract LB13). In this study, 30 stable HAART-treated patients with self-reported body shape changes (confirmed by the investigator) were randomized to receive rosiglitazone or matching placebo. Objective measures of subcutaneous fat by magnetic resonance imaging and serum samples for lipids and insulin were collected. After 24 weeks, despite improvements in insulin sensitivity, there was no change in subcutaneous fat or in the waist-to-hip ratio measurements. Interestingly, the percentage of liver fat appeared to decrease in the rosiglitazone group and increase in the placebo group.

Despite the small size of the study, the absence of any insulin resistance entry criteria, and the short follow-up time, the negative results of this study were clearly disappointing. In addition, the safety issues identified in this study with the 8 mg dose of rosiglitazone (early elevations in triglycerides and development of anemia) should be noted. Given these results, it will be critical to see if other ongoing studies evaluating the impact of rosiglitazone on visceral fat in subjects with insulin resistance show a benefit.

The collective results of studies to evaluate interventions for lipodystrophy seem to indicate that this process is multifactorial and that no one approach will be sufficient to reverse changes that have developed over years. Efforts to identify combinations of antiretroviral agents with the lowest risk of promoting these changes in treatment-naive patients are urgently needed while the work continues to identify the mechanisms by which antiretroviral drugs facilitate these changes.

Lactic Acidosis

Lactic acidosis remains a rare but serious adverse effect of nRTI therapy. A late-breaker presentation made the point that severe neuromuscular weakness may accompany lactic acidosis, but the relationship between these findings is uncertain. Marcus and colleagues reviewed US Food and Drug Administration (FDA) records and the literature after a report of a cluster of cases of profound motor weakness associated with lactic acidosis was submitted to the FDA in 2001 (Abstract LB14). They searched for reports of lactic acidosis in HIV-infected patients receiving antiretroviral therapy. There were 25 cases, 7 of which were fatal. The nRTI therapy was not interrupted promptly in 6 fatal cases and in 12 additional cases. In the same presentation, 8 cases of pancreatitis and/or lactic acidosis in pregnant women were reported. Seven women were taking didanosine plus stavudine, and 3 of these women died. This report underscores the risk of this combination in pregnant women.

Much more common than lactic acidosis is asymptomatic or mildly symptomatic elevations in lactate levels. Cross-sectional studies presented at the conference reported an incidence of elevated lactate levels in the 5% to 10% range (Abstracts 710-T and 711-T). Predictors of elevated lactate levels included duration of nRTI use and age. Data from longitudinal studies in adults suggested that fluctuations in lactate levels are very common over time and that the predictive value of asymptomatic elevations in lactate for progression to lactic acidosis is very low. Brinkman estimated that the incidence of clinically significant hyperlactatemia was 11 per 1000 person-years on antiretroviral therapy (Abstract 709-T). Lonergan presented an analysis of the predictors of symptomatic hyperlactatemia (Abstract 35). His case definition was abdominal symptoms or elevation of liver enzymes in the presence of a confirmed elevation in lactate. A greater number of nRTIs in

the regimen was associated with a higher risk of developing the syndrome. Highest rates were observed in patients receiving stavudine, abacavir, and lamivudine and stavudine, didanosine, and lamivudine. In the pediatric population, elevated lactate levels were present in over 90% of infants exposed to antiretroviral therapy during gestation (Abstract 113). The clinical significance of this observation is not known.

Bone Disease

As reported previously, bone loss can be found in HIV-infected patients even before treatment with antiretroviral therapy (Abstract 715-T). Bone disease appears more common in patients with low CD4+ cell counts and in those with abnormalities in glucose tolerance (Abstracts 712-T and 716-T). Protease inhibitors are associated with reduced bone mineral density in cross-sectional studies, and indinavir exposure leads to bone loss in a mouse model (Abstracts 713-T and 717-T). In humans, cortical bone is more affected than trabecular bone. Data from cross-sectional studies are conflicting on the contribution of protease inhibitors to bone disease. Mondy and colleagues (Abstract 718-T) reported the results of one of the first prospective studies of bone mineral density. After 1 year of follow-up there was a slight improvement in bone mineral density among carefully monitored patients receiving protease inhibitor regimens. Clearly, longer-term data in larger population bases are needed to more fully understand this complication of HIV disease and perhaps therapy. Notably absent were any studies on approach and treatment to bone disease.

Abacavir Hypersensitivity Reactions

Hypersensitivity reactions (HSR) are an uncommon (5%) but potentially life-threatening complication of abacavir. Postulating that hypersensitivity reactions are immune-mediated reactions influenced by genetic factors, 2 groups of investigators sought to identify genetic predictors of susceptibility to abacavir hypersensitivity. Mallal examined haplotypes in 200 Australians prescribed abacavir (Abstract 91). The presence of HLA-B*5701 and DRB1*0701 + DQ3 had a positive predictive value of 100% and a negative predictive value of 97%. In a second case control study of 200 subjects participating in clinical trials of abacavir (Abstract 92), HLA-B57 was present in 46% of cases versus 3% of controls (P<.001). These studies are very important and illustrate that in the future, clinicians may be able to use genetic testing to individualize drug regimens. Much more work needs to be done on broader patient populations before these findings are incorporated into practice; however, existing databases may facilitate this process in this rapidly moving and exciting field.

Hepatitis and Opportunistic Infections

Hepatitis Coinfection

This year, presentations on pathogenesis and treatment of HIV and hepatitis coinfection represented one of the high points of the meeting. There were randomized treatment trials and accompanying studies of viral dynamics as well as interesting studies on pathogenesis of HIV and hepatitis. Early outcomes of liver transplantation in the hepatitis-infected HIV population were presented. There was a standing-room-only symposium on HIV and hepatitis coinfection with Peters, Thomas, Ray, and Chung providing superb overviews of the field (Abstracts S13-S16).

Chung and colleagues presented 24-week data from a randomized study of pegylated interferon alfa-2a and ribavirin versus interferon alfa-2a and ribavirin for the treatment of HCV coinfection (Abstract LB15). Virologic response rates (HCV RNA <60 IU) were higher in the pegylated interferon alfa arm (44%) than in the interferon alfa group (15%). About a third of all virologic nonresponders exhibited histologic improvement on liver biopsies. CD4+ cell counts declined in both arms, but there were no changes in HIV RNA suppression. In this cohort, declines in HCV RNA could be fitted to biphasic decay curves, with faster phase I decay rates present in the pegylated interferon alfa-2a group (Abstract 122). Defining optimal treatment regimens and predictors of response will be enhanced by additional follow-up in this cohort, incorporating relapse rates in the overall response rates.

Torriani (Abstract 121) presented early HCV RNA dynamics from another ongoing study of patients treated with combinations of interferon alfa-2a, pegylated interferon alfa-2a, and ribavirin. She reported a single phase of decay in HCV RNA levels and also observed declines in liver enzymes (ALT levels) that paralleled reductions in HCV RNA levels.

Sulkowski (Abstract 651-M) presented the 12-week results of a randomized treatment trial of daily versus thrice-weekly interferon alfa-2b, both given with ribavirin, in HCV/HIV coinfected persons. Early virologic response rates (undetectable serum HCV RNA) were higher in the daily dosing (25%) group than in the thrice-weekly (10%) group. Up to a quarter of patients in both arms discontinued therapy prematurely. Another randomized study was presented by Perez-Olmeda (Abstract 653-M). Subjects (n=111) were randomized to thrice-weekly interferon alfa plus daily ribavirin versus a 6-week course of interferon alfa and ribavirin followed by thrice-weekly interferon alfa and daily ribavirin. The sustained response rate was 23% and did not differ between arms. Interestingly, the reduction in HCV RNA level at 1 month was not predictive of a sustained response, as delayed reductions in HCV RNA levels were observed in some responders.

Taken together, these data suggest that continuous exposure to interferon alfa is associated with greater early response rates, but tolerance of the therapy is difficult for a significant proportion of patients. Despite good adherence, a substantial number of patients do not respond to available therapies. More data are needed to characterize the dynamics of HCV clearance and rebound and to better define predictors of response and determinants of failure.

Progress in the treatment of hepatitis B virus (HBV) infection was encouraging. In a randomized study of 3 doses of emtricitabine for the treatment of HBV in HIV-infected patients (Abstract 674-M), 61% of patients receiving the highest dose (200 mg daily) had undetectable viremia after 1 year of therapy. Half of the HBV e antigen-positive

patients in this group became HBV e antigen-negative. Among virologic nonresponders, the incidence of the YMDD mutation was 6%.

Efficacy of adefovir and tenofovir disoproxil fumarate (tenofovir) against HBV was demonstrated in cohorts of patients receiving antiretroviral therapy in which one of these agents was added to the regimen. In the 907 trial (Abstract 124), HBV levels decreased by 4.6 log in groups randomized to tenofovir (n=12) and increased by 1.2 log in the 2 patients receiving placebo. An open-label study of 10 patients who added tenofovir to their regimen showed similar reductions in HBV DNA levels (Abstract 675-M). In another study of 35 patients, adefovir was added to the regimen of patients already receiving lamivudine who had the YMDD mutation in HBV DNA polymerase (Abstract 123). Serum HBV DNA levels decreased by 5 $\log_{10}$ copies/mL at week 72, and there were improvements in liver transaminase levels and liver histology. Data from an analysis of more than 13,000 patients in the US-based Adult/Adolescent Spectrum of Disease Project suggested that lamivudine may have some protective effects against HBV (Abstract 672-M). In this study, HBV vaccine and lamivudine were associated with a lower risk for development of acute HBV infection.

In HIV-infected patients who have advanced liver disease due to either HBV or HCV, liver transplantation has been performed at a small group of centers. In a summary of the experience of 23 patients, HCV was associated with a worse prognosis (Abstract 125). Overall, control of HIV replication and continued antiretroviral therapy after transplantation was associated with higher survival rates. Roland (Abstract 655-M) evaluated outcome in 23 patients who received either a liver or kidney transplant. Overall, there was a 30% rejection rate and 1 death. Better prognosis was observed in patients with higher CD4+ cell counts and control of HIV viral replication with antiretroviral therapy. These data will be very useful in developing guidelines for patients most likely to benefit from transplantation, and stress the importance of maintaining optimal control of HIV during the post-transplantation period.

HIV infection accelerates the course of HCV infection, and a similar trend was observed in patients with HBV infection (Abstract 656-M). Data on the influence of hepatitis on outcome of HIV disease are still conflicting. One study by Rimland reported shortened survival time from HIV and AIDS diagnosis in coinfected patients (Abstract 658-M). However, another study of 852 patients in the HOPS cohort found that survival rates in patients with and without HCV coinfection were no different when analyses were adjusted for antiretroviral therapy use (Abstract 659-M). In terms of CD4+ cell count rises in response to antiretroviral therapy, one small study found no effect of HCV coinfection after 1 year of therapy (Abstract 637-M). Two larger studies did report diminished increases in CD4+ cell counts in coinfected patients, which were most pronounced after 2 years of therapy (Abstracts 638-M and 639-M).

Data on hepatitis-specific immune responses and viral replication in various compartments were addressed in several presentations. HCV-specific immune responses appear diminished compared with HIV immune responses in the face of ongoing viral replication (Abstract 640-M). One report by Barrett proposed that induction of interleukin-10 (IL-10) by HCV proteins down-regulates HCV responses (Abstract 641-M). Laskus reported evidence supporting HCV replication in the central nervous system, acknowledging that clinical significance needs further study (Abstract 649-M). HCV can also be found in cervical-vaginal lavage specimens, and Nowicki and colleagues proposed that HCV in this compartment plays a role in sexual and mother-to-child transmission of HCV (Abstract 648-M). One study found much lower levels of HCV in the liver but higher levels in the plasma in patients with HCV and HIV coinfection, than in those with HCV infection only (Abstract 643-M).

GB Virus-C Coinfection

Several presentations focused on the mechanism to explain the epidemiologic observation that patients coinfected with HIV and GB virus-C (GBV-C) have slower rates of HIV disease progression. Nunnari proposed that more intact Th-1 cytokine profiles in patients with GBV-C infection could be contributing to slower HIV disease progression (Abstract 667-M). Differences in chemokine receptor mutations (Abstract 670-M) could not explain mortality differences between patients with and without GBV-C. George and colleagues reported differing in vitro replication capacity among GBV-C isolates (Abstract 668-M) and this same group reported reductions in GBV-C levels in patients who were treated with interferon alfa and also identified a GBV-C protein that may be involved in interferon alfa sensitivity (Abstract 669-M).

Tuberculosis

A symposium on TB provided an excellent overview of challenges of HIV and TB coinfection. Beyers presented molecular fingerprinting data demonstrating that many TB infections are recently acquired and that prolonged exposure is not necessary even in the HIV-uninfected population (Abstract S5). A presentation on TB transmission in Harare, Zimbabwe, underscored the point that many TB infections are recent (Abstract 621-W).

Whalan summarized the current model of HIV and TB copathogenesis (Abstract S6). Efforts to reduce immune activation TB, and hence HIV replication and disease progression, with immunomodulators during TB treatment have been unsuccessful to date. Flynn described the many candidate vaccines that are in the pipeline for TB (Abstract S7). The inability to define components of a protective immunologic response to TB as well as the ease with which latent infection is established and maintained represent 2 formidable obstacles. Maartens presented data on the large experience in Cape Town, South Africa, with HIV/TB coinfection (Abstract S8). He outlined the challenges of delivering HIV and TB therapy in a resource-limited setting. He showed encouraging data that the use of antiretroviral therapy in this setting was associated with dramatic reductions in TB cases. Girardi made the point that atypical presentations of TB occur both in patients with low CD4+ cell counts and in patients with immune reconstitution from antiretroviral therapy (Abstract 623-W).

Discontinuation of Opportunistic Infection Prophylaxis

The major themes of the presentations on discontinuation of opportunistic infection prophylaxis were that HIV-related complications do occur, but rarely in severely immune-compromised patients who have responded to antiretroviral therapy and have discontinued primary prophylaxis (Abstracts 630-W and 631-W). Regarding secondary prophylaxis, 1 in 17 patients with toxoplasmosis (Abstract 633-W), 1 in 48 patients with disseminated *Mycobacterium avium* complex (Abstract 634-W), and 3 of 58 patients with cryptococcal disease (Abstract 635-W) developed recurrent infections after treatment with antiretroviral therapy and discontinuation of secondary prophylaxis.

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Management of Antiretroviral Therapy

Timothy J. Wilkin, MD, C. Mhorag Hay, MD, Christine M. Hogan, MD, and Scott M. Hammer, MD

As in previous years, the 9th Conference on Retroviruses and Opportunistic Infections provided a forum for a state-of-the-art update in antiretroviral therapy. Highlights included the status of new antiretroviral agents from both existing and new drug classes; presentation of trials in antiretroviral-naive and antiretroviral-experienced persons; updates on strategic approaches to therapy, including when to start therapy, treatment interruptions, and immune-based therapies; mechanisms and evolution of viral drug resistance; clinical applications of drug resistance testing; and therapeutic drug-level monitoring.

Antiretroviral Chemotherapy: New Investigational Agents

The advent of currently available antiretroviral medications has substantially reduced HIV-1-related morbidity and mortality. However, the increasing emergence of drug-resistant HIV-1 variants as well as short-term and long-term toxic effects of these agents limit their overall effectiveness. Several presentations at the conference addressed new antiretroviral agents, including new agents in existing classes with more favorable resistance or toxicity profiles, as well as agents in new classes with non-overlapping resistance mechanisms compared with currently available classes.

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Entry Inhibitors

The chemokine receptors CCR5 and CXCR4 are coreceptors used by many strains of HIV-1 in addition to CD4 to enter cells. Attempts are under way to develop antiretroviral agents that inhibit HIV-1 entry by blocking these requisite coreceptors.

CXCR4 Receptor Blockers. AMD-3100 is a small-molecule CXCR4 receptor blocker with potent in vitro anti-HIV activity. Results of an open-label dose-escalation study to test the safety, pharmacokinetics, and antiviral effect of AMD-3100 were presented (Abstract 391-T). Forty HIV-infected volunteers with plasma HIV-1 RNA levels above 5000 copies/mL, on no or stable antiretroviral regimens, were enrolled and received 10 days of continuous intravenous infusion of AMD-3100 at a dose escalating from 2.5 µg/kg/hr up to 160 µg/kg/hr. Presence of the syncytium-inducing (SI) phenotype (one method for determining presence of CXCR4-using variants) was not part of the inclusion criteria, and only 28% of volunteers harbored SI variants.

The study was discontinued early because of adverse effects and lack of antiviral effect. Adverse experiences, particularly gastrointestinal in nature, were generally common. Two patients experienced unexpected adverse events of premature ventricle contractions, and some patients in each dose group had atrial tachycardia. Three volunteers discontinued the study drug because of adverse events. No volunteer harboring SI virus showed a 1-$\log_{10}$ or higher drop in HIV-1 RNA, but 1 patient harboring SI virus had a 0.9-$\log_{10}$ drop at day 10 of the highest dose. Of note however, through use of an entry assay that can identify HIV-1 isolates that are X4-, X5-, or dual-tropic, investigators observed that 9 of 19 patients with dual (X4/R5) or mixed (X4 and R5) virus at baseline exhibited a complete loss of X4 virus by day 11 of treatment. This result suggested the ability of the drug to eliminate X4 variants (Abstract 2). The drug is not currently going forward in clinical development, but proof of principle appears to have been established.

CCR5 Receptor Blockers. Laughlin presented the results for the first 12 HIV-infected volunteers treated with SCH-C, an orally bioavailable CCR5 receptor antagonist with potent in vitro antiviral activity against a broad range of primary HIV-1 isolates (Abstract 1). In this ongoing, sequential rising-dose trial, in which there will be 12 subjects per group, HIV-infected volunteers receive 10 days of SCH-C monotherapy with total daily doses of 50, 100, and 200 mg. To date, 12 HIV-1-infected adults, with CD4+ cell counts above 250/µL, currently not receiving antiretroviral therapy and with a non-SI phenotype, have received SCH-C 25 mg orally every 12 hours for 10 days and have undergone intensive pharmacokinetic and plasma HIV-1 RNA monitoring.

SCH-C was well tolerated, although in electrocardiogram testing, subtle prolongation of the mean QTc interval was seen over 10 days of the lowest dose. Ten of 12 volunteers experienced at least a 0.5-$\log_{10}$ reduction in plasma HIV-1 RNA level from baseline during dosing, and 4 subjects experienced a 1-$\log_{10}$ or greater drop in plasma HIV-1 RNA level from baseline. Thus these preliminary proof-of-principle data for SCH-C support further exploration of the CCR5 receptor as a target for antiretroviral therapy. The clinical future of SCH-C will depend in part on electrocardiographic findings at the higher doses.

One of the concerns of targeting the CCR5 coreceptor is that doing so could select for X4-using strains of HIV-1 that have been associated with more rapid CD4+ T-cell count decline and clinical progression. HIV-1 variants resistant to SCH-C were generated by in vitro passaging of HIV-1 strains in peripheral blood mononuclear cells (PBMCs) in the presence of increasing concentrations of SCH-C (Abstract 397-T). Characterization

of the emerging variants with reduced sensitivity to SCH-C showed no switch to other chemokine receptors including CXCR4. However, it has not been determined whether this switch occurs in vivo. Similar findings in terms of continued CCR5 coreceptor use by resistant virus were reported from in vitro serial passaging experiments in the presence of SCH-D, another potent small-molecule antagonist of CCR5 in preclinical development (Abstract 396-T).

PRO 140 is an anti-CCR5 monoclonal antibody that potently inhibits HIV-1 entry in vitro. Results of a study evaluating the antiviral activity of PRO 140 in vivo in the hu-PBL-SCID mouse model of HIV-1 infection were presented (Abstract 403-T). The mice were infected with the R5 isolate HIV-1 JR-CSF and then treated intraperitoneally with PRO 140 or a control antibody. Both single-dose (1 mg) and multiple-dose (0.1-1.0 mg every 3 days for 3 weeks) PRO 140 reduced plasma HIV-1 RNA to levels below detection in all treated animals, with the highest plasma HIV-1 RNA level reduction being 1.8 $\log_{10}$ copies/mL. Dose-dependent differences were observed in the kinetics of the antiviral response. Further studies of this compound in HIV-infected volunteers are planned.

Novel Entry Inhibitors. Colonno described the identification and characterization of a novel small-molecule inhibitor of HIV-1 entry, BMS-806, which was identified using a cell-based screen and is believed to target the HIV-1 envelope protein (Abstracts 9 and 10). In vitro assays have demonstrated that the compound competitively inhibits the binding of gp120 to CD4 and that the radiolabeled inhibitor binds selectively to purified gp120 protein. The compound potently inhibits HIV-1 clinical isolates and laboratory strains (R5-, X4-, and dual-tropic variants) with a median effective concentration (EC_{50}) of 62 nM in culture assays with subtype-B isolates, and is inactive against HIV-2 and simian immunodeficiency virus (SIV). BMS-806 has low cytotoxicity and is orally bioavailable in rats, dogs, and monkeys. Preliminary animal toxicology studies have revealed no safety concerns as of yet. In vitro passaging of HIV-1 strains in the presence of the compound selected for resistant strains, with mutations located within either gp41 or the CD4 binding site of gp120.

A cautionary note was sounded regarding the targeting of the very heterogeneous HIV-1 envelope protein: although 20 of 24 subtype-B isolates were inhibited by BMS-806 with an EC_{50} below 100 nM, 4 outliers had an EC_{50} as high as 10,000 nM. Future studies with this promising compound will elucidate the mechanism of this diminished susceptibility and the potential of this agent to inhibit a wide variety of HIV-1 strains.

Integrase Inhibitors

In vitro data for a new HIV-1 integrase inhibitor in clinical development were presented by Fujiwara and colleagues (Abstract 8). S-1360 is an orally available small-molecule inhibitor of HIV-1 integrase, the enzyme essential for the integration of HIV-1 proviral DNA into host-cell chromosomes. The compound is an integrase inhibitor with an EC_{50} of 28 to 74 ng/mL in vitro against clinical isolates, and has demonstrated anti-HIV activity in a mouse-MT4 in vivo assay. HIV-1 variants resistant to S-1360 have been isolated in vitro and the amino acid substitutions responsible for drug resistance have been shown to be in close proximity to the integrase active site (eg, T66I). This compound is currently being investigated in a phase 1/2 study of HIV-infected volunteers.

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

DPC 817 (Abstract 385-T) is a cytidine nucleoside reverse transcriptase inhibitor (nRTI) with activity against many lamivudine- and zidovudine-resistant HIV-1 isolates. It is rapidly converted to the active triphosphate form, which has an intracellular half-life of 13 to 17 hours. DPC 817 inhibits wild-type laboratory and clinical isolates of HIV-1 with a mean 90% inhibitory concentration value of 855 nM, and shows less than 5-fold reduction in activity against recombinant viruses containing as many as 10 mutations, including M41L, M184V, D67N, L74V, K70R, T215Y, or K219Q. Thus DPC 817 may be effective in individuals with resistance to other nRTIs and is currently under investigation in a phase 1/2 clinical trial.

Tenofovir disoproxil fumarate (tenofovir) is a recently approved nucleotide reverse transcriptase inhibitor for treating HIV infection. Louie and colleagues assessed the antiviral potency of this agent by obtaining frequent measurements of HIV-1 RNA during the first 3 weeks of monotherapy with tenofovir in 10 HIV-infected patients (Abstract 3). The decay rate of HIV-1 RNA was calculated and compared with the decay rates from similar previous experiments with other agents. They found that tenofovir monotherapy led to a decay rate similar to that seen in ritonavir monotherapy, indicating that this agent has robust activity against HIV-1.

Nonnucleoside Reverse Transcriptase Inhibitors

TMC125 is a novel, second-generation investigational nonnucleoside reverse transcriptase inhibitor (NNRTI) with equally potent in vitro activity against wild-type HIV-1 and NNRTI-resistant HIV-1 bearing the L100I, K103N, Y181C, Y188L, or G190A/S mutations. Gazzard (Abstract 4) presented results of a trial evaluating the antiviral activity of TMC125 in patients on failing NNRTI-containing regimens. Sixteen male volunteers with documented resistance to efavirenz (>10-fold decrease in susceptibility by VirtualPhenotype and/or Antivirogram [Tibotec-Virco, Mechelen, Belgium]), in whom an efavirenz- or nevirapine-containing regimen was failing, were enrolled. They received 900 mg of TMC125 orally twice daily for 7 days in place of the failing NNRTI, and continued to take their nRTIs unchanged. One patient was withdrawn because of nonadherence. Median baseline plasma HIV-1 RNA level was 10,753 copies/mL and median baseline CD4+ cell count was 389/µL. Median fold-change in EC_{50} to efavirenz at screening was 111 (range, 16-659), and all patients had greater than 35-fold decreased sensitivity to nevirapine.

TMC125 was well tolerated in this study, with 11 patients reporting grade 1 adverse events, the most common of which were diarrhea and headache. No lab abnormalities or electrocardiographic changes were observed. The median drop in plasma HIV-1 RNA level at day 8 was 0.89 $\log_{10}$ copies/mL (mean, 0.86

$\log_{10}$; range, 0.18-1.71 $\log_{10}$; intragroup comparison vs baseline, P<.001). Twelve patients (75%) experienced a decrease in plasma HIV-1 RNA level of at least 0.5 $\log_{10}$ copies/mL, and 7 patients (44%) experienced a decrease greater than 1 $\log_{10}$ copies/mL. Thus TMC125 is well tolerated and has significant antiviral potency against NNRTI-resistant HIV-1 in vivo.

One question raised by this presentation is why the plasma HIV-1 RNA decline was less than that seen in NNRTI-naive individuals treated with TMC125 in a separate study (Abstract 5), despite the in vitro activity profile of the drug against NNRTI-resistant isolates. The possibility of pharmacokinetic interactions with lingering efavirenz or nevirapine was given as one possible explanation, but this needs to be clarified in future studies.

In the study of TMC125 in 12 NNRTI-naive subjects (Abstract 5), the initial rate of decline of plasma HIV-1 RNA observed during 1 week of monotherapy with TMC125 900 mg twice daily was compared retrospectively with that obtained during the previously performed 13-patient ERA study of a 5-drug combination of zidovudine, lamivudine, abacavir, indinavir, and nevirapine. The median decline in plasma HIV-1 RNA level was comparable between the 2 groups: 1.92 $\log_{10}$ copies/mL for TMC125-treated patients and 1.55 $\log_{10}$ copies/mL for ERA patients (P=.40). The 2 groups, however, did differ significantly in terms of age (mean, 25 years for the TMC125 group and 40 years for the ERA group), and there was a trend toward higher baseline CD4+ counts in the TMC125 group (458 vs 360 cells/µL). The authors concluded that TMC125 is a highly potent NNRTI.

DPC 083 is another investigational NNRTI with activity against NNRTI-resistant isolates. Preliminary 8-week results were presented of Study DPC 083-203, an ongoing study of the use of DPC 083 (either 100 mg or 200 mg once daily) and 2 nRTIs (selected based on treatment history and baseline genotype) in patients on failing NNRTI-containing regimens (Abstract 6). Fifty-one patients were enrolled, with a mean baseline plasma HIV-1 RNA level of 3.85 $\log_{10}$ copies/mL and a mean baseline CD4+ cell count of 473/µL. Nevirapine had failed in 61% and efavirenz had failed in 39%. In 94% of patients, baseline mutations were consistent with virologic failure on an NNRTI regimen. The on-treatment response rate at week 8 (HIV-1 RNA level <400 copies/mL), pooled for the 100 mg and 200 mg doses, was 57% and varied according to the number of new nRTIs used: 4 of 10 (40%) for patients starting no new nRTIs, 13 of 18 (72%) for patients starting 1 new nRTI, and 10 of 15 (66.7%) for patients starting 2 new nRTIs. Thus, data at 8 weeks suggest that DPC 083 has activity in patients in whom currently available NNRTIs are failing, but that the response rate improves when DPC 083 is used in combination with at least 1 new nRTI. However, almost 30% of patients enrolled were discontinued from the study, mostly because of protocol violations.

The 24-week results of a phase 2, double-blind, dose-ranging study (Study DPC 083-201) of DPC 083 (50, 100, and 200 mg once daily) versus efavirenz in combination with fixed-dose lamivudine/zidovudine in antiretroviral-naive patients were also presented (Abstract 7). As a result of this study, the 100-mg dose of DPC 083 was selected for a phase 3 study in NNRTI-naive patients. At this lower dose, DPC 083 was associated with less dizziness and the same frequency of rash as efavirenz.

Protease Inhibitors

Atazanavir is a once-daily protease inhibitor in development that has been shown not to increase total cholesterol, low-density lipoprotein (LDL), or triglyceride levels in antiretroviral-naive individuals. Haas presented the results of a randomized, active-controlled, blinded study that evaluated the safety, tolerability, and efficacy of atazanavir (400 or 600 mg qd)/saquinavir (1200 mg qd) and 2 nRTIs versus ritonavir (400 mg bid)/saquinavir (400 mg bid) and 2 nRTIs (Abstract 42). Study subjects were volunteers in whom a prior regimen was virologically failing. Efficacy and lipid results at week 48 were presented for 85 subjects having a plasma HIV-1 RNA level of 1000 to 100,000 copies/mL and CD4+ cell counts of at least 100/µL. There were fewer treatment discontinuations due to adverse effects in the atazanavir arms than in the ritonavir arm (9% vs 30%). The mean decrease in plasma HIV-1 RNA levels at week 48 was 1.44 $\log_{10}$ copies/mL in the 400-mg atazanavir arm, 1.19 $\log_{10}$ copies/mL in the 600-mg atazanavir arm, and 1.66 $\log_{10}$ copies/mL in the ritonavir arm.

Subjects receiving the atazanavir-containing regimen experienced decreases in cholesterol, LDL, and triglyceride levels with mean percent change from baseline of 1, –1, and –5, respectively, for the 400-mg dose of atazanavir; and –5, –7, and –27, respectively, for the 600-mg dose of atazanavir. In contrast, subjects in the ritonavir-containing arm experienced sustained increases in total cholesterol, LDL, and triglyceride levels, with mean percent change from baseline of +11, +23, and +93, respectively. A new protease inhibitor without adverse effects on lipids would be a welcome addition to the antiretroviral armamentarium.

Antiretroviral Chemotherapy in Antiretroviral-Naive Subjects

Timing of Initial Antiretroviral Therapy

Optimal timing of antiretroviral therapy initiation for HIV-infected patients remains unclear. Chaisson addressed this topic during the "Controversies in Antiretroviral Therapy" symposium (Abstract S17). He discussed whether data exist to justify the following rationales for early treatment:

1. Will early treatment lead to eradication? *No, not with current therapy.*

2. Does early therapy lead to better virologic response? *Probably not; in studies that have shown a worse virologic response when treatment is initiated with CD4+ cell counts below 200/µL, the results may have been confounded by poorer adherence in the delayed initiators.*

3. Do patients who are treated later experience more drug-related toxicity? *Perhaps in the short-term, but some long-term toxicities such as new-onset hyperglycemia are common to all.*

4. Is immune function restored if treatment is begun late? *Yes, although the durability is unknown.*

Thus the remaining question is whether early treatment improves clinical outcome. The answer to this question remains elusive in part because of the difficulty in performing a randomized clinical trial to address the question. Chaisson discussed a previously published observational cohort study from the Johns Hopkins HIV program that followed 2 groups of patients who entered the clinic after July 1, 1996 (Sterling et al, AIDS, 2001). The first group initiated antiretroviral therapy for at least 90 days, and the second group did not initiate antiretroviral therapy. Patients who initiated antiretroviral therapy were more likely to be men, less likely to be African American or injection-drug users, and had lower baseline CD4+ cell counts and higher baseline plasma HIV-1 RNA levels than the group that did not initiate antiretroviral therapy.

Among persons with CD4+ cell counts below 200/µL at entry, patients who initiated antiretroviral therapy experienced a lower rate of progression to AIDS or death. Patients with CD4+ cell counts from 201/µL to 350/µL or higher experienced no change in clinical disease progression whether or not therapy was initiated. By multivariate analysis of persons on antiretroviral therapy, low CD4+ cell count (<200/µL) at the time of initiation predicted progression to AIDS, but the plasma HIV-1 RNA level was not as predictive.

Chaisson thus concluded that patients who initiate antiretroviral therapy at CD4+ cell counts above 350/µL have not been shown to benefit clinically and that the optimal time to initiate antiretroviral therapy for patients with CD4+ cell counts from 200/µL to 350/µL has not been determined. Patients with CD4+ cell counts below 200/µL should initiate treatment. He also concluded that a high plasma HIV-1 RNA level by itself should not be an indication for treatment, but might suggest more frequent monitoring. He acknowledged the following caveats to these conclusions: observational cohorts are subject to measurable and unmeasurable confounding and cannot replace randomized controlled trials; variability between cohorts is problematic; and follow-up is limited—we do not as yet know whether 5 or 10 years of follow-up will show that either early or delayed initiation is more beneficial. Survival data have been based on 2- or 3-year follow-up.

Palella presented data from the HIV Outpatient Study (HOPS), which suggested that patients who initiate antiretroviral therapy at higher CD4+ cell counts experience lower mortality (Abstract 13). They grouped patients observed at 8 US clinics participating in the HOPS from January 1996 to March 2001 into 1 of 3 pretreatment CD4+ cell count strata: 501 to 750 cells/µL (n=126), 351 to 500 cells/µL (n=315), and 201 to 350 cells/µL (n=377). In a prospective analysis, they looked at mortality rates in each preantiretroviral therapy CD4+ count stratum, comparing patients who initiated antiretroviral therapy while in that pretherapy stratum with patients who delayed antiretroviral therapy until they reached a lower stratum.

For patients with CD4+ counts of 201 to 350 cells/µL, 20.8 deaths per 1000 person-years of observation occurred in 325 "initiators" and 70.6 deaths per 1000 person-years of observation occurred in 52 "delayers" (rate ratio [RR]=0.29, P<.001; median years of follow-up, 3.0 for initiators and 3.3 for delayers, P>.3). For patients with CD4+ counts between 351 and 500 cells/µL, 10.7 deaths per 1000 person-years of observation occurred in 229 initiators and 18.2 deaths per 1000 person-years of observation occurred in 86 delayers (RR=0.59, P>.3; 95% confidence interval [CI], 0.21, 1.65; median years of follow-up, 3.7 for initiators and 3.4 for delayers, P>.3). For patients with CD4+ counts of 501 to 750 cells/µL, 7.5 deaths per 1000 person-years of observation occurred in 54 initiators and 3.0 per 1000 person-years occurred in 72 delayers (RR=2.25, P>.4), but only 3 deaths occurred in this stratum, none apparently HIV-related (median years of follow-up, 5.9 for initiators and 5.3 for delayers, P>.3).

The authors concluded that these preliminary data suggest that initiation of antiretroviral therapy for patients with CD4+ counts of 201 to 350 cells/µL, and possibly for patients with CD4+ counts of 351 to 500 cells/µL, is associated with reduction in mortality in comparison with those who delay therapy.

Trials in Antiretroviral-Naive Subjects

The results of trials of initial antiretroviral therapy in treatment-naive patients are selectively summarized in Table 1.

AIDS Clinical Trials Group 388 Study. Fischl presented the results of ACTG 388, a phase 3 open-label randomized study comparing 2 4-drug antiretroviral regimens with a 3-drug regimen in patients with advanced HIV disease (CD4+ cell count <200/µL or plasma HIV-1 RNA level >80,000 copies/mL) and no prior antiretroviral or limited nRTI therapy (Abstract 41). The trial compared the use of zidovudine and lamivudine with either indinavir (800 mg tid), efavirenz and indinavir (1000 mg tid), or nelfinavir (1250 mg bid) and indinavir (initially 1000 mg bid but increased to 1200 mg bid during the study). Among the 517 enrolled, the mean baseline CD4+ cell count was 161/µL and the mean plasma HIV-1 RNA level was 5.42 $\log_{10}$ copies/mL; median follow-up was 2.1 years. The primary endpoint was time to virologic failure, which occurred in 172 subjects: 52 in the indinavir arm, 39 in the efavirenz/indinavir arm, and 81 in the nelfinavir/indinavir arm. Virologic failure occurred at a lower rate in the efavirenz/indinavir arm (P=.04) and at a higher rate in the nelfinavir/indinavir arm than in the indinavir-only arm (P=.006). There was a trend toward less discontinuation in the efavirenz/indinavir arm.

Grade 3 or 4 signs and symptoms occurred in 126 individuals in the study: 35 in the indinavir arm, 41 in the efavirenz/indinavir arm, and 50 in the nelfinavir/indinavir arm. Grade 3 or 4 laboratory abnormalities occurred in 178 subjects (57, indinavir; 58, efavirenz/indinavir; and 63, nelfinavir/ indinavir). There was a trend toward increased occurrence of adverse events in the nelfinavir/indinavir arm as compared with the indinavir arm (P=.07), but no significant difference was seen in occurrence of adverse events between the efavirenz/indinavir arm and the indinavir arm (P=.97). Fischl and colleagues concluded that compared with the 3-drug regimen, treatment with zidovudine, lamivudine, efavirenz, and indinavir was comparably well tolerated and yielded a superior virologic response. Treatment with zidovudine, lamivudine, nelfinavir, and indinavir, on the other hand, yielded an inferior viro-

Table **1.** Trials in Antiretroviral-Naive Patients

Authors, Study (Abstract No.), and Regimens	N	Follow-up	Baseline Values		Change in Values	
			HIV-1 RNA (copies/mL)	CD4+ (cells/μL)	HIV-1 RNA (copies/mL)	CD4+ (cells/μL)
Fischl et al, ACTG 388 (41)						
1. zidovudine/lamivudine/ indinavir 800 mg tid	168	2.1 years (median)	5.42 $\log_{10}$	161	86% <200 by week 24	Increase
2. zidovudine/lamivudine/efavirenz/ indinavir 1000 mg tid	173				87% <200 by week 24	Increase
3. zidovudine/lamivudine/nelfinavir 1250 mg bid/indinavir 1000 mg bid (later increased to 1200 mg bid)	176				78% <200 by week 24	Increase
Eron et al, M99-056 (409-W)						
1. stavudine/lamivudine and lopinavir/ritonavir 800/200 mg qd	19	48 weeks	4.7 $\log_{10}$	264	74% <50 by ITT at week 48	+235
2. stavudine/lamivudine and lopinavir/ritonavir 400/100 mg bid	19				79% <50 by ITT at week 48	+248
Domula et al (408-W)						
1. zidovudine/lamivudine/efavirenz	35	48 weeks	4.9 $\log_{10}$	275	37% <50 by ITT; 81% <50 by OT	+180
2. lamivudine/stavudine/efavirenz	35			163	40% <50 by ITT; 82% <50 by OT	+245
3. didanosine/stavudine/efavirenz	38			165	37% <50 by ITT; 74% <50 by OT	+281

ACTG indicates AIDS Clinical Trials Group; ITT, intent-to-treat analysis; OT, on-treatment analysis.

logic response.

CHARM Study. The CHARM study was a phase 3, open-label, randomized, multicenter study to evaluate the efficacy and tolerability of adding nevirapine and/or hydroxyurea to a triple-nRTI regimen in treatment-naive HIV-1-infected subjects (Abstract 410-W). Volunteers with plasma HIV-1 RNA levels above 5000 copies/mL were randomized using a factorial design to add nevirapine and/or hydroxyurea to the combination of zidovudine, lamivudine, and abacavir. The primary endpoint was treatment failure defined as plasma HIV-1 RNA level above 50 copies/mL at or after week 24, or discontinuation of or change in randomized treatment. A total of 229 volunteers were enrolled, with baseline CD4+ cell count of 269/μL and baseline plasma HIV-1 RNA level of 4.6 $\log_{10}$ copies/mL.

By intent-to-treat analysis at week 48, treatment failure had occurred in 60% of volunteers receiving nevirapine, compared with 62.3% of patients not receiving nevirapine (P=.826). The as-treated failure rates were 21.1% and 27.1%, respectively (P=.445). By intent-to-treat analysis at week 48, treatment failure had occurred in 69.3% of volunteers receiving hydroxyurea, compared with 53.9% of patients not receiving hydroxyurea (P=.017). The as-treated failure rates were 23.9% and 24.3%, respectively (P=.963). The odds ratio of experiencing treatment failure at week 48 was 1.71 (95% CI, 1.11, 2.62) for hydroxyurea use.

Treatment-limiting adverse events occurred more frequently in subjects taking hydroxyurea (51.8%) than in those not taking hydroxyurea (26%; P<.001); adverse events also occurred more frequently in subjects taking nevirapine (46.1%) than in those not taking nevirapine (31.6%; P=.024). In the intent-to-treat analysis, a slower increase in mean CD4+ cell count was seen in subjects receiving hydroxyurea than in subjects not receiving hydroxyurea. Thus, neither the addition of hydroxyurea nor the addition of nevirapine to the triple-nRTI regimen decreased the primary endpoint of treatment failure, and addition of either hydroxyurea or nevirapine increased the incidence of adverse events.

Study M99-056. Eron presented the 48-week results of study M99-056 comparing once-daily and twice-daily dosing of

Comments

The efavirenz/indinavir group had superior virologic response: 39 virologic failures vs 52 in indinavir arm (*P*=.04). The nelfinavir/indinavir group had inferior virologic response: 81 virologic failures vs 52 in indinavir arm (*P*=.006).

Adverse events and adherence were similar in the 2 groups. The qd group had lower lopinavir trough levels.

36 patients (33%) discontinued therapy because of adverse events: 10, efavirenz-related rash or central nervous system symptoms; 6, neuropathy; 3, nausea; 2, leukopenia or anemia; 1, lipodystrophy; 1, asthenia; 2, emergence of resistance; and 11, reasons not related to therapy. Overall cholesterol levels increased by 28% from baseline.

coformulated lopinavir/ritonavir in combination with stavudine and didanosine (Abstract 409-W). Thirty-eight antiretroviral-naive patients with median baseline plasma HIV-1 RNA level of 4.7 $\log_{10}$ copies/mL and CD4+ cell count of 264/µL were randomized to receive lopinavir/ritonavir 800/200 mg once daily or lopinavir/ritonavir 400/100 mg twice daily in addition to the standard doses of stavudine and lamivudine. Lopinavir area-under-the-curve and maximum concentration (C_{max}) values were similar for the daily and twice-daily regimens, but overall median lopinavir trough concentration/IC_{50} was lower in the daily than the twice-daily regimen (40 vs 84). Pharmacokinetic data from this study were also given in an oral presentation by Bertz (Abstract 126).

By intent-to-treat analysis in which missing data equaled failure, 74% and 79% of patients in the daily and twice-daily groups, respectively, had plasma HIV-1 RNA levels below 50 copies/mL at week 48. The mean CD4+ cell count increases from baseline to week 48 were 238/µL and 248/µL for the daily and twice-daily groups, respectively. Adherence was similar between the treatment groups as measured by medication event monitoring system (MEMS cap) analysis. The frequency of adverse events (nausea, diarrhea, lipid abnormalities) was comparable across the 2 groups.

Comparison of 3 nRTI Combinations With Efavirenz. Domula presented the results of a study evaluating the safety and efficacy of efavirenz in combination with 3 different dual nRTI combinations in antiretroviral-naive HIV-1-infected patients (Abstract 408-W). Patients received efavirenz in combination with zidovudine/lamivudine (n=35), lamivudine/stavudine (n=35), or didanosine/stavudine (n=38). Median baseline plasma HIV-1 RNA level was 4.9 $\log_{10}$ copies/mL and CD4+ cell count was 174/µL. By intent-to-treat analysis at 48 weeks, the percentage of patients with plasma HIV-1 RNA level below 50 copies/mL was 37% in the zidovudine/lamivudine group, 40% in the lamivudine/stavudine group, and 37% in the didanosine/stavudine group. (By on-treatment analysis, the percentages were 81%, 82%, and 74%, respectively.) There were no statistically significant differences in virologic response among the 3 groups.

Over 48 weeks, 36 patients (33%) discontinued therapy because of adverse events, although in 11, these were not related to therapy: 10 stopped because of efavirenz-related effects (rash and central nervous system effects), 6 because of didanosine/stavudine-related neuropathy, 3 because of nausea, 2 because of anemia or leukopenia, 1 because of lipodystrophy, 1 because of asthenia, and 2 because of development of resistance. Overall, cholesterol levels increased by 28% from baseline to week 48 (P<.0001), with a preponderance of cholesterol elevations in the didanosine/stavudine arm, and triglyceride levels increased by 38% from baseline (P=.004). The authors conclude that efavirenz in combination with any of the 3 different nRTI pairs is an effective initial antiretroviral regimen. However, 33% of volunteers terminated therapy early because of adverse events, of which approximately two-thirds were therapy related, and these protease inhibitor-sparing regimens were not immune to adverse effects on lipids.

Antiretroviral Chemotherapy in Antiretroviral-Experienced Subjects

Trials in Antiretroviral-Experienced Patients

The results of trials in antiretroviral therapy-experienced patients are summarized in Table 2.

ACTG 398 Study. The results of ACTG 398 were given by Mellors in an oral presentation that focused on the baseline predictors of virologic suppression (Abstract 45). The stimulus for this trial was to address whether the addition of a second protease inhibitor to a new 4-drug salvage regimen would lead to improved virologic suppression among patients in whom protease-inhibitor-based regimens were failing. Participants were eligible if they had a plasma HIV-1 RNA level above 1000 copies/mL, prior exposure to 1 to 3 protease inhibitors for more than 16 weeks, and no prior experience with abacavir, adefovir, or amprenavir. Fifty-six percent of participants were NNRTI-naive. All participants received abacavir, adefovir, efavirenz, and amprenavir, and were randomized to indinavir 1200 mg twice daily, saquinavir soft-gel capsule 1600 mg twice daily, nelfinavir 1250 mg twice daily, or placebo. The median baseline HIV-1 RNA level was 4.7 $\log_{10}$ copies/mL and the median CD4+ cell count was 202/µL. Virologic failure was defined as a confirmed rise of HIV-1 RNA level above baseline, a less than 0.5-$\log_{10}$ decline in HIV-1 RNA level by week 8, a confirmed 1.0-$\log_{10}$ rise above HIV-1 RNA nadir, 2 consecutive HIV-1 RNA levels of at least 200 copies/mL after 2 consecutive values below this limit, or a confirmed HIV-1 RNA level of at least 200 copies/mL at week 24 or 48. The virologic failure rate in the 3 dual protease inhibitor arms

Table **2.** Trials in Treatment-Experienced Patients

Authors, Study (Abstract No.), and Regimen (s)	N	Follow-up (weeks)	Baseline Values		Change in Values	
			HIV-1 RNA (copies/mL)	CD4+ (cells/µL)	HIV-1 RNA (copies/mL)	CD4+ (cells/µL)
Haas et al, AI424-009 (42) 1. atazanavir 400 mg/saquinavir sgc 1200 mg qd/2 nRTIs	34	48	3-5 $\log_{10}$	>100	-1.44 $\log_{10}$ (mean change)	+109
2. atazanavir 600 mg/saquinavir sgc 1200 mg qd/2 nRTIs	28				-1.19 $\log_{10}$	+55
3. ritonavir 400 mg/saquinavir sgc 400 bid/2 nRTIs	23				-1.66 $\log_{10}$	+149
Squires et al, Study 907 (413 W) 1. tenofovir 300 qd plus stable background antiretrovirals	368	24 (48)	3.4 $\log_{10}$	427	24 weeks: -0.61 $\log_{10}$ (48 weeks: -0.56 $\log_{10}$)	+12.5
2. placebo plus stable background antiretrovirals (for 24 weeks prior to cross-over)	182	24 (on placebo)			24 weeks: -0.03 $\log_{10}$	-10.8
3. group 2 after cross-over to tenofovir		24 (on tenofovir)			24-48 weeks: -0.7 $\log_{10}$	
Mellors et al, ACTG 398 (45) 1. amprenavir/abacavir/ efavirenz/adefovir/saquinavir sgc 1600 mg or indinavir 1200 mg or nelfinavir 1250 mg bid	322	48	4.7 $\log_{10}$	212	23% <200	N/A
2. amprenavir/abacavir/ efavirenz/adefovir/protease inhibitor placebo	157				18% <200 (*P*=.17)	

ACTG indicates AIDS Clinical Trials Group; NNRTI, nonnucleoside reverse transcriptase inhibitor; nRTI, nucleoside reverse transcriptase inhibitor; sgc, soft-gel capsule; tenofovir, tenofovir disoproxil fumarate.

combined was not significantly different than the placebo arm at 48 weeks (77% vs 82%, respectively; P=.17).

Mellors presented an extensive analysis of the predictors of virologic failure. In a multivariate analysis, baseline phenotypic susceptibility to efavirenz was the most important predictor of virologic failure. Other important predictors were oral efavirenz clearance, NNRTI experience, medication adherence as measured by MEMS cap monitoring, and specific adherence to efavirenz. NNRTI-naive patients with a 0.4-fold or less change in baseline phenotypic resistance to efavirenz (ie, IC_{50} 60% lower than laboratory strain), also known as "hypersusceptibility," had less

Comments

Atazanavir arms had fewer discontinuations due to adverse effects (10% vs 30%) and had a more favorable lipid profile.

Outcome was a time-weighted average decline of log_{10} plasma HIV-1 RNA level. Tenofovir had a significantly greater decline in plasma HIV-1 RNA levels than placebo (*P*<.0001). The subjects were highly antiretroviral-experienced: 48% had baseline NNRTI mutations, 58% had baseline protease inhibitor mutations, and 94% had nRTI mutations. The mean length of antiretroviral use was 5.4 years. Grade 3 or 4 abnormalities were <2% in all groups. Serum creatinine did not rise above 2.0 mg/dL in any patients. A change of >.5 mg/dL was seen in 12 (3%) participants receiving tenofovir for 48 weeks compared with 2 (1%) receiving placebo for 24 weeks. No one discontinued study drug because of change in creatinine or hypophosphatemia.

Of the participants, 44% were NNRTI-experienced. Virologic suppression was strongly predicted by efavirenz hypersusceptibility (<.4-fold resistance) having a 0.27 odds of virologic failure (*P*<.001). There was a high dropout rate due to toxicities (30% at 24 weeks and 42% at 48 weeks).

(table continued on next page)

virologic failure at 48 weeks than NNRTI-naive patients with a more than 0.4- to 2.5-fold change (43% vs 74%, P<.01).

Study 907. Squires presented the results of Study 907 in a poster presentation (Abstract 413-W). Participants enrolled in this study were antiretroviral-experienced and were on a stable regimen with a plasma HIV-1 RNA level of 400 to 10,000 copies/mL. The mean baseline plasma HIV-1 RNA level was 3.36 log_{10} copies/mL and mean CD4+ cell count was 427/µL. These participants were highly treatment-experienced with a mean of 5.4 years of prior antiretroviral use. They were randomized 2:1 to the addition of tenofovir or placebo to the patient's own stable background antiretroviral regimen. After 24 weeks, all participants received open-label tenofovir. The primary outcome was time-weighted average change from baseline log_{10} plasma HIV-1 RNA at 24 weeks ($DAVG_{24}$). The $DAVG_{24}$ was –.61 in the tenofovir group and –.03 in the placebo group (P<.0001). The participants crossing over to tenofovir at 24 weeks showed a similar subsequent decline in log_{10} plasma HIV-1 RNA level ($DAVG_{24}$, –.71). Those originally randomized to tenofovir maintained a .56-log_{10} decline at 48 weeks.

A detailed discussion of the virologic response as predicted by baseline mutations in the reverse transcriptase gene is given in the "Viral Resistance" section in this review. There were a low number of adverse events that did not vary significantly by treatment group. Specifically, no participants developed a creatinine level of more than 2.0 mg/dL or discontinued the drug because of creatinine elevations or hypophosphatemia. Similar conclusions were drawn in a safety analysis combining tenofovir DF 907 study data with data from previous tenofovir clinical trials (Abstract 416-W). Similar virologic response and safety profiles were reported in the expanded access program of 7317 subjects (Abstract 415-W).

Strategies for Antiretroviral Therapy

Structured Treatment Interruptions

Hirschel gave an overview of the controversies associated with structured treatment interruptions (STIs) during the "Controversies in Antiretroviral Therapy" symposium (Abstract S18). The main reasons he outlined for considering stopping therapy were to decrease cost, avoid adverse effects, and boost HIV-specific immunity. The 3 situations in which STI is currently being studied are (1) patients who began potent antiretroviral therapy prior to seroconversion and are chronically virologically suppressed, (2) patients who began potent antiretroviral therapy during the chronic phase of infection (ie, established infection) and who are virologically suppressed, and (3) prior to a salvage regimen in patients with highly drug-resistant virus, to induce resensitization of virus. He stressed that large studies are needed to compare STI to simply discontinuing therapy and to weigh the risks and benefits of STI. Abstracts from the conference examining STI in each of these situations will be discussed in the following sections.

Primary Infection. Miró and colleagues (Abstract 529-M) reported preliminary results from an ongoing study of 12 patients who began highly active antiretroviral therapy (HAART) during primary HIV infection at least 1 year prior to enrollment and who had sustained virologic suppression. These participants will undergo 4 cycles of STI: 2 months off followed by 2 to 4 months on therapy. Viral suppression to below 5000 plasma HIV-1 RNA copies/mL was achieved in 4 of 12 patients after the third STI. A strong CD8+ cytotoxic T lymphocyte (CTL) response developed in 7 of 9 participants after the third STI.

Yu and colleagues described the CTL response in a single patient treated with HAART during acute HIV infection (Abstract 537-M). They were able to document a broadening CTL response in this patient during 2 subsequent STIs using 505 overlapping peptides spanning the entire expressed HIV-1 sequence. Only 2 epitopes were targeted during acute infection compared with 25 at the end of the second STI. However, as of the end of the second STI, virologic control in this patient was not maintained off HAART.

Chronic (Established) Infection. Several presentations examined the outcomes associated with treatment interruptions in the setting of established infection. The largest of these studies came from the EuroSIDA group (Abstract 48) in

Table **2.** Trials in Treatment-Experienced Patients *(continued from page 24)*

Authors, Study (Abstract No.), and Regimen (s)	N	Follow-up (weeks)	Baseline Values		Change in Values	
			HIV-1 RNA (copies/mL)	CD4+ (cells/µL)	HIV-1 RNA (copies/mL)	CD4+ (cells/µL)
Lalezari et al, T20-206 (418-W) 1. Pentafuside (50, 75, or 100 mg) bid/abacavir/efavirenz/ amprenavir/ritonavir bid	52	48	4.28 $\log_{10}$	279	54.9% <400 (pentafuside arms grouped); 47.1% <50	+132
2. abacavir/efavirenz/ amprenavir/ritonavir bid	19		4.25 $\log_{10}$	201	36.8% <400; 36.8% <50	+90
Boyd et al, HIV-NAT 005 (422-W) 1. zidovudine/lamivudine/indinavir 800 mg/ritonavir 100 mg bid	50	76	4.0 $\log_{10}$	168	1.8-$\log_{10}$ decline (66% <50)	+101
2. zidovudine/lamivudine/ indinavir tid	54				1.6-$\log_{10}$ decline (69% <50)	+128
Baldini et al (423-W) Single arm: lopinavir/ritonavir 400 mg/100 mg bid/amprenavir 600 mg bid/and 2 nRTIs	22	24	4.8 $\log_{10}$	177	1.18-$\log_{10}$ decline at week 8; 1.13-$\log_{10}$ decline at week 24	+88
Albrecht et al, ACTG 364 (425-W) 1. nelfinavir/placebo/2 nRTIs	195	144	3.9 $\log_{10}$	350	48% <50	+171
2. efavirenz/placebo/2 nRTIs					58% <50	
3. nelfinavir/efavirenz/2 nRTIs					71% <50	
Lafeuillade et al, HYDILE (424-W) 1. didanosine/stavudine/abacavir/ efavirenz	24	48	4.2 $\log_{10}$	386	21% <50	+118
2. didanosine/stavudine/ abacavir/efavirenz/hydroxyurea	22		3.8 $\log_{10}$		55% <50	-27
3. didanosine/stavudine/ abacavir/efavirenz/hydroxyurea/ interleukin-2	23		3.9 $\log_{10}$		48% <50	+78

ACTG indicates AIDS Clinical Trials Group; NNRTI, nonnucleoside reverse transcriptase inhibitor; nRTI, nucleoside reverse transcriptase inhibitor; sgc, soft-gel capsule; tenofovir, tenofovir disoproxil fumarate.

which 565 of 3610 assessable patients interrupted HAART. The median nadir CD4+ cell count prior to beginning HAART for those subsequently interrupting therapy was 130/µL and the median CD4+ cell count at time of interruption was 242/µL. Participants had to be followed up for at least 3 months after stopping to be included in this analysis. The risk of developing a new AIDS-defining event or death was 6 times higher among those stopping antiretroviral therapy than among those who did not. When controlling for the last-known CD4+ cell count and HIV-1 RNA level,

Comments

The most common adverse effect was local injection site reaction (in 69%), leading to discontinuation in 3 participants (8%). There were no other adverse effects clearly related to pentafuside. This study was not powered to show efficacy.

All participants had at least 3 months of prior zidovudine use. Although not statistically significant, nephrolithiasis, hyperbilirubinemia, and hyperlipidemia were more common in the bid dose group. Drug interruptions or dose reduction was more common in the bid arm than in the tid arm (48% vs 30%, *P*=.05).

Pharmacokinetic data showed lopinavir levels were in the expected range but amprenavir levels were reduced by about 30%.

The efavirenz and efavirenz/nelfinavir arms were superior to the nelfinavir-only arm (*P*=.028 and *P*<.001, respectively). The nRTIs were open-label and based on prior regimens.

All patients were naive to NNRTIs and abacavir, but nearly all had received stavudine and didanosine. Plasma HIV-1 RNA level in the hydroxyurea arms was more likely to be suppressed (*P*=.008), but toxicities were more common in these groups, including 2 cases of lactic acidosis, 2 cases of peripheral neuropathy, and 1 case of grade 3 hepatitis.

the risk was still 2.4 times higher in those interrupting therapy (*P*=.0001). This implies that antiretroviral regimens having poor virologic and immunologic response are associated with a slower disease progression. The magnitude of this risk was strongly correlated with CD4+ cell count. The rate of AIDS-defining events or death was .48 per person-years of observation in those interrupting therapy at a CD4+ cell count below 200/µL, compared with .03 per person-years of observation in those interrupting therapy at a CD4+ cell count above 200/µL. As this is an observational cohort study, caution should be exercised in interpreting the implications of the findings for STIs in the setting of chronic HIV infection.

A note of caution was also made by investigators studying the dynamics of HIV in the cerebrospinal fluid (CSF) after treatment interruption (Abstract 49). Ellis and colleagues demonstrated a rapid rebound of HIV in the CSF among patients interrupting therapy, which lagged only several days behind the plasma HIV-1 RNA level. Four of 12 patients tested also developed a brisk pleocytosis (white blood cell count >10/µL), which followed viral rebound. The neurocognitive consequences of this viral rebound are a planned focus of future investigations.

Another theoretical concern about treatment interruption is that viral rebound can expand the size of the viral reservoir in latently infected T-cells that decay slowly on HAART. Blankson and colleagues (Abstract 491-M) closely followed 5 individuals during STI to characterize the latent reservoir in CD4+ T cells. They found that the frequency of latently infected CD4+ T cells rapidly increased to levels similar to those in primary HIV infection, but also decayed rapidly after reinstitution of HAART, leading the investigators to conclude that the size of the latent reservoir was not dramatically increased during STI.

The Swiss-Spanish Intermittent Treatment Trial is a prospective trial of treatment interruptions in patients beginning HAART in the chronic phase of infection. Hirschel presented data on behalf of the study team in both the previously mentioned symposium on controversies in the management of HIV and a poster session (Abstracts 528-M, S18). This is the largest study to date examining STI in this situation. They studied 133 individuals, 96% of whom began antiretroviral therapy during the chronic phase of their infection with a median CD4+ cell count of 740/µL. All participants underwent the same protocol of STI: 2 weeks off therapy followed by 8 weeks on therapy for 4 cycles, followed by discontinuation of all antiretroviral medications. The primary outcome was proportion with plasma HIV-1 RNA level below 5000 copies/mL ("responders") at week 52 (12 weeks off therapy) and week 96 (56 weeks off therapy). The proportion of responders was 18% at week 52 and 11% at week 96. Response was predicted by a low pre-HAART plasma HIV-1 RNA level and lack of rebound during STI and was not correlated to HIV-specific immunity as measured. This led the investigators to conclude that this intervention would rarely be sufficient for the long-term management of patients and that the "autovaccination" hypothesis was problematic. The largest CD4+ cell drop occurred during the first 12 weeks off therapy followed by a slower decline thereafter. One person required salvage therapy because of the emergence of virologic resistance, and 2 patients developed symptoms consistent with the acute retroviral syndrome.

Plana and colleagues evaluated STI with and without hydroxyurea (Abstract 535-M). Twenty patients who began HAART in chronic infection with a baseline plasma HIV-1 RNA level above 5000 copies/mL and CD4+ cell count above 500/µL who had achieved virologic suppression for more than 32 weeks were enrolled in this study. The antiretroviral regimens were changed to stavudine/didanosine/nelfinavir with or without hydroxyurea for 24 weeks. The patients then underwent 5 treatment interruptions separated by 2 months using the same HAART regimen. Hydroxyurea was continued after the third interruption without subsequent discontinuation. They found that 8 of 9 hydroxyurea recipients maintained a plasma HIV-1 RNA level below 5000 copies/mL compared with 4 of 10 without hydroxyurea, (P=.02). The HIV-specific CTL did not differ between arms. It is not possible to distinguish whether STI had an effect in addition to the antiretroviral activity of hydroxyurea in this study.

Prior to Salvage Therapy. Ruiz and colleagues evaluated the utility of an STI prior to a salvage regimen in 46 patients

in whom a third HAART regimen was failing and who had resistance mutations in all 3 drug classes (Abstract 421-W). Patients eventually received a "mega-HAART" regimen consisting of didanosine, abacavir, lamivudine, saquinavir soft-gel capsule, and lopinavir/ritonavir. They were randomized to an immediate switch to this regimen or to starting after discontinuing their previous antiretroviral medications for 3 months. There was a high prevalence of genotypic mutations that subsequently faded in those randomized to treatment interruption. The plasma HIV-1 RNA level increased by 0.9 $\log_{10}$ copies/mL and the CD4+ cell count decreased by 131/µL in those off therapy. In 47% of patients receiving the STI, plasma HIV-1 RNA level declined below 80 copies/mL compared with 36% of those not receiving the STI (P=not significant). This study had limited power to detect subtle treatment effects. No adverse events were noticed, but participants started with a high median CD4+ cell count, 392/µL and 322/µL in the STI and immediate switch arms, respectively.

Switch Studies and Simplification

NEFA is a multicenter, randomized, open-label trial examining the virologic response and adverse effect profiles of changing either a single or dual protease inhibitor to one of 3 drugs: nevirapine, efavirenz, or abacavir (Abstract LB17). Four hundred sixty participants were enrolled and the primary outcome was proportion with undetectable plasma HIV-1 RNA after 12 months. The intent-to-treat analysis showed 78%, 74%, and 77% of individuals had plasma HIV-1 RNA levels below 200 copies/mL at 12 months in the nevirapine, efavirenz, and abacavir arms, respectively (P=.7). The on-treatment analysis showed 94%, 94%, and 87% had plasma HIV-1 RNA levels below 200 copies/mL in the 3 arms respectively (P=.06). More treatment discontinuations due to adverse effects were seen in the efavirenz (17%) and nevirapine (16%) arms than in the abacavir arm (7%), but abacavir was associated with a higher rate of virologic failure. Twenty-three of 28 participants from all 3 arms who developed virologic failure had received single or dual nRTI therapy prior to beginning HAART.

Hydroxyurea combined with didanosine was studied as an attempt to simplify the antiretroviral therapy regimens of patients with virologic suppression on HAART for more than 1 year (Abstract 533-M). Patients were randomized to continuing HAART or changing to hydroxyurea/didanosine. In an intent-to-treat analysis, 41 (38%) of 107 patients in the continuing HAART arm maintained virologic suppression at 48 weeks compared with 45 (39%) of 116 patients in the hydroxyurea arm. Success on the hydroxyurea/didanosine regimen was correlated with lower baseline plasma HIV-1 RNA level, lack of didanosine experience, higher nadir CD4+ cell count, and shorter time on HAART. Patients continuing on HAART had an increased number of adverse reactions compared with patients in the hydroxyurea arm.

Therapeutic Vaccines

Autran reviewed immune reconstitution and the state of therapeutic vaccine trials (Abstract L3). Patients in the chronic phase of HIV infection commonly have HIV-specific T-cell responses as determined by more sensitive assays such as the interferon-gamma enzyme-linked immunospot (ELISPOT). However, the strength of these responses is diminished compared with those in individuals treated during primary infection. The HIV-specific CD8+ T cells decrease proportionately with the decline in plasma HIV-1 RNA level associated with HAART. This led researchers to explore reconstitution of HIV-specific T-cell responses using HIV itself through STI. Preexisting immunodominant HIV-specific CD8 T cells have been found to rebound with STI, but this rebound is directly related to plasma HIV-1 RNA level, and control of viremia in the absence of HAART has not been predictably or routinely achieved.

Autran then discussed the work of her laboratory and others in the search for immune, viral, and genetic correlates of protection against HIV by studying long-term nonprogressors. She was able to rule out any viral factors being responsible in the patients studied. There did seem to be genetic factors such as CCR5-Δ32 heterozygosity and various human leukocyte antigen alleles that were associated with virologic control. Both the intensity and breadth of the CD4+ T-helper response was increased among the long-term nonprogressors and negatively correlated with HIV-1 RNA level and viral DNA. In addition, the antibody response was also negatively correlated with HIV-1 RNA level, in particular the IgG2 response. The combination of IgG2 response and T-helper response as measured by interferon-gamma ELISPOT was the best predictor of the maintenance of the long-term nonprogressor status in a multivariate model.

The immunologic goals of a therapeutic vaccine, as outlined by Autran, are to produce a strong and durable T-helper response and a more intense and broader CTL response. This vaccine would be given during HAART prior to a treatment interruption. The clinical goal would be to lower the viral set point and prolong the time off antiretroviral therapy. Several trials constructed in this manner are currently under way using viral vectors (canarypox and replication-defective adenovirus) that express portions of the HIV genome, some in combination with interleukin-2 (IL-2) or a DNA prime. Although no results are available, these vaccines were able to induce T_H1 responses, and the measurement of the CD8+ cell response is in progress. She ended with the promise of new trials involving improved vaccines in the context of a large international effort.

Several poster presentations discussed therapeutic vaccines in both animal models and human subjects (Abstract 312-W). DermaVir (Georgetown University Research Institute for Genetic and Human Therapy, Washington, DC) is a novel topical immunization composed of plasmid DNA combined with polyethylenimine-mannose (PEIm). The PEIm allows the plasmid to enter the dendritic cells and avoid degradation by the endosome. The dendritic cells then present the DNA-based antigens to naive T cells. The investigators studied 10 SIV-infected macaques with late-stage AIDS that were randomized to HAART alone or STI/HAART for 6 cycles followed by DermaVir (using SIV DNA) and 4 additional cycles of STI/HAART. All of the continuous HAART macaques died, but only 1 STI macaque died. The macaques had consistent viral rebounds during the first 6 cycles, but these rebounds declined sharply after

DermaVir and the median viral load after the last STI was below 200 copies/mL. Virologic control was associated with a strong SIV-specific T-cell response. The authors note that the pattern of progressive virologic control in association with DermaVir was similar to macaques treated early after infection with STI/HAART, and was remarkable considering the macaques' advanced stage of disease when starting this treatment.

Tryniszewska and colleagues studied 2 highly attenuated poxvirus vectors expressing different SIV proteins (NYVAC-SIV-*gpe* and NYVAC-SIV-*rtn*) with and without IL-2 in SIV251-infected rhesus macaques receiving HAART compared with controls for 8 months (Abstract 313-W). They were able to demonstrate CD8+ T-cell response to the immunodominant Gag epitope in vaccinated macaques. The vaccinated monkeys had a significantly lower viral rebound after discontinuing HAART. The authors argue that this provides proof-of-concept for therapeutic vaccines in the model that best predicts HIV infection.

There were several studies using REMUNE (Immune Response Corporation, Carlsbad, Calif), an envelope-depleted, inactivated Zairian isolate given with incomplete Freund's adjuvant. Bucy and colleagues studied REMUNE compared with the adjuvant in 28 human subjects who underwent treatment interruption (Abstract 314-W). They found a non-significant decrease in the peak and post-peak viral loads off therapy. Robbins and colleagues were able to demonstrate an augmentation of HIV-specific helper T-cell responses in 5 of 5 REMUNE-vaccinated individuals compared with 0 of 4 controls (Abstract 315-W). All patients remained on therapy and did not undergo a treatment interruption.

Fernandez-Cruz and colleagues presented data from the STIR-2102 trial that studied time to virologic failure for patients receiving zidovudine/didanosine or stavudine/lamivudine/indinavir with and without REMUNE every 3 months (Abstract 318-W). They found that REMUNE was associated with more durable virologic suppression (plasma HIV-1 RNA <5000 copies/mL) than antiretroviral therapy alone. They did not stratify time to virologic failure by the use of dual or triple antiretroviral therapy.

Immunotherapy

Levy and colleagues presented the final analysis of the ANRS 079 trial, which studied the efficacy of IL-2 therapy in HIV infection (Abstract 514-M). Patients naive to antiretrovirals or protease inhibitors were randomized to start HAART (stavudine, lamivudine, and indinavir) or HAART plus 10 cycles of IL-2 given over 74 weeks. The median length of follow-up of the 118 patients randomized was 35 months. The study had some protocol deviations, with participants in both arms receiving cycles of IL-2 after week 74. The IL-2 arm had a significantly higher and faster CD4+ cell count rise through week 74 than the HAART-only arm (835/µL vs 262/µL, P<.0001). The CD4+ cell count rise remained significantly higher in the IL-2 arm than in the HAART-only arm at the last analysis (604/µL vs 365/µL, P=.0002). The proportion of participants with a plasma HIV-1 RNA level below 50 copies/mL was similar in both groups (76% vs 78%).

In a substudy of ANRS 079, investigators examined the change in HIV proviral DNA in PBMCs over time (Abstract 515-M). The decay in log DNA/10^6 PBMCs was similar in the HAART-only and IL-2 arms, suggesting that IL-2 did not enhance the effect of HAART on the reservoir of proviral DNA in PBMCs nor did it expand the pool of latently infected T cells.

The ESPRIT trial is an open-label, randomized, controlled trial assessing HAART versus HAART plus IL-2 in terms of clinical outcome (Abstract 517-M). This ambitious effort will study 4000 participants for 5 years. Labriola and colleagues presented preliminary data on the predictors of CD4+ cell count rise associated with IL-2. The CD4+ cell count response among patients receiving IL-2 was greater among those with a higher nadir CD4+ cell count and was inversely related to length of time on antiretroviral therapy.

Hecht and colleagues presented preliminary results of a randomized study comparing HAART alone and HAART with IL-2 in the treatment of early HIV infection (<12 months post-seroconversion). Data were presented on the first 43 subjects (Abstract 527-M). At 48 weeks, the mean CD4+ cell count was higher in the IL-2 group (1669/µL vs 686/µL, P<.001), with 87% having an HIV-1 RNA level below 50 copies/mL compared with 70% of controls (P=not significant). Three of 5 participants tested in the IL-2 arm developed CTL responses to new epitopes compared with 1 of 7 controls. By protocol, all subjects were to remain on HAART, but the 1 responding participant in the HAART-only arm and 1 of the 3 responding patients in the IL-2 arm had a treatment interruption that can increase the CTL response. The authors found the 2 additional CTL responses in the IL-2 arm encouraging but say that they may have been due to undetected "blips" associated with IL-2 injections. These data are too preliminary to draw any conclusions at this time.

Lu and colleagues reviewed the gene therapy studies of the National Institutes of Health/National Institute of Allergy and Infectious Diseases involving serodiscordant monozygotic twins (Abstract 525-M). The 2 studies involved syngeneic lymphocytes virally transduced with the chimeric receptor gene (CD4/CD3-zeta) or the neomycin phosphotransferase gene. Genetically modified CD4+ T cells persisted for a mean of 3.3 and 5.2 years, respectively, and this persistence was enhanced by IL-2 administration. They argue that these results provide a basis for pursuing genetic strategies for the treatment of HIV infection.

Pomerantz and colleagues presented results from the Residual HIV-1 Disease Eradication Trial, an attempt to eradicate the latent reservoir of HIV in 3 patients (Abstract 405-T). These patients were on potent antiretroviral therapy with HIV-1 RNA levels below 50 copies/mL for 1 year prior to enrollment. Their regimens were intensified for at least 1 month with hydroxyurea and didanosine. After receiving anti-CD3 antibodies and IL-2, they continued the same antiretroviral regimen for an additional 5 to 6 months. Tonsillar biopsies showed no HIV-1 RNA by in situ hybridization in either follicular dendritic cells or lymphocytes. Unfortunately, the plasma HIV-1 RNA level eventually rebounded in all 3 participants.

Blips

Blips in viral load are defined as single measurements of HIV-1 RNA level above 50 copies/mL with subsequent measurements below 50 copies/mL. Previous reports indicate that these blips are not associated with subsequent virologic failure. Havlir and colleagues presented data on blips occurring during salvage therapy of heavily treatment-experienced patients (Abstract 93). These data came from participants enrolled in ACTG 398—a study of protease inhibitor- and NNRTI-experienced patients randomized to efavirenz, abacavir, adefovir, and amprenavir, with or without a second protease inhibitor—and ACTG 359, in which indinavir- and nRTI-experienced patients were randomized to nelfinavir/saquinavir or ritonavir/saquinavir with either delavirdine, adefovir, or both. They found that these blips did not predict subsequent virologic failure (RR, 1.13; 95% CI, .42-3.05).

Di Mascio and colleagues examined whether the frequency of blips in viral load varied with time. They found that 77.5% of 123 patients on their first HAART regimen exhibited blips at a mean frequency of .09 per sample with a mean amplitude of 165 plasma HIV-1 RNA copies/mL. They concluded that viral blips appeared randomly, and that neither blip frequency nor amplitude increased with time.

Postexposure Prophylaxis

A concern that has been expressed about offering postexposure prophylaxis (PEP) after high-risk sexual encounters is that sexual behavior may be disinhibited, leading to an increased frequency of high-risk behavior. To address this question, Schechter and colleagues prospectively studied 202 HIV-seronegative homosexual men in a trial of the acceptability and behavioral impact of PEP (Abstract 15). All participants received counseling on high-risk sexual behavior at baseline and were provided with a 4-day supply of zidovudine/lamivudine. During the 2-year follow-up period, participants began antiretrovirals after any sexual encounter they deemed to be high risk. They were instructed to present to the study site for evaluation within 4 days of beginning medications. Sexual behavior and HIV serostatus were assessed at baseline and every 6 months for 2 years.

The investigators found that high-risk sexual behavior actually decreased after beginning the study. Seventy-three participants began PEP 110 times, and 101 (91.8%) of the sexual acts that preceded PEP initiation met criteria for high-risk behavior, prompting investigators to prescribe a 28-day course of zidovudine/lamivudine. Eleven seroconversions occurred during the study, 10 among participants who did not start PEP after high-risk encounters and 1 who did. The viral genotype from this person showed the M184V mutation.

Viral Resistance

A number of presentations focused on resistance to antiretroviral therapies and the mechanisms thought to underlie resistance.

Resistance to Lamivudine

In an overview of the major resistance mechanism for lamivudine (and other "L-nRTIs," including emtricitabine, L-d4FC, and dOTC), Mellors (Abstract L6) described the mechanism of action of the M184V mutation, which confers 50- to 100-fold resistance to these drugs. Studies have shown that M184V does not affect lamivudine's binding to the active site of reverse transcriptase but does markedly decrease its incorporation into the growing DNA chain. This is thought to occur because of steric hindrance. In the 3-dimensional view, the ring structure of L-nRTIs points up whereas the ring structures of endogenous deoxynucleotide triphosphates (dNTPs) point down. When the methionine at position 184 mutates to a valine, steric hindrance between the relatively bulky valine molecule and the lamivudine ring occurs, malpositioning lamivudine and preventing its incorporation into the growing DNA chain.

Eron and colleagues (Abstract 570-T) evaluated 119 subjects with plasma HIV-1 RNA levels below 120 copies/mL who were enrolled in the NZTA4002 study, an open-label trial of zidovudine/lamivudine/abacavir/amprenavir versus zidovudine/lamivudine/nelfinavir. Their objective was to determine if emergence of the M184V mutation during virologic suppression was predictive of virologic failure. Of 26 patients having M184V at 24 weeks, 12 (46%) eventually had treatment failure compared with 28 of 93 subjects (30%) without M184V. These differences were not statistically significant and the authors concluded that emergence of M184V during virologic suppression was not predictive of treatment failure.

Resistance to Zidovudine and Stavudine

Mellors' overview of nRTI resistance (Abstract L6) also described the currently accepted mechanism of zidovudine resistance. Mutations conferring resistance to zidovudine do not appear to affect incorporation of zidovudine into the growing DNA chain in the manner seen with lamivudine resistance. Phosphorolysis, a process by which terminal dNTPs are removed from the DNA chain by a phosphate donor such as adenosine triphosphate (ATP), is thought to play a significant role in zidovudine resistance. It is believed that phosphorolysis, which is more efficient in zidovudine-resistant viruses, removes bound zidovudine from the DNA chain, freeing the 3'-OH group and allowing for DNA synthesis to continue. Because zidovudine has a relatively long side chain, it is not efficiently translocated away from the nucleotide binding position (N) to the polymerization position (P) that protects nucleotides from phosphorolysis. Mutations such as T215Y increase ATP binding to the template, resulting in more efficient phosphorolysis.

The importance of nRTI-associated mutations (NAMs) in cross-nRTI resistance was stressed by a number of presenters. Mellors noted that increasing numbers of NAMs correlated with increased cross-resistance among zidovudine, stavudine, and abacavir (Abstract L6). Ross and colleagues (Abstract 568-T) noted that NAMs, specifically M41L, K70R, L219W, T215Y/F, and K219Q/E, were observed more frequently in patients treated with the combination of stavudine and didanosine than in patients treated with stavudine and lamivudine (41% vs 31%), suggesting

that the choice of dual-nRTI therapy may influence the development of NAMs.

Garcia-Lerma and colleagues (Abstract 571-T) have previously shown that viruses with T215D/C, a naturally occurring polymorphism that may be due to revertant T215Y mutants, are more likely than wild-type viruses to select for T215Y in the presence of zidovudine. In this presentation they showed that 4 of 6 viruses with T215D/C selected for T215Y in the presence of stavudine in vitro, compared with 0 of 3 wild-type viruses. They suggest that patients infected with T215D/C viruses and treated with zidovudine or stavudine may be at increased risk of quickly developing T215Y mutants.

Whitcomb and colleagues (Abstract 569-T) looked at nRTI susceptibilities from 2500 samples with matched phenotypic and genotypic measurements and saw that increasing numbers of NAMs correlated with decreased susceptibilities to all nRTIs. M184V modulates this cross-resistance, decreasing susceptibility to didanosine, zalcitabine, abacavir, and lamivudine and increasing susceptibility to zidovudine, stavudine, and adefovir.

Resistance to Tenofovir

Miller and colleagues reported on the effect of baseline nRTI mutations in response to tenofovir therapy (Abstract 43). Based on pooled data from 2 studies, they noted that the type and number of NAMs at baseline had significant effects on tenofovir response. Patients with no NAMs at baseline had a 0.8-$\log_{10}$ copies/mL drop in HIV-1 RNA on tenofovir, and those with 1 to 2 NAMs had a 0.7-$\log_{10}$ copies/mL drop. Patients with 3 or more NAMs including either M41L, L210W, or T215Y/F had only a 0.2-$\log_{10}$ copies/mL decline in HIV-1 RNA on tenofovir. Patients with 3 or more NAMs but without M41L, L210W, or T215Y/F had a 0.7-$\log_{10}$ copies/mL decline. Furthermore, the presence of L210W was diagnostic of 3 or more NAMs and was the strongest single marker of lack of response to tenofovir. Resistance to tenofovir now appears to be mediated by K65R (a rarely occurring mutation with tenofovir therapy), the T69S insertion, and multiple NAMs (>3.8 by statistical analysis). Phenotypically, a 4-fold decrease in susceptibility correlates with a diminished response to tenofovir.

Tuske and colleagues (Abstract 44) solved the crystal structure of tenofovir complexed with reverse transcriptase and suggest that the acyclic nature of tenofovir allows it to avoid steric hindrance, as occurs with lamivudine and M184V. Additionally, the flexible nature of tenofovir allows it to assume multiple conformations at the reverse transcriptase active site, making it a poor substrate for excision by phosphorolysis as is seen with zidovudine. They concluded that the structure of tenofovir could account for its slow development of resistance.

NNRTI Hypersusceptibility

Several sessions touched on NNRTI hypersusceptibility, which has been described in the presence of nRTI mutations. Swanstrom and colleagues looked at the development of resistance to delavirdine in the presence of nRTI-associated mutations conferring NNRTI hypersusceptibility (Abstract 567-T). In the subset of patients who had NNRTI hypersusceptibility at baseline and who developed delavirdine resistance (K103N), nRTI-associated mutations conferring NNRTI hypersusceptibility were retained. Additionally, the presence of NNRTI hypersusceptibility did not improve treatment outcome in this study although it was associated with 0.54-$\log_{10}$ copies/mL lower baseline plasma HIV-1 RNA level. Mellors and colleagues reported on the positive effect of NNRTI hypersusceptibility on the virologic response to an efavirenz-containing salvage regimen in ACTG 398 (Abstract 45; please see the "Trials in Treatment-Experienced Patients" section).

Protease Inhibitor Resistance

Obry and colleagues reported on hypersusceptibility to protease inhibitors using resistance phenotypes obtained from participants in the ANRS 088 (NARVAL) trial of the effect of resistance testing on outcome (Abstract 557-T). They reported that mutations at codons 30 and 88 in protease are associated with significant cross-protease inhibitor resistance, but they confer hypersusceptibility to amprenavir and ritonavir. They further noted that N88S/T was associated with hypersusceptibility to amprenavir and D30N confers hypersusceptibility to ritonavir.

Isaacson and colleagues used data from the lopinavir/ritonavir expanded access database comprising 792 antiretroviral-experienced patients who started on combination regimens including lopinavir/ritonavir to determine the genotypic predictors of lopinavir/ritonavir failure (Abstract 559-T). They determined that the presence of mutations at positions 10, 20, 33, 36, 54, and 82 in the presence of multiple other mutations was statistically significantly associated with virologic failure. Mutations at 24, 47, 48, and 84 also seemed to influence virologic failure, but the association was not statistically significant. They suggested that a weighted algorithm based on these findings may be a better predictor of response to lopinavir/ritonavir than the current mutation score. Conversely, Loutfy and colleagues looked at 167 patients on lopinavir/ritonavir therapy and found that the current mutation score had a linear relationship to virologic failure (Abstract 560-T). They further found that the presence of L90M was highly predictive of failure.

Schwartz and colleagues (Abstract 562-T) followed 41 patients on the investigational drug tipranavir for 1 year looking for reduced susceptibility. Commonly seen protease inhibitor cross-resistance mutations including 46, 82, 84, and 90 did not confer tipranavir resistance. The V82T mutation in combination with an L33I/F/V was associated with decreased susceptibility in 4 of 6 patients.

A molecular mechanism for amprenavir resistance was suggested by Xu and colleagues (Abstract 563-T). Amprenavir resistance is primarily mediated through I50V, although multiple other mutations are required for high-level resistance. It is known that the presence of I50V decreases the affinity of protease for amprenavir, but the molecular correlates of this finding are not known. The authors suggest that the loss of a methyl group when valine (V) replaces isoleucine (I) results in loss of hydrophobic contacts, creation of space, and loss of the close contact of protease with amprenavir needed for the drug to inhibit enzymatic activity.

Other Agents

True diketoacid integrase inhibitors have now been identified and resistance has been induced in vitro by numerous passages of virus in the presence of these agents. Witvrouw and colleagues (Abstract 573-T) identified new integrase inhibitor resistance mutations selected for by L-708,906, a novel investigational integrase inhibitor, in vitro. As had been shown previously by Hazuda and colleagues, the T66I mutation appeared early. With further passages, L74M and S230R mutations were also detected. This virus was highly resistant to L-708,906 but retained full susceptibility to entry inhibitors, nRTIs, and NNRTIs, and protease inhibitors.

Resistance in Non-B Subtypes

Several abstracts addressed potential differences in treatment and resistance of non-B subtypes. Agwale and colleagues phenotypically analyzed 14 subtype-G and 4 subtype-A/G recombinants from patients in Nigeria prior to starting antiretroviral therapy and found that all but 1 exhibited full susceptibility to all antiretroviral medications, with the remaining sample having a 3.4-fold change to nelfinavir and ritonavir (Abstract 461-W). Portugal has an increasing prevalence of subtype-G infections, leading Gomes and colleagues to review the patterns of resistance for individuals in whom a nelfinavir-based antiretroviral regimen is failing (Abstract 46). They found that a nelfinavir-based regimen was 3 times more likely to fail in subtype-G patients than in subtype-B patients. Moreover, none of the 10 subtype-G patients in whom a nelfinavir-based regimen had failed developed the D30N mutation compared with 6 of 11 patients with subtype-B ($P<.01$). The subtype-G patients exhibited either the L90M pathway or other mutations on genotypic analysis.

Pillay and colleagues reviewed 113 pediatric patients from the Penta 5 trial, 67 (59%) of whom had non-B subtypes (Abstract 813-W). They did not find a difference in treatment outcomes or resistance patterns with respect to subtype, but the number of each of the 7 non-B subtypes or recombinants was small. Grossman and colleagues compared 41 subtype-C patients and 67 subtype-B patients in whom antiretroviral therapy had failed (Abstract 565-T). They found a mutation pattern that was generally similar in both groups.

Additional information regarding treatment and resistance of non-B subtypes should be forthcoming as antiretroviral treatment programs in Africa and Asia expand. Non-B subtypes continue to spread through Europe, as evidenced by J/A recombinants in newly seroconverting injection drug users in Lausanne, Switzerland (Abstract 17), and by the diverse subtype-G recombinants spreading through Southern Europe (Abstract 759-W).

Resistance and Fitness

There has been considerable interest in the issue of viral fitness in patients with multiply resistant viruses. Barbour and colleagues evaluated specimens from 20 patients who were experiencing virologic failure on protease inhibitor-based regimens but who had plasma HIV-1 RNA levels lower than their baseline levels (Abstract 575-T). Early virologic failure (ie, <6 months) in these patients was associated with reduced viral replicative capacity. The degree of reduction in replicative capacity was directly associated with the decrease in plasma HIV-1 RNA level relative to pretherapy level. However, with long-term failure, plasma HIV-1 RNA levels did increase and this was associated directly with protease inhibitor resistance.

Weber and colleagues evaluated samples from 4 patients participating in ACTG 315 (zidovudine/lamivudine/ritonavir recipients) to determine if the baseline genetic background of the virus correlated with viral fitness (Abstract 576-T). Two patients retained wild-type virus and 2 patients developed resistant virus. The resistant viruses had lower replicative capacities than wild-type virus. One of the 2 patients had baseline natural compensatory mutations, and this patient's virus had an increase in viral fitness over time. The authors suggest that the presence of background compensatory mutations may allow for more rapid recovery of replicative capacity.

Soderberg and colleagues looked at the accumulation of NNRTI mutations in relation to viral fitness (Abstract 577-T). They determined that, although substantial variability in fitness exists, in general, viral fitness decreases as the number of NNRTI mutations increases. The M184V lamivudine-associated mutation has been shown to result in decreased viral fitness. Wei and colleagues analyzed a number of M184V mutant viruses to determine the biochemical explanation for this finding (Abstract 578-T). They presented data suggesting that reverse transcriptase containing the M184V mutation does not recognize the initiation complex for synthesis of viral DNA as well as wild-type enzyme, and they postulated that this may account for decreased viral fitness in these viruses.

Resistance Testing

The utility of genotypic or phenotypic testing in managing HIV infection has been controversial. Several studies addressing the issue were presented. Torre and colleagues presented the results of a meta-analysis of 6 randomized controlled trials designed to determine the impact of resistance-guided antiretroviral therapy on virologic outcome (Abstract 584-T). At 6 months, 38.8% of patients who received genotypic resistance testing had undetectable plasma HIV-1 RNA levels versus 28.7% of patients receiving standard of care. Expert interpretation offered in conjunction with genotypic testing increased the rate of viral suppression (50.7% vs 35.8%). Phenotypic testing did not seem to offer an advantage over standard of care in this small meta-analysis.

Perez-Elias and colleagues presented the results of a prospective study of 276 patients in whom antiretroviral therapy was failing who were randomized to receive either actual phenotype or virtual phenotype testing (Realvirfen study, Abstract 586-T). In a multivariate linear regression analysis, patients in the virtual phenotype arm had a significantly greater decrease in plasma HIV-1 RNA level than those in the actual phenotype group ($P=.01$). Mazzotta and colleagues presented the results of the GenPherex trial comparing virtual and real phenotypes in 173 patients in whom antiretroviral therapy was failing (Abstract 589-T). Virologic outcome did not differ

between the 2 groups and CD4+ cell counts rose in both groups, with a trend toward a greater increase in the virtual phenotype group. The authors conclude that virtual phenotype is as reliable as standard phenotype.

Workman and colleagues presented the results of CREST, a multicenter randomized comparison of the effect of genotype and virtual phenotype testing on antiretroviral therapy-prescribing patterns (Abstract 587-T). The study included 330 patients in whom antiretroviral therapy was failing. No difference was seen between the genotype and virtual phenotype groups in the numbers of changes made to planned regimens after resistance-testing results were available. It was noted that the virtual phenotype arm had significantly less resistance reported than did the genotype arm; however, the clinical significance of this finding is not known. This, however, is to be expected, because for a number of drugs, multiple mutations are needed before a significant change in susceptibility can be detected.

Pharmacology

Therapeutic Drug Monitoring

The clinical utility of therapeutic drug monitoring (TDM) is currently being debated. In a plenary talk, Back explored the pros and cons of TDM and reviewed a number of trials (Abstract S20). In favor of TDM are the well-defined relationship between drug exposure and efficacy and toxicity, the large interpatient variability in drug levels, and the narrow therapeutic window. Against the use of TDM are high intrapatient variability, unclear concepts of the role of protein binding, logistics (more blood draws, scheduling, etc), lack of expert interpretation, and the lack of randomized controlled trials showing efficacy. Only a few randomized controlled trials of TDM have been carried out to date. The ATHENA trial looked at the role of TDM in 92 antiretroviral therapy-naive patients starting on a nelfinavir-based regimen. At 12 months, those patients receiving TDM had a significantly lower plasma HIV-1 RNA level than those without TDM. In a separate arm, 55 patients starting on indinavir were randomized to receive TDM or standard of care. Those in the TDM arm had significantly lower toxicity than those in the standard-of-care arm.

Castagna and colleagues looked at the predictive value of the normalized inhibitory quotient (NIQ) in determining response to lopinavir in combination with ritonavir (Abstract 128). An NIQ was defined as the ratio of the patient's trough drug concentration to the fold change in IC_{50} of the patient's virus (inhibitory quotient [IQ]) divided by the ratio of the median population trough drug concentration to the population cutoff fold change in IC_{50}. This NIQ obviates the need for correcting for protein binding. In the study, 52 antiretroviral therapy-experienced patients were given lopinavir/ritonavir in combination with other antiretroviral therapy chosen by their health care providers. Although NIQ was not predictive of initial response, it was highly predictive of response from week 12 onward, and at 48 weeks was more predictive than resistance testing. Also, although 100% of patients with the highest NIQs had plasma HIV-1 RNA levels below detection limits, only 15% of those with the lowest NIQ responded to therapy.

Fletcher presented the results of the predictive value of IQs in patients on saquinavir plus either ritonavir or nelfinavir as part of ACTG 359 (Abstract 129). They found that IQ predicted response at weeks 4, 8, and 12 but not at week 16; and had decreasing correlation with outcome after week 4.

Phillips and colleagues reported on a study of virtual inhibitory quotients (VIQs) in antiretroviral therapy-experienced patients taking amprenavir and lopinavir/ritonavir in combination (Abstract 130). A VIQ was defined as the patient's trough drug concentration divided by the virtual phenotype and the protein-adjusted IC_{50}. The VIQ of amprenavir was highly predictive of suppression and there was a trend toward this with lopinavir. Eighty percent of patients with a lopinavir VIQ greater than 15 and an amprenavir VIQ greater than 1.3 had plasma HIV-1 RNA levels less than 50 copies/mL.

The protein binding of antiretroviral drugs, especially the protease inhibitors, is thought to limit the usefulness of IQs. A presentation by de Béthune and colleagues suggested that the effect of plasma protein binding to the protease inhibitors may be overestimated and may not need to be included in IQ calculations (Abstract 449-W). They reached this conclusion by looking at the effect of plasma protein binding on physiologic doses of saquinavir, ritonavir, nelfinavir, amprenavir, and the investigational protease inhibitor TMC 114. There was a less than 5-fold decrease in potency in the presence of the major protease inhibitor binding protein alpha-1-acid glycoprotein.

TDM has been thought to be difficult to implement for nRTIs because it is the concentration of the intracellular drug triphosphates that is important in their efficacy. Becher and colleagues (Abstract 452-W) developed a direct liquid chromatography/tandem mass spectrometry assay to measure the active intracellular triphosphorylated anabolites of stavudine and didanosine in peripheral blood mononuclear cells. They were able to quantify median intracellular concentration (ICC) in 22 patients with plasma HIV-1 RNA levels below detection limits for both stavudine and didanosine and suggest that further studies of ICCs of nRTIs may be useful.

The effect of intracellular triphosphate anabolite concentrations was also studied by Hoggard and colleagues (Abstract 455-W). They looked at levels of intracellular lamivudine triphosphate (lamivudine-TP) and the ratio of lamivudine-TP to endogenous deoxycytidine triphosphate (dCTP) in patients responding to therapy and those in whom therapy had failed. They determined that ICCs of lamivudine-TP and lamivudine-TP/dCTP were lower in nonresponders than in those responding to therapy despite no differences in levels of endogenous dCTP between the groups.

Pharmacokinetics of Antiviral Drugs

Lopinavir/ritonavir Daily Versus Twice Daily. A great deal of interest is currently being shown in once-daily preparations of antiviral agents. M99-056, a study of once-daily versus standard twice-daily dosing of lopinavir/ritonavir was presented by Bertz and colleagues (Abstract 126). Lopinavir/ritonavir was given as a single 800 mg/200 mg dose

daily or as 400 mg/100 mg twice daily in a prospective trial. At 38 weeks, no significant difference was seen between the groups in the numbers of patients who achieved plasma HIV-1 RNA levels below detection limits. However, it was noted that the median IQ was lower in patients receiving the once-a-day dose compared with those on standard dosing (40 vs 84) and that the 24-hour trough concentration was lower in patients receiving once-daily dosing. These findings suggested that once-daily dosing may have a narrower therapeutic window than standard dosing, and the conclusion was reached that twice-daily dosing is still the optimal way to dose lopinavir/ritonavir.

Stavudine Extended Release. Kaul and colleagues studied the pharmacokinetics of once-daily versus twice-daily stavudine in 2 studies. The first was a multiple-dose study (Abstract 429-W). Fifteen HIV-infected volunteers received either stavudine extended release 100 mg daily or the standard 40 mg twice daily dosing over a 9-day period. The once-daily dosing formulation achieved higher maximal concentrations and 24-hour area-under-the-curve values than standard dosing. No accumulation of drug was seen, and interpatient and intrapatient variability was low. It was believed that the pharmacokinetic profile supported once-daily dosing.

The second study was a 48-week phase 2 trial of stavudine extended release versus standard stavudine in combination with lamivudine and efavirenz (Abstract 430-W). Intensive pharmacokinetic studies on a subset of patients were performed during the first 2 weeks of the trial. For both preparations, pharmacokinetic parameters were similar on days 1 and 14. The geometric mean maximum concentration of the once-daily preparation was approximately 50% lower than the standard preparation. However, the geometric minimum concentration was 5.5 times higher for the once-daily preparation. These authors again concluded that the pharmacokinetic studies supported the use of once-daily stavudine preparations.

Drug-Drug Interactions. Several presentations focused on the pharmacokinetic interactions among antiretroviral agents. Wire and colleagues studied the pharmacokinetics of amprenavir, given as the prodrug GW433908, when given in combination with ritonavir (100 or 200 mg) and efavirenz (Abstract 431-W). In the 26 patients completing pharmacokinetic analysis, the addition of efavirenz to amprenavir and ritonavir had no effect on plasma concentrations of amprenavir. Additionally, giving 200 mg of ritonavir instead of 100 mg did not significantly increase plasma amprenavir levels.

Solas and colleagues (Abstract 440-W) looked at the effect of coadministration of lopinavir/ritonavir with amprenavir. Plasma trough concentrations of amprenavir and lopinavir were measured in 46 patients on 2 different doses of amprenavir (600 mg vs 750 mg bid) in combination with lopinavir/ritonavir (400 mg/100 mg). Decreases of 51% in the 600-mg dose group and 33% in the 750-mg dose group were noted for patients taking amprenavir in combination with lopinavir/ritonavir when compared with those taking amprenavir/ritonavir. It was noted that 85% of these patients still had median minimum concentration values up to 3-fold higher than standard, non-boosted amprenavir dosing. Lopinavir levels were not affected by coadministration with amprenavir. It was suggested that TDM may play a role in amprenavir/lopinavir/ritonavir combination regimens.

Preston and colleagues evaluated the pharmacokinetics of atazanavir in combination with efavirenz (Abstract 443-W). Coadministration of these agents resulted in atazanavir levels that were significantly lower than atazanavir alone, leading the authors to suggest that atazanavir dosing should be adjusted if used in combination with efavirenz. O'Mara and colleagues looked at the effect of adding low-dose ritonavir to atazanavir plus efavirenz (Abstract 444-W). Adding 200 mg of ritonavir to the regimen increased atazanavir levels 3-fold over atazanavir alone.

Other studies looked at the effect of other agents on antiretroviral pharmacokinetics. Agarwala and colleagues evaluated the effect of rifabutin on atazanavir with or without ritonavir boosting (Abstract 445-W). They concluded that rifabutin may be coadministered with atazanavir without dose modification of atazanavir but suggested that rifabutin dose modification may be necessary. Moyle and colleagues looked at the effect of pravastatin on protease inhibitors in patients suppressed on protease inhibitor therapy (Abstract 446-W). No impact of pravastatin was seen on protease inhibitor trough concentrations and the authors concluded that the efficiency and lack of interactions with this agent make it a good choice for therapy in patients with hypercholesterolemia on antiretroviral therapy. Cardiello and colleagues studied the effect of itraconazole on saquinavir soft-gel formulation (Abstract 447-W). They determined that lower doses of saquinavir (800 or 1200 mg vs standard 1400 mg bid) resulted in adequate pharmacokinetic values when combined with 100 mg of itraconazole.

Compartmental Penetration. The distribution of antiretroviral agents into the cerebrospinal fluid and genital tract was the subject of several presentations. Haas and colleagues looked at the effect of ritonavir boosting on indinavir levels in the cerebrospinal fluid (Abstract 437-W) and found that low-dose ritonavir increased indinavir levels 3-fold primarily by increasing plasma levels. Sankatsing and colleagues looked at seminal plasma levels of lopinavir in HIV-infected men on lopinavir-containing regimens for more than 4 weeks (Abstract 439-W) and found that seminal plasma levels were significantly lower than plasma levels. They concluded that lopinavir has poor penetration into the seminal plasma and are currently investigating whether this will lead to suboptimal viral suppression and resistance in this compartment.

Conclusion

The 9th Conference on Retroviruses and Opportunistic Infections once again revealed itself to be a premier scientific meeting devoted to bringing together advances in basic and clinical HIV research in 1 forum. Antiretroviral therapy remained a dominant component of the meeting and although no major breakthroughs were evident, substantial advances were reported with respect to new antiretroviral agents, strategies of therapy, and the applications of drug

resistance testing and therapeutic drug level monitoring. In parallel, the many unanswered questions in the field that were highlighted will no doubt form the focus of many of next year's presentations.

Additional Suggested Reading

Sterling TR, Chaisson RE, Moore RD. HIV-1 RNA, CD4 T-lymphocytes, and clinical response to highly active antiretroviral therapy. AIDS. 2001;15: 2251-2257.

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Perspective

Managing Treatment Failure

The International AIDS Society–USA presented an interactive symposium at the 2001 Interscience Conference on Antimicrobial Agents and Chemotherapy in Chicago in December. Daniel R. Kuritzkes, MD, discussed management of antiretroviral treatment failure, centering his discussion on 2 cases of drug failure encountered in clinical practice.

For a patient in whom an initial antiretroviral regimen has failed, a guiding principle in considering options is that ongoing viral replication in the setting of continued therapy selects for increasing drug resistance. Available data suggest that potentially half of patients on antiretroviral therapy have detectable plasma levels of HIV-1 RNA and that nearly all patients with detectable HIV-1 RNA have drug-resistant virus.

Case 1: Maintain, Switch, or Intensify Therapy After Initial Failure?

Case Presentation

A 21-year-old gay man presented 2 years ago with newly diagnosed HIV-1 infection. The patient was found to be HIV-1-infected by screening at a sexually transmitted disease clinic, and was referred for management of HIV-1 disease. At the time of initial evaluation, the patient was asymptomatic, with a normal physical exam, white blood cell count of 4300/µL, CD4+ count of 362 cells/µL, and a plasma HIV-1 RNA level of 33,000 copies/mL. After several additional visits and a repeat plasma HIV-1 RNA level that was 31,600 copies/mL, the patient was started on antiretroviral therapy with a twice-daily regimen of zidovudine/lamivudine/nelfinavir. A repeat plasma HIV-1 RNA test 4 weeks after initiating therapy showed a level of 249 copies/mL, but the patient complained of nausea and loose stools. The loose stools were controlled with loperamide, but nausea persisted, necessitating a switch from zidovudine to stavudine. A follow-up plasma HIV-1 RNA level was less than 50 copies/mL, and the CD4+ count was 451 cells/µL.

The patient continued to do well over the subsequent year with regular follow-up every 2 to 3 months. Plasma HIV-1 RNA levels remained below 50 copies/mL and the CD4+ cell count increased modestly over this interval. At a subsequent visit, the patient's plasma HIV-1 RNA level was 2300 copies/mL, with a CD4+ cell count of 511/µL; a confirmatory test 2 weeks later showed an HIV-1 RNA level of 7200 copies/mL. A genotype of the patient's plasma virus showed an M184V mutation in the reverse transcriptase gene, consistent with lamivudine resistance.

The possible treatment options discussed for this patient were:

1. Continue the patient on the current therapy
2. Change to abacavir/didanosine/efavirenz
3. Change to stavudine/didanosine/lopinavir/ritonavir
4. Change to stavudine/didanosine/nelfinavir
5. Intensify without removing drugs from the regimen
6. Discontinue antiretrovirals and monitor

Discussion

The discontinuation of all antiretrovirals has recently become more of a consideration in patients such as this one. Upon initial presentation, the patient was at relatively low risk of near-term progression of disease based on CD4+ cell count and relatively low HIV-1 RNA level. It is now recognized that delaying initiation of treatment in early infection is not associated with increased risk of near-term progression, and in the past several years, many patients were started on antiretroviral therapy earlier than they would be under more current guidelines. Accumulating data from patients started early on therapy who have discontinued treatment suggest that CD4+ cell count gradually returns to pretreatment levels over several months, with such patients appearing to be at no increased risk of short-term progression. Likewise, plasma HIV-1 RNA levels gradually increase back to the pretreatment set point. Thus, supervised discontinuation of treatment with continued monitoring is an option in this case.

Among the other options, the least favorable is maintaining the current regimen. Factors in favor of changing the regimen include: (1) the potential for achieving maximum viral suppression with a compact regimen that minimizes the number of pills taken per dose, given the relatively limited viral resistance; and (2) the fact that clinical benefit of treatment is related to duration of viral suppression (primarily because such suppression is related to the overall magnitude of the CD4+ cell count increase).

Factors arguing against changing the regimen include the relatively low risk of clinical progression in this patient and the fact that CD4+ cell count appears to have been maintained in the presence of low-level viral replication. The factor that tips the balance in favor of changing therapy sooner rather than later in a patient in whom alternative treatment options exist is the concern that persistent virus replication in the setting of continued therapy will allow the accumulation of additional resistance mutations, leading eventually to a highly resistant virus. In such a patient, virus

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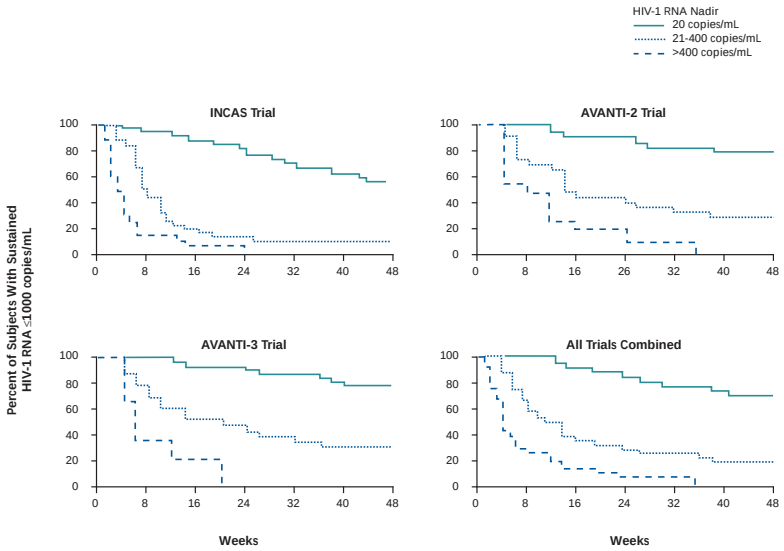

Figure **1.** Proportions of patients with HIV-1 RNA level of 1000 copies/mL or less according to HIV-1 RNA nadir in INCAS, AVANTI-2, and AVANTI-3 studies and combined. Adapted from Raboud et al, *J Infect Dis,* 1999.

would likely accumulate additional nucleoside reverse transcriptase inhibitor (nRTI)-associated resistance mutations, eventually resulting in loss of utility of the whole nRTI class, and would begin to accumulate protease inhibitor resistance mutations as well. Although preservation of future treatment options has been considered a reason to avoid early switching, recent data suggest that early switching may in fact preserve treatment options by minimizing the development of broad cross-resistance.

A primary factor in treatment failure in many patients, and a primary factor to consider in selecting alternative regimens, is poor adherence to the drugs. A recent analysis by Paterson and colleagues (*Ann Intern Med*, 2000) showed that the virologic failure rate was 21.7% in patients with 95% or greater adherence and increased to 54.5% in those with 90% to 94.9% adherence. The failure rate was 66.7%, 71.4%, and 82.1% in patients with 80% to 89.9%, 70% to 79.9%, and less than 70% adherence, respectively. Other data have shown that increases in HIV-1 RNA can be detected in close temporal association with treatment interruptions, with eventual evolution of viral resistance being observed.

A variety of data support the notion that time to treatment failure is related to magnitude of viral suppression. Studies from the potent antiretroviral therapy era demonstrate that risk of virologic failure, defined as plasma HIV-1 RNA level greater than 1000 copies/mL, is lowest among patients in whom the HIV-1 RNA nadir is less than 20 copies/mL compared with patients with higher HIV-1 RNA nadir values (Figure 1; Raboud et al, *J Infect Dis*, 1999). Data from these studies indicate that HIV-1 RNA nadirs in the 21 to 400 copies/mL range are associated with relatively little improvement in risk of failure compared with nadirs greater than 400 copies/mL.

A meta-analysis conducted by investigators from the US Food and Drug Administration, using data primarily from the era of dual nRTI therapy, showed that risk of clinical progression was related to duration of viral suppression, with viral suppression defined as an HIV-1 RNA decrease of 0.5 $\log_{10}$ or greater from the pretreatment level (Murray et al, AIDS, 1999). Such data tend to support switching regimens with the intention of maximizing viral suppression.

Some direct evidence of the benefit of switching earlier rather than later comes from analyses of virologic outcome according to plasma HIV-1 RNA level at the time of switching. Tebas and colleagues (AIDS, 1999) conducted a study of patients in whom saquinavir/ritonavir was substituted for nelfinavir in a failing regimen. They reported that the likelihood of sustaining viral suppression at less than 500 copies/mL was significantly greater in those who switched drugs when plasma HIV-1 RNA level was less than 30,000 copies/mL than in those whose switched at a higher plasma HIV-1 RNA level (Figure 2). This difference in outcome was also related to the accumulation of drug resistance mutations.

In terms of evolution of resistance, the genotypic pattern in the virus in the patient described is characteristic of that in patients in whom a first protease inhibitor-based regimen including lamivudine is failing. Available data

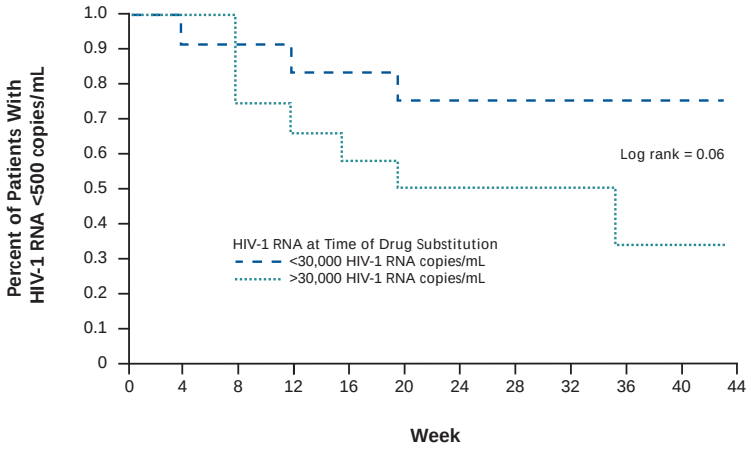

Figure **2.** Proportions of patients maintaining virologic response after substitution of saquinavir/ritonavir for nelfinavir in a failing regimen according to whether HIV-1 RNA level was below or above 30,000 copies/mL at the time of substitution. Adapted from Tebas et al, *AIDS,* 1999.

indicate that the first resistance mutation to develop in patients receiving potent antiretroviral regimens tends to be the one that confers the highest level of resistance and is a single-step mutation. For protease inhibitor-based regimens and triple nRTI regimens containing lamivudine, it typically is lamivudine resistance that occurs first. In a study comparing zidovudine/lamivudine/abacavir and zidovudine/lamivudine/indinavir in treatment-naive patients (Melby et al, 8th CROI, 2001), the only mutation present for 28 weeks in a patient with virologic failure on zidovudine/lamivudine/abacavir was the lamivudine M184V mutation. Other nRTI-associated mutations subsequently appeared. Examination of the evolution of resistance patterns in the entire study population showed that, over time, the proportion of patients with the M184V mutation plus any other nRTI-associated resistance mutation increased, and the proportion of patients with just the M184V mutation or wild-type virus decreased.

Among patients having first treatment failure while receiving protease inhibitor-based regimens, lamivudine resistance was found in 14 of 17 patients and indinavir resistance in 1 of 26 patients receiving zidovudine/lamivudine/indinavir or indinavir alone in one study (Havlir et al, JAMA, 2000). In another study, lamivudine resistance was found in 17 of 23 patients and indinavir resistance in 5 of 23 patients receiving zidovudine/lamivudine/indinavir (Boden et al, JAMA, 1999). In 16 patients in whom a regimen of zidovudine/lamivudine/amprenavir was failing, lamivudine resistance was found in 14, zidovudine resistance in 4, and amprenavir resistance in 2 (De Pasquale et al, *Antiviral Ther,* 1998). In studies of patients with plasma HIV-1 RNA levels greater than 400 copies/mL during weeks 24 to 60 of treatment that included lamivudine and lopinavir/ritonavir or nelfinavir, protease inhibitor resistance mutations were found in 0 of 40 and lamivudine resistance in 15 (38%) of 40 patients in the lopinavir/ritonavir arm. Nelfinavir resistance mutations were found in 31 (37%) of 84 patients and lamivudine resistance in 68 (81%) of 84 patients in the nelfinavir arm (Kempf et al, 1st IAS Conf, 2001).

A similar pattern has been observed in patients receiving efavirenz in combination with a protease inhibitor, with efavirenz resistance being found in 10 of 14 patients and indinavir resistance in 3 of 14 patients receiving failing efavirenz/indinavir therapy (Holder et al, 6th CROI, 1999). With subsequent accumulation of protease inhibitor mutations, phenotypic susceptibility to the protease inhibitor being used decreases. These observations support earlier switching to prevent the predictable accumulation of mutations that will result in reduced effectiveness of alternative drugs, as well as to attempt to achieve resuppression of a viral population not yet characterized by accumulated mutations.

Although the patient in this case has a sustained elevation in viral load, there remain questions about whether "blips" in HIV-1 RNA level predict treatment failure. A study by Havlir and colleagues (JAMA, 2001) found that there was no significant difference in the rate of virologic failure, defined as sustained viremia greater than 200 copies/mL, in 97 patients with at least 1 episode of viremia of more than 50 copies/mL versus patients without blips (9.7% vs 13.9%). This result suggests that such intermittent viremia does not predict failure. Data presented recently by Di Mascio and colleagues support this conclusion (9th CROI, 2002). However, an analysis by Greub and colleagues (8th CROI, 2001) showed treatment failure rates of 5.1 per 100 person-years-of-observation in patients with no blips, 7.9 in those with 1 to 3 blips, and 21 in those with 4 or more blips. Blip was defined as an episode of viremia of 50 to 500 copies/mL. The 3.01 odds ratio for progression in the 4 or more-blip group versus the no-blip group was statistically significant. Ramratnam and colleagues (*Nat Med*, 2000) reported that viremia blips may be associated with a significant slowing of rate of decay of latently infected peripheral blood mononuclear cells or an increase in the viral reservoir of latently infected cells.

With regard to the option of intensification, a number of studies have shown benefit of the addition of abacavir or tenofovir to existing regimens. Katlama and colleagues (AIDS, 2000) found that the addition of abacavir to suboptimal background therapy produced a decrease in HIV-1 RNA of at least 0.5 $\log_{10}$ copies/mL over 16 weeks compared with a slight increase in those continuing therapy. Rozenbaum and colleagues (6th CROI, 1999) found that the addition of abacavir to zidovudine/lamivudine therapy in patients with the M184V resistance mutation alone improved virologic response rates (<400 copies/mL) from 5 of 31 patients (16%) to 22 of 31 patients (71%) at 48 weeks, with 17 (55%) of these patients achieving HIV-1 RNA levels less than 20 copies/mL. Tenofovir produced maximal reductions in HIV-1 RNA in the treatment failure setting of 0.6 to 0.7 $\log_{10}$ copies/mL, with smaller reductions being observed with decreased viral susceptibility to tenofovir at baseline. These effects were associated with the presence or absence of nRTI-associated resistance mutations. Although intensification is thus an option, there currently is relatively little information on this strategy in patients in whom initial antiretroviral regimens were failing.

Clinical Decision and Outcome

The available data indicate that the patient in this case, if he is not to have a supervised treatment discontinuation, should have his antiretroviral therapy changed and sooner rather than later. In fact, the patient opted to change from nelfinavir to lopinavir/ritonavir, and to change from lamivudine to didanosine. In this case, the need to change nelfinavir was based on issues related to tolerability rather than to drug resistance. Lopinavir/ritonavir was a good substitution because the patient was already taking a protease inhibitor-based regimen, and this change preserved the nonnucleoside reverse transcriptase inhibitors (NNRTIs) as a future option. The switch from lamivudine to didanosine was prompted by the presence of the lamivudine-associated M184V mutation.

Case 2: Options in the Setting of Complicated Treatment History

Case Presentation

A 49-year-old woman presented with heterosexually acquired HIV infection. She received initial therapy with zidovudine, lamivudine, and indinavir in 1995,

but was forced to discontinue zidovudine as a result of gastrointestinal intolerance. Substitution of stavudine led to development of severe peripheral neuropathy, which persisted despite discontinuation of stavudine and required methadone for pain management. During subsequent indinavir monotherapy, her HIV-1 RNA level was 12,650 copies/mL with a CD4+ count of 325 cells/µL. Abacavir/ritonavir/saquinavir was substituted and HIV-1 RNA level decreased to less than 50 copies/mL, but abacavir had to be discontinued because of apparently associated worsening of peripheral neuropathy.

Nevertheless, the HIV-1 RNA level remained suppressed to less than 400 copies/mL on ritonavir/saquinavir until ritonavir liquid replaced the capsule formulation, at which point the patient was unable to tolerate her medications and discontinued all antiretroviral therapy. The plasma HIV-1 RNA level increased to 47,320 copies/mL and the CD4+ count decreased to 283 cells/µL. A genotype assay demonstrated presence of the V32I, M46I, V82A, and L90M mutations in the protease gene and the M184V mutation in the reverse transcriptase gene. The patient was then started on zidovudine/lamivudine/efavirenz, but took her medications only intermittently because of the occurrence of numerous adverse effects. HIV-1 RNA level initially declined to 650 copies/mL and CD4+ count increased to 340 cells/µL, but the HIV-1 RNA level again increased to 43,520 copies/mL and the CD4+ count declined to 298 cells/µL when the patient discontinued her medications because of epigastric pain. Endoscopy revealed presence of a benign gastric ulcer, which was treated with omeprazole and ranitidine. A phenotype assay demonstrated resistance only to efavirenz, and sensitivity to all protease inhibitors and nRTIs.

The possible treatment options discussed for this patient were:

1. Start tenofovir/abacavir/ritonavir/amprenavir
2. Start zidovudine/lamivudine/ritonavir/indinavir
3. Start zidovudine/lamivudine/ritonavir/lopinavir
4. Start zidovudine/lamivudine/delavirdine/nelfinavir
5. Continue to monitor the patient off therapy

Discussion

At the time that this patient was seen, it was difficult to determine what the next step in management should be. She had experienced multiple toxicities with different agents. Lopinavir/ritonavir had just become available and tenofovir was not yet available. Although the patient showed phenotypic susceptibility to indinavir, the prior evidence of indinavir resistance argued against use of ritonavir-boosted indinavir in the context of other potential options, since it was reasonable to assume that the resistant virus remained present and would reemerge with reinstitution of indinavir. It was thought best to avoid the current formulation of amprenavir because of concern over gastrointestinal adverse effects.

In considering protease inhibitors in salvage therapy, it is important to note that there are greater differences among the resistance mutation patterns of these drugs than was initially believed. Data from the VIRA 3001 study, for example, show that virus with greater than 4-fold phenotypic resistance to indinavir is likely to be cross-resistant to nelfinavir and ritonavir but susceptible to amprenavir and saquinavir; virus with greater than 4-fold resistance to nelfinavir is likely to remain susceptible in varying degrees to ritonavir, indinavir, saquinavir, and amprenavir (Figure 3) (Cohen et al, AIDS, 2002).

Lopinavir/ritonavir is a good choice in the case of the current patient. Responses to lopinavir/ritonavir have been observed even in patients with virus exhibiting 4 or 5 protease inhibitor resistance mutations. Kempf and colleagues (*Antivir Ther*, 2000) reported response rates of 67% and 50% in multiple protease inhibitor-experienced patients with virus having 20- to 40-fold and greater than 40-fold resistance to lopinavir at baseline, respectively. In NNRTI-naive, multiple protease inhibitor-experienced patients, Clumeck and colleagues (XIII Int AIDS Conf, 2000) observed a decrease in HIV-1 RNA level to less than 400 copies/mL in 92% of patients receiving lopinavir/ritonavir 533/133 mg twice daily plus efavirenz and 80% of patients receiving 400/100 mg twice daily plus efavirenz in on-treatment analysis (82% and 69%, respectively, in intent-to-treat analysis with missing data equal to failure).

Protease inhibitor inhibitory quotient (IQ) appears to be the best predictor of response to boosted protease inhibitor treatment. The IQ provides an integrated measure of resistance and drug concentrations in the individual patient. One way of measuring protease inhibitor IQ is to divide the trough plas-

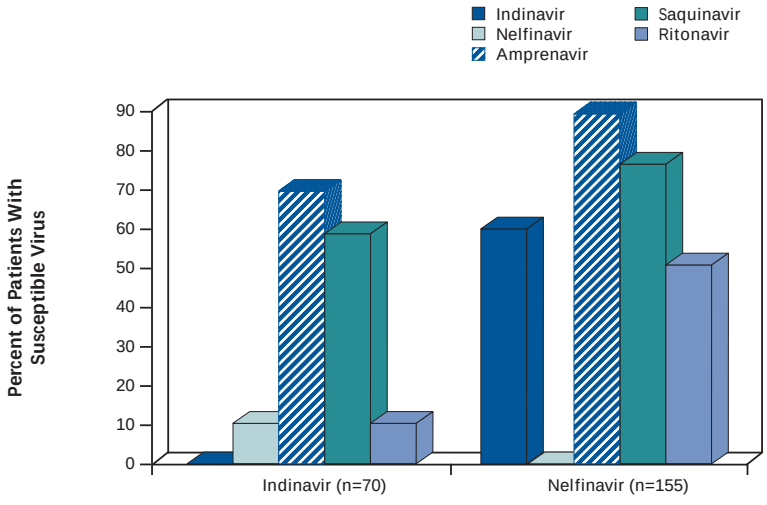

Figure **3.** Distribution of susceptibility to protease inhibitors of virus with more than 4-fold phenotypic resistance to indinavir or nelfinavir. Adapted from Cohen et al, *AIDS,* 2002.

ma concentration by the 50% inhibitory concentration of the drug. The IQ of lopinavir has been shown to predict response to lopinavir/ritonavir plus efavirenz/nRTI therapy in multiple protease inhibitor-experienced, NNRTI-naive patients (Hsu, 5th Int Cong Drug Ther HIV Infect, 2000).

A virtual IQ can be derived from a phenotype database rather than from measurement of phenotypic susceptibility. Kempf and colleagues (8th CROI, 2001) used the virtual IQ in place of a phenotype determined by direct measurement in order to calculate the virtual IQ. In their study of 37 patients with HIV-1 RNA levels of 50 to 50,000 copies/mL on stable indinavir-containing therapy, use of indinavir virtual IQ showed that more than 80% of patients with indinavir IQ greater than 2 maintained virologic response to a ritonavir-boosted indinavir regimen at 48 weeks compared with no patients with indinavir IQ less than 2. (Virologic response was defined as a 0.5-$\log_{10}$ decline in plasma HIV-1 RNA from baseline or plasma HIV-1 RNA below detection levels at week 24.) In this study, indinavir virtual IQ proved to be a better predictor of virologic response at week 3 than virtual phenotype, number of protease inhibitor mutations, or number of reverse transcriptase mutations (Figure 4).

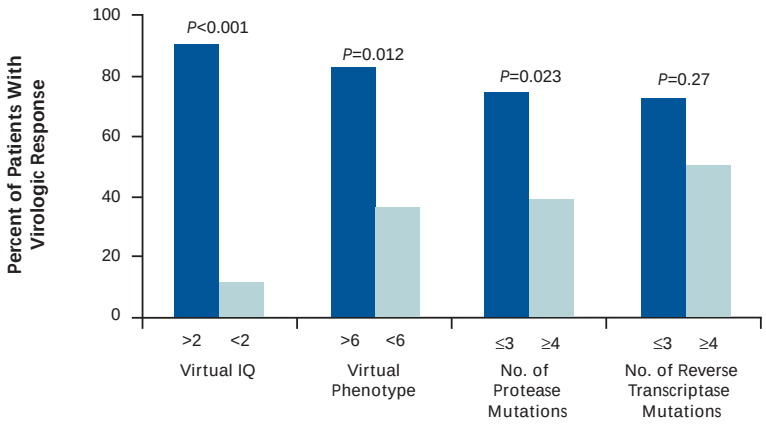

Figure **4.** Ability of indinavir virtual inhibitory quotient (virtual IQ), virtual phenotype, number of protease inhibitor mutations, and number of reverse transcriptase mutations to predict virologic response to regimen containing indinavir/ritonavir at 3 weeks. Adapted from Kempf et al, 8th CROI, 2001.

Clinical Decision and Outcome

The patient in Case 2 was treated with the ritonavir-boosted lopinavir regimen (Option 3) and has done quite well on this treatment.

Conclusions

Management of treatment failure differs according to whether the failure emerges on the first or second regimen or after more regimens have been used. In all patients, treatment benefit is a function of immune reconstitution and viral suppression. For patients in whom initial regimens have failed, ongoing viral replication in the setting of continued treatment with a regimen to which resistance has emerged allows accumulation of additional resistance mutations and eventual emergence of highly resistant virus. In more advanced patients in whom options for achieving full viral suppression may be exhausted, residual virus suppression confers residual treatment benefit and persistent viral replication leads ultimately to immunologic decline; thus, some treatment is better than none in most such patients.

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Perspective

Overview of Mitochondrial Toxicity of Nucleoside Reverse Transcriptase Inhibitors

At the International AIDS Society–USA course in New York in October 2001, Marshall J. Glesby, MD, PhD, reviewed potential mechanisms of nucleoside reverse transcriptase inhibitor-associated mitochondrial toxicity and discussed the potential clinical manifestations of mitochondrial dysfunction. For a review of new research on this topic presented at the 2002 Retrovirus Conference, please consult the update on complications of HIV infection and antiretroviral therapy on page 11 of this issue.

Mitochondria provide energy required for normal cell function, and thus tissue function, by producing adenosine triphosphate (ATP) via oxidative phosphorylation. They also regulate a number of other cellular processes, including apoptosis. Mitochondria are present in all cells, except erythrocytes, in numbers of 1 to more than 1000. The number of mitochondria correlates with the degree of cellular and tissue metabolic activity. Mitochondria have their own DNA, likely reflecting a bacterial origin and endocytosis by primitive eukaryotic cells during early evolution.

Mitochondrial DNA (mtDNA) is a small circular DNA species, consisting of approximately 16,000 bases, that codes for 13 polypeptides (as well as transfer and ribosomal RNAs), some of which are key proteins in oxidative phosphorylation. Whereas nuclear DNA (nDNA) is replicated by alpha DNA polymerase (Figure 1A), mtDNA is replicated by a gamma polymerase (Figure 1B), which has a relatively high error rate and some repair capacity. Most mitochondrial proteins are coded by nDNA.

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Nucleoside reverse transcriptase inhibitors (nRTIs) act via their incorporation into the growing viral DNA chain during reverse transcription, with incorporation resulting in chain termination. The nRTIs also inhibit gamma polymerase (Figure 1C) in vitro, and thus inhibit mtDNA synthesis. Consequent mtDNA depletion (or mutation) can result in insufficient energy production and cell dysfunction and in tissue and organ dysfunction when sufficient numbers of normally functioning mitochondria are not present (Lewis and Dalakas, *Nat Med*, 1995). In addition to the potential effects of gamma polymerase inhibition, nRTIs may also be associated with oxidative damage to mitochondria (de la Asuncion et al, *J Clin Invest*, 1998), inhibition of mitochondrial enzymes (Barile et al, *Biochem Pharmacol*, 1994), uncoupling of the electron transport chain from ATP synthesis, and induction of apoptosis (Kakuda, *Clin Ther*, 2000).

Probable Clinical Manifestations of nRTI-Related Mitochondrial Toxicity

Spurring the identification of a potential association between nRTI treatment and mitochondrial toxicity was the recognition that effects observed in nRTI-treated patients resembled clinical manifestations of inherited mitochondrial diseases. Many of these diseases involve a variety of organs and organ systems, including the brain, peripheral nerves, heart muscle, kidney, liver, endocrine system, gastrointestinal system, and bone marrow. Many of the effects associated or believed to be associated with mitochondrial toxicity, however, are difficult to distinguish from effects associated with HIV infection itself. It is also recognized that nRTIs differ in regard to potential mitochondrial toxicities.

Probable manifestations of mito-

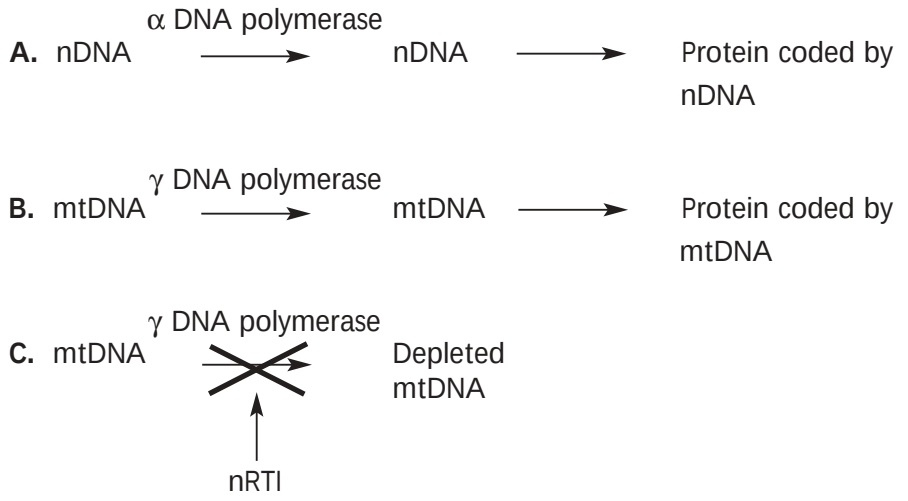

Figure **1.** Replication of nuclear DNA (nDNA) and mitochondrial DNA (mtDNA). In row A, normal nDNA replication in cells by alpha DNA polymerase; in row B, normal mtDNA replication in mitochondria by gamma DNA polymerase; and in row C, the hypothesized inhibition of gamma DNA polymerase by a nucleoside reverse transcriptase inhibitor (nRTI), resulting in the depletion of mtDNA and mtDNA-encoded proteins and consequently mitochondrial dysfunction. Adapted from Brinkman et al, *Lancet*, 1999.

chondrial dysfunction in patients receiving nRTIs include cardiomyopathy, myopathy, peripheral neuropathy, pancreatitis, proximal renal tubular dysfunction, and hepatic steatosis and lactic acidosis.

Cardiomyopathy

HIV infection itself has been demonstrated to cause cardiomyopathy. Cardiac muscle has a large energy demand and thus features a large mitochondria population. Studies to date, although not providing definitive data, implicate zalcitabine, didanosine, and zidovudine in cardiomyopathy; most evidence is in the form of case studies showing reversal of cardiomyopathy when nRTI treatment was stopped. There is some evidence of a cardiotoxic effect of high doses of zidovudine in animals. Autopsy series in non-HIV-infected patients with ischemic heart disease have shown mtDNA damage or mutations in the heart (Corral-Debrinski et al, JAMA, 1991), and it has been suggested that mitochondrial dysfunction might contribute to atherosclerosis in HIV-infected patients (Lewis, *J Mol Cell Cardiol*, 2000).

Myopathy

Both HIV infection and zidovudine treatment have been associated with myopathy, with the respective disorders being difficult to distinguish on a clinical basis. In AIDS Clinical Trials Group (ACTG) study 016, myopathy developed in 1.8% of patients receiving zidovudine monotherapy at 1200 mg per day. Analysis of data from 1067 treatment-naive patients in ACTG 175, in which zidovudine was used at the current dosage of 600 mg per day, showed that only 6 developed myopathy (Simpson et al, AIDS, 1998). Four of these patients received didanosine, 1 received zidovudine/zalcitabine, and 1 received zidovudine/didanosine. There are data indicating that both clinical and tissue abnormalities in myopathy can be reversed when zidovudine treatment is discontinued, and there are some data indicating the presence of mtDNA depletion in zidovudine-associated myopathy.

Peripheral Neuropathy

HIV-associated distal sensory polyneuropathy is similar to the peripheral neuropathy associated with stavudine, zalcitabine, and, to a lesser extent, didanosine. Results of one recent study (Brew et al, 8th CROI, 2001) indicate that elevated lactate levels may distinguish between the disorders. Subjects with stavudine-associated peripheral neuropathy were identified as such if they had been taking stavudine and if symptoms of neuropathy improved after cessation of stavudine use; subjects with HIV neuropathy were identified as such if they were not taking stavudine (none of the subjects was on zalcitabine or didanosine). Increased lactate levels that resolved with treatment discontinuation were found in 13 of 15 patients with stavudine-associated peripheral neuropathy versus 1 of 6 with HIV neuropathy.

> Many of the effects associated with mitochondrial toxicity are difficult to distinguish from effects associated with HIV infection itself

Nerve biopsy findings have indicated the presence of damaged mitochondria in patients with neuropathy associated with didanosine, stavudine, or zalcitabine. A study using the in vitro axon degeneration model indicates that toxicities of zalcitabine and didanosine, but not stavudine, were correlated with mtDNA depletion.

Pancreatitis

There are a number of factors predisposing to risk of pancreatitis in HIV-infected patients, including some opportunistic infections (eg, cytomegalovirus infection, *Mycobacterium avium* complex infection, and tuberculosis), malignancies, hypertriglyceridemia, high alcohol intake, and use of pentamidine.

Antiretrovirals associated with risk are the nRTIs didanosine and stavudine, with risk increasing when either is used in combination with hydroxyurea. Some cases of pancreatitis in HIV-infected patients receiving nRTIs have been associated with lactic acidosis. Didanosine does not produce pancreatic toxicity in rats. A toxic effect on mitochondria has, however, been observed in vitro in human pancreatic cell culture systems. A relationship of pancreatitis to mitochondrial dysfunction is suggested by characteristics of Pearson's marrow-pancreas syndrome, a condition associated with mtDNA deletions. These include cytopenias, exocrine dysfunction (malabsorption), pancreatic fibrosis, and acinar cell atrophy. Didanosine's toxicity extends to other exocrine glands, eg, the salivary glands, with elevated levels of salivary amylase and the sicca syndrome.

Proximal Renal Tubular Dysfunction

The kidney features a large mitochondrial population that is needed to satisfy the high energy requirement for driving sodium-potassium pumps in the proximal renal tubule. Inherited mitochondrial disease affecting the kidney most commonly takes the form of proximal renal tubular dysfunction (PRTD) or Fanconi's syndrome. The nucleotide reverse transcriptase inhibitor (nt*R*TI) adefovir, which is no longer being investigated for the treatment of HIV disease but is in development for potential use in hepatitis B virus infection, was associated with PRTD in approximately 50% of HIV-infected patients in a large multicenter trial (Kahn et al, JAMA, 1999). A recent case report of a patient with adefovir-associated PRTD described abnormal mitochondria, deficiency of cytochrome C oxidase (a mitochondrial enzyme coded by mtDNA), and reduced mtDNA in a kidney biopsy (Tanji et al, *Hum Pathol*, 2001).

Hepatic Steatosis and Lactic Acidosis

Cases of liver failure with macrovesicular and microvesicular steatosis have been

reported in association with nRTI therapy. It is believed that mitochondrial dysfunction in the liver results in inhibition of fatty acid oxidation, resulting in accumulation of triglycerides and fatty acids in vesicles. Lactic acidosis is a feature of the hepatic steatosis syndrome. Inhibition of oxidative metabolism results in anaerobic metabolism and increased lactate production, and there are data demonstrating that nRTIs increase lactic acid production in cell culture systems (Chen et al, *Mol Pharmacol*, 1991). The incidence of hepatic steatosis is relatively low (1.3-3.9 cases per 1000 patient-years of nRTI use) but the case fatality rate is high (Fortgang et al, *Am J Gastroenterol*, 1995; John et al, AIDS, 2001).

There appears to be a spectrum of lactate abnormalities in HIV-infected patients. A recent study has indicated a frequency of milder symptomatic hyperlactatemia (defined as reproducible hyperlactatemia with abdominal symptoms or increased alanine aminotransferase level or both) of 14.5 per 1000 patient-years on nRTIs (Lonergan et al, 8th CROI, 2001). The frequency in patients receiving stavudine was 26 per 1000 patient-years, compared with 1.9 per 1000 patient-years of exposure to other nRTIs. Of 6 patients with stavudine exposure in this study undergoing liver biopsy, 5 had steatosis, suggesting a possible link between steatosis and hyperlactatemia.

The prevalence of asymptomatic hyperlactatemia in patients on nRTIs has been estimated at 8% to 21% (Vrouenraets et al, XIII Int AIDS Conf, 2000; Harris et al, *Antivir Ther*, 2000); mild lactate increases are common in patients beginning potent antiretroviral therapy including an nRTI (John et al, AIDS, 2001). Mild elevations in lactate levels are also found in a smaller percentage of antiretroviral-naive patients. The spectrum of clinical findings observed in patients with hyperlactatemia (Figure 2) ranges from an asymptomatic presentation associated with lactate levels of 2.1 to 5 mmol/L, to mild to moderate symptoms associated with lactate levels of 5 to 10 mmol/L, to fatal lactic acidosis and steatosis with levels above 10 mmol/L.

Risk of progression to serious complications, which is associated with lactate levels above 10 mmol/L, does not appear to be significant in patients with asymptomatic, mild elevations in lactate (levels of 2.1-5 mmol/L). Risk of progression remains undefined in those with greater elevations (5-10 mmol/L) and mild-moderate symptoms, whereas there is high risk of serious complications in patients with lactate levels above 10 mmol/L.

Recent case reports have prompted some concern over the potential for steatosis and pancreatitis in patients receiving nRTIs and treatment with interferon alfa and the nucleoside analogue ribavirin. In a report on 2 patients with hepatitis C virus (HCV) and HIV coinfection who were receiving interferon alfa/ribavirin (Lafeuillade et al, *Lancet*, 2001), steatosis, pancreatitis, diabetes, weight loss, and increased lactate level were observed in 1 patient receiving stavudine/didanosine/saquinavir, and steatosis, increased amylase level, and increased lactate level were observed in the other patient receiving stavudine/didanosine/lamivudine. Subsequently, pancreatitis was reported in 3 additional patients on didanosine who were also receiving interferon alfa/ribavirin treatment. Of note, there is literature from the 1980s showing that ribavirin reduces levels of intracellular dATP, thus enhancing didanosine activity (and toxicity).

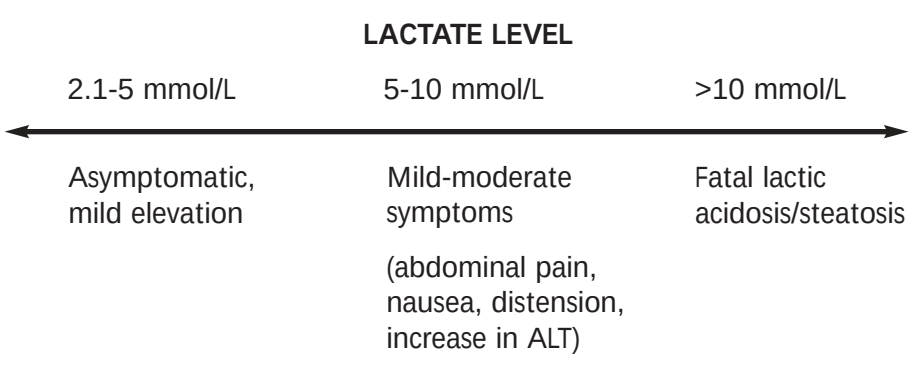

Figure **2.** The spectrum of clinical findings observed in patients with hyperlactatemia. ALT indicates alanine aminotransferase.

Possible Clinical Manifestations of nRTI-Related Mitochondrial Toxicity

Possible, but as yet unproven, clinical manifestations of nRTI-related mitochondrial toxicity include hematologic toxicity, lipodystrophy and lipoatrophy, and osteopenia.

Hematologic Toxicity

There is at least a superficial resemblance of the hematologic abnormalities observed in patients with Pearson's marrow-pancreas syndrome to the anemia and neutropenia associated with zidovudine (Lewis and Dalakis, *Nat Med*, 1995). However, data from in vitro studies of the effect of zidovudine on mtDNA in bone marrow progenitor cells are conflicting. The mechanisms of zidovudine-associated hematologic toxicity remain unclear despite prolonged use of the drug. Mechanisms other than mitochondrial toxicity (eg, effects on heme metabolism) could also be hypothesized.

Lipodystrophy and Lipoatrophy

The phenotype of lipoatrophy in HIV-infected patients receiving antiretroviral therapy at least superficially resembles that in Madelung's disease (multiple symmetric lipomatosis), which is associated with mtDNA mutations. It has been hypothesized that mitochondrial toxicity of adipocytes associated with antiretroviral therapy may lead to adipocyte apoptosis and thus lipoatrophy (Brinkman et al, *Lancet*, 1999; Kakuda et al, AIDS, 1999). Some support for this hypothesis is provided by the following findings from studies in patients receiving therapy: an association of lipoatrophy with hyperlactatemia and liver dysfunction in a patient series (Carr et al,

AIDS, 2000); abnormal adipocyte mitochondria on fat biopsies in a small number of patients with lipoatrophy (Mallal et al, AIDS, 2000); a 60% frequency of decreased mtDNA levels in subcutaneous fat biopsies (neck, abdomen, thigh) in patients with lipodystrophy versus a frequency of 0% to 30% in patients without lipodystrophy or in HIV-seronegative subjects (Shikuma et al, AIDS, 2001); and the association of nRTI use with a decrease in mtDNA (mean, 44%) in fat biopsies in buttocks (Walker et al, *JAIDS*, 2000).

Osteopenia

In one study of 221 HIV-infected men (32 were antiretroviral-naive and 189 were receiving nRTI-containing regimens), osteopenia was associated with asymptomatic hyperlactatemia (odds ratio, 2.39 per 1 mmol/L increase in lactate level) and lower body weight prior to starting antiretroviral therapy (Carr et al, AIDS, 2001). It has been hypothesized that osteopenia may result from mitochondrial dysfunction in bone. Osteopenia has been reported in HCV-infected patients without HIV infection receiving ribavirin/interferon alfa therapy (Solis-Herruzo et al, *J Hepatol*, 2000).

Overview

There are many issues remaining to be clarified about the effects of nRTIs on mitochondria and the potential for clinical manifestations of these effects. Some of these issues involve the differing adverse effects among nRTIs that may be associated with mitochondrial toxicity—eg, why is zidovudine associated with myopathy, whereas stavudine is associated with neuropathy?

Manifestations of mitochondrial defects are likely to occur in tissue dependent on oxidative phosphorylation, and it may be that nRTIs differ in capacity to penetrate different tissues or that the cellular kinases that phosphorylate nRTIs function differently for different drugs and in different tissues. Further, the different nRTIs have been reported to have different magnitudes of inhibitory effect on gamma polymerase in vitro (Martin et al, *Antimicrob Agents Chemother*, 1994), although effects in vivo remain undefined.

Similarly, there may be differences among nRTIs regarding the ability of gamma polymerase to proofread and excise the nRTI once it is incorporated into the DNA chain. It has been reported that lamivudine, for example, is readily recognized and excised after incorporation. It also remains unclear whether nRTIs have additive or synergistic effects on mitochondria when used in combination. Finally, it is not understood why only some patients appear to have mitochondrial toxicity or clinical manifestations of such toxicity. In addition to potential drug effects, roles in this regard may be played by HIV infection itself, HCV coinfection, alcohol use, or genetics.

In summary, inhibition of mtDNA polymerase by nRTIs may explain many of the toxicities associated with drugs in this class. Data from cell culture systems and animal studies and, in some cases, biopsy studies in humans, provide some support for this hypothesis. However, the in vitro data are sometimes conflicting with respect to effects of the nRTIs, and it needs to be emphasized that generalizations from these data to potential in vivo effects in humans may not be appropriate.

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Switching Antiretroviral Drugs for Treatment of Metabolic Complications in HIV-1 Infection: Summary of Selected Trials

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Metabolic complications in HIV-1-infected patients, such as insulin resistance, lipid abnormalities, and changes in body fat distribution, are becoming more prevalent and of increasing concern to patients and clinicians. A switch in antiretroviral therapy to include classes of drugs not epidemiologically associated with metabolic complications is a potential strategy for treatment of metabolic complications. In general, treatment of the underlying HIV-1 infection should take precedence over the potential benefits of antiretroviral switching.

A number of switch studies have been conducted in which a protease inhibitor has been switched for a nonnucleoside reverse transcriptase inhibitor (NNRTI) or abacavir. It is difficult to draw conclusions from these studies because of their generally small sample size and differences in the study populations, treatment regimens, duration of follow-up, reasons for switching therapy, and methodology. Randomized clinical trials with larger numbers of patients are needed to evaluate the efficacy and safety of switch strategies in various settings. In the aggregate, however, several trends emerge:

- A switch from a protease inhibitor to nevirapine or abacavir is usually associated with an improvement in cholesterol and triglyceride levels. A switch from a protease inhibitor to efavirenz is associated with a more mixed result.
- A switch from a protease inhibitor to abacavir is associated with an improvement in insulin resistance. A switch from a protease inhibitor to nevirapine or efavirenz varies in result from no change to improvement.
- A switch from a protease inhibitor to nevirapine, efavirenz, or abacavir seems to have little impact on visceral, truncal, or other fat accumulation abnormalities.

Clinicians must take the entire treatment history (eg, prior abacavir hypersensitivity) into account before making a switch in a patient's antiretroviral therapy, and candidates for switching antiretroviral therapy should be chosen with care.

A current research question concerns the result of switching the "background" nucleoside reverse transcriptase inhibitors (nRTIs; eg, stavudine or zidovudine) in a regimen for other drugs, such as tenofovir, when the protease inhibitor remains the same. It is unclear whether such a switch would result in reversal of any metabolic abnormalities.

Selected available data on the impact of antiretroviral drug substitutions on glucose metabolism, lipid levels, and body fat distribution abnormalities are summarized in the following tables. Studies with at least 20 subjects and for whom metabolic data were collected or observations were made for at least 24 weeks are included. In cases where numerous presentations of study data were made by the same group of investigators, only the most recent data are included.

These data were compiled and used by the International AIDS Society–USA Metabolic Complications Guidelines Panel as part of its effort to develop guidelines for the diagnosis and management of metabolic complications associated with antiretroviral therapy and HIV-1 infection. These guidelines were recently submitted for publication.

Table **1.** Nevirapine Switch Studies

Regimen	N	Follow-up	TGs	Chol	Glu/IR	Body Change	Comments
2 nRTIs + PI → 2 nRTIs + nevirapine[1]	23	24 weeks	↓	↓	↓	↓ WHR	Diet not reported.
2 nRTIs + PI → 2 nRTIs + nevirapine[2]	104	24 weeks	~↓	~↓	–	↓ WHR	Rebound in HIV-1 RNA occurred more often in PI group than nevirapine group (18% vs 4%, *P* = .015).

Chol indicates cholesterol; Glu, glucose; HDL, high-density lipoprotein; IR, insulin resistance; N, the number of subjects in switch group(s); nRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TGs, triglycerides; VAT, visceral adipose tissue; WHR, waist-to-hip ratio; ↑ or ↓, significant increase or decrease; ~↑ or ~↓, nonsignificant trend of increase or decrease.

Table **1.** Nevirapine Switch Studies *(continued)*

Regimen	N	Follow-up	TGs	Chol	Glu/IR	Body Change	Comments
2 nRTIs + PI → 2 nRTIs + nevirapine[3]	60	36 weeks	↓	↓	NC	NC	Randomized study. Virologic failure: 4 with nevirapine; 3 with PI.
2 nRTIs + PI → 2 nRTIs + nevirapine + adefovir + hydroxyurea[4]	49	48 weeks	↓	↓	NC	↓ VAT ↓ WHR ↑ lipoatrophy	Randomized (2:3) study. No difference in HDL chol. Weight and CD4+ cell count decreased. Virologic failure: 3 (6%) in experienced patients; 6 (19%) with PI. Intolerance in 15 experienced patients.
2 nRTIs + PI → 2 nRTIs + nevirapine[5]	40	48 weeks	↓	NC	↓	NC	Severe rash in 6 patients; therapy changed to efavirenz. One patient with virologic failure.
2 nRTIs + PI → 2 nRTIs + nevirapine[6]	26	52 weeks	↓	↓	–	NC	Randomized to nevirapine, efavirenz, or control. Only 1 patient had rebound in plasma HIV-1 RNA level in nevirapine group.
2 nRTIs + PI → 2 nRTIs + nevirapine[7]	73	52 weeks	↓	NC	–	NC	Nonrandomized; 10 patients on efavirenz, 63 nevirapine. Infrequent virologic failure.
2 nRTIs + PI → 2 nRTIs + nevirapine[8]	68	24 weeks	~↓	NC	–	–	Virologic failure in 4 cases.
2 nRTIs + PI → 2 nRTIs + nevirapine, abacavir, or efavirenz[9]	81	24 weeks	↓	NC	↓	–	Randomized substudy of[10]. Glu/IR same in all 3 groups. Nevirapine and efavirenz arms had increase in HDL; abacavir arm had decrease in HDL.
2 nRTIs + PI → 2 nRTIs + nevirapine, abacavir, or efavirenz[10]	460	48 weeks	↓	NC/ ↑ HDL	↓	–	Abacavir arm had greater decrease in TGs; there was a greater decrease in total chol with abacavir, but HDL increased only in the nevirapine and efavirenz arms.

Table **2.** Efavirenz Switch Studies

Regimen	N	Follow-up	TGs	Chol	Glu/IR	Body Change	Comments
2 nRTIs + PI → 2 nRTIs + efavirenz[11]	33	40 weeks	NC	NC	NC	NC	Subset analysis of a cohort of 624 patients evaluated for body fat, lipid, and glucose abnormalities.
2 nRTIs + PI → 2 nRTIs + efavirenz[12]	39	24 weeks	~↑	NC	NC	NC	Virologic control maintained. Modest increase in HDL chol.
2 nRTIs + PI → 2 nRTIs + efavirenz[13]	43	24 weeks	~↑	NC	–	NC	HIV-1 RNA remained <50 copies/mL in all patients. HDL chol was unchanged.
2 nRTIs + PI → 2 nRTIs + efavirenz[14]	20	24 weeks	↓	NC	↓	↓ WHR ↓ VAT	HIV-1 RNA became detectable in 1 patient.
2 nRTIs + PI → 2 nRTIs + efavirenz[6]	25	24 weeks	~↓	NC	–	NC	Randomized to nevirapine, efavirenz, or control. Only 1 patient had HIV-1 RNA rebound in the nevirapine group vs 2 in the efavirenz group and 1 in the PI group.
2 nRTIs + PI → 2 nRTIs + efavirenz[15]	25	24 weeks	~↑	~↑	↓	~↓ VAT	HIV-1 RNA remained <500 copies/mL for all patients.
2 nRTIs + PI→ 2 nRTIs + efavirenz[16]	164	24 weeks	–	NC	–	–	Improvement in HDL chol in efavirenz group.

Chol indicates cholesterol; Glu, glucose; HDL, high-density lipoprotein; IR, insulin resistance; N, the number of subjects in switch group(s); NC, no change; nRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TGs, triglycerides; VAT, visceral adipose tissue; WHR, waist-to-hip ratio; ↑ or ↓, significant increase or decrease; ~↑ or ~↓, nonsignificant trend of increase or decrease.

Table 2. Efavirenz Switch Studies *(continued)*

Regimen	N	Follow-up	TGs	Chol	Glu/IR	Body Change	Comments
2 nRTIs + PI → 2 nRTIs + abacavir + efavirenz[17]	27	36 weeks	~↓	~↓	~↓	NC	Some overall fat loss by BIA (2.5 kg), but no change in symptoms of fat redistribution. Virologic failure in 1 patient.
2 nRTIs + PI → 2 nRTIs + efavirenz[18]	56	24 weeks	↓	↑ HDL	–	NC	No virologic failure. Some increase in lipoatrophy (5 patients).
2 nRTIs + PI → 2 nRTIs + efavirenz[19]	45	48 weeks	↓	~↓	–	–	Virologic failure in 2 patients.
2 nRTIs + PI → 2 nRTIs + efavirenz[20]	20	24 weeks	NC	NC	NC	NC	No virologic failures. Subjective improvement in morphologic appearance but no change in anthropometric studies.
2 nRTIs + PI → 2 nRTIs + efavirenz[21]	46	52 weeks	↓	NC	↓	↓ WHR ↓ VAT	Moderate increase in HDL chol with efavirenz; no difference in HIV-1 RNA outcome or SAT loss.
2 nRTIs + PI → 2 nRTIs + efavirenz[22]	41	52 weeks	–	–	NC	–	Patients with lipodystrophy syndrome; only IR and Glu tolerance evaluated.
2 nRTIs + PI → 2 nRTIs + efavirenz or nevirapine[23]	100	52 weeks	↓	↓	NC	NC	HIV-1 RNA suppression maintained in 80%; no difference between efavirenz and nevirapine groups.
2 nRTIs + PI → 2 nRTIs + efavirenz[24]	226	48 weeks	~↑	NC	–	–	Virologic failure in 7% of switch group vs 15% of controls (*P*=.024). TGs increased in both groups. Significant increase in HDL in switch group.

Table 3. Nucleoside Reverse Transcriptase Inhibitor Switch Studies

Regimen	N	Follow-up	TGs	Chol	Glu/IR	Body Change	Comments
Stavudine → zidovudine or abacavir[25]	59	36 weeks	↓	NC	NC	↑ SAT NC in VAT	Some patients (n=18) on dual nRTIs; remainder (n=41) on PI/nRTI; lactate declined significantly.
2 nRTIs + PI → 2 nRTIs + abacavir[26]	211	24 weeks	~↓	↓	↓	–	Randomized to continue PI or not. Virologic failures: abacavir (9; 3 virologic); PI (14; 2 virologic).
2 nRTIs + PI → 2 nRTIs + abacavir[27]	84	52 weeks	↓	↓	–	–	Randomized to continue PI or not. Virologic failures: abacavir, 11; PI, 5.
2 nRTIs + PI → 2 nRTIs + abacavir[28]	105	45 weeks	~↓	~↓	–	–	Randomized to continue PI (106) or not (105). Virologic failures: abacavir, 4; PI, 2.
Stavudine + nRTI + PI → zidovudine + lamivudine + abacavir[29]	40	48 weeks	–	~↓	–	↑ SAT	Randomized trial. No virologic failure in switch group.
Stavudine → abacavir or zidovudine[30]	86	24 weeks	–	–	–	~↑ SAT	Increase in SAT was detected by DEXA scan. 11% - 26% subjective improvement in lipoatrophy reported. No loss of virologic control.
Stavudine or zidovudine → abacavir[31]	55	24 weeks	NC	NC	NC	↑ SAT NC in VAT	Randomized to continue current therapy or switch. No virologic failure in switch group. Increase in SAT detected by DEXA and CT.

BIA indicates bioelectrical impedance analysis; Chol, cholesterol; CT, computed tomography; DEXA, dual-energy x-ray absorptiometry; Glu, glucose; HDL, high-density lipoprotein; IR, insulin resistance; N, the number of subjects in switch group(s); NC, no change; nRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SAT, subcutaneous adipose tissue; TGs, triglycerides; VAT, visceral adipose tissue; WHR, waist-to-hip ratio; ↑ or ↓, significant increase or decrease; ~↑ or ~↓, nonsignificant trend of increase or decrease.

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144-M. Physical and Functional Interaction between Viral Protein R and p21WAFI. B. E. Sawaya, S. P. Singh, K. Khalili, A. Clavo, A. Srinivasan, and S. Amini.
145-M. HIV-1 Vpr Causes Cell Cycle Arrest via a Pathway Involving p38 MAP Kinase and ATR. M. Roshal, Y. Zhu, and V. Planelles.
146-M. Vpr Mutation R77Q Is Associated with Long-Term Non-Progressive HIV-Infection and an Impaired Ability to Induce T-Cell Depletion in Vivo. J. Lum, O. J. Cohen, D. H. Lynch, A. A. Pilon, J. E. Kim, Z. Chen, M. Montpetit, J. Sanchez-Dardon, N. Hawley-Foss, G. Garber, and A. D. Badley.
154-M. Differential Interaction with Actin by HIV-1 Gag and Matrix Protein. C. Gomez and T. Hope.
162-M. A Dual Role for Leader Sequences Downstream of the SIV Stem-Loop 1 in RNA Packaging and Dimerization of Simian Immunodeficiency Virus RNA. J. B. Whitney, M. Olivera, B. Spira, Y. Guan, M. A. Wainberg.
163-M. Identification of Novel Sequences Involved in HIV-1 Genomic RNA Dimerization. R. S. Russell, J. Hu, M. A. Wainberg, and C. Liang.
166-M. Temporal Modulation of Monocyte-Derived Macrophage Gene Expression During HIV-1 Infection. F. Ottones, C. Royer, and J. Corbeil.
168-M. Gene Expression Studies of in Vitro HIV-1 Infection: HIV-1 Activates Transcription of the Sterol Biosynthesis Pathway. A. van't Wout, G. Lehrman, S. Mikheeva, G. O'Keeffe, G. Geiss, R. Bumgarner, and J. Mullins.
171-M. A Role for PI3-Kinase Signaling during HIV Infection of Primary CD4+ T Lymphocytes and Macrophages. F. Francois and M. E. Klotman.
186-M. HIV-1 Env Signaling in Primary Human Macrophages through CCR5 and CXCR4: Role in HIV-1 Pathogenesis. M. Del Corno, C. H. Lee, M. Chen, Q. H. Liu, B. Freedman, and R. G. Collman.
312-W. Control of Viral Load Rebound during Treatment Interruptions in Macaques with AIDS Induced by a Novel Topical DNA Immunization (DermaVir). J. Lisziewicz, J. Xu, J. Trocio, L. Whitman, M. G. Lewis, and F. Lori.
313-W. Containment of Viral Rebound after Antiretroviral Therapy Suspension in Macaques Chronically Infected with SIV following Vaccination with NYVAC-SIV Recombinant Vaccines. E. Tryniszewska, M. G. Lewis, Z. Hel, J. Nacsa, W-P. Tsai, L. Stevceva, R. W. Parks, M. Moniuszko, S. Cairns, K. A. Smith, J. Tartaglia, and G. Franchini.
314-W. Therapeutic Immunization with Remune Alters Kinetics of Viral Rebound after Analytical Therapy Interruption (ATI). R. P. Bucy, R. B. Moss, and M. Gersten for the 806A Study Team.
315-W. Immunogenicity of Remune in Subjects with Established HIV Infection. G. Robbins, M. M. Addo, H. Troung, A. Rathod, K. Habeeb, N. Basgoz, B. Davis, H. Heller, B. Walker, and E. Rosenberg.
318-W. Augmentation of HIV-1-Specific Memory Subsets of T Lymphocytes and Decrease of Immune Activation in HIV-1+ Individuals Treated with a Therapeutic Vaccine plus Antiretrovirals: Impact on Viral Load. E. Fernandez-Cruz, J. Navarro, M. L. Abad, L. Díaz-Muñoz, C. Cantó, J. Carbone, S. Moreno, B. Clotet, J. Pérez Molina, J. M. Gatell, and M. Munoz-Fernandez for the Spanish 2102 Team.
385-T. DPC 817: A Cytidine Nucleoside Analog with Activity against AZT- and 3TC-Resistant Viral Variants. S. Erickson-Viitanen, R. F. Schinazi, J. Mellors, R. Geleziunas, G. Trainor, J. T. Wu, K. Gallagher, R. Klabe, M. Otto, M. Pierce, and D. E. Martin.
391-T. AMD-3100 CXCR4 Receptor Blocker Fails to Reduce HIV Viral Load by ≥ 1 Log following 10-Day Continuous Infusion. C. Hendrix, A. C. Collier, M. Lederman, R. Pollard, S. Brown, M. Glesby, C. Flexner, G. Bridger, K. Badel, R. MacFarland, G. Henson, and G. Calandra for the AMD-3100 HIV Study Group.
396-T. HIV-1 Mutants Less Susceptible to SCH-D, a Novel Small-Molecule Antagonist of CCR5. Z. Chen, B. Hu, W. Huang, T. He, Y. Huang, J. Strizki, S. Xu, L. Wojcik, J. M. Whitcomb, L. Zhang, C. J. Petropoulos, B. Baroudy, and D. Ho.
397-T. Genotypic and Phenotypic Analysis of in Vitro Generated HIV-1 Escape Isolates to the CCR5 Antagonist SCH-C. J. Riley, L. Wojcik, S. Xu, and J. Strizki.
402-T. Identification of CCR5 Co-Receptor Inhibitors that Potently and Selectively Block HIV-1 Replication. W. Olson, T. Dragic, B. O'Hara, K. Nagashima, F. Tsamis, M. Westby, and N. Cammack.
403-T. The CCR5 Co-Receptor Inhibitor PRO 140 Effectively Controls Established HIV-1 Infection in Vivo. M. Franti, K. Nagashima, P. Maddon, D. R. Burton, W. Olson, and P. Poignard.
404-T. Reduction of Persistent HIV-1 Replication Using Cell-Reservoir Specific Anti-Retroviral Therapy. B. Patterson, S. L. Becker, J. Snidow, B. Pobiner, D. Grundhoefer, and A. Landay.
405-T. Residual HIV-1 Disease Eradication (RHIDE) Trial: An HIV-1 Reservoir Eradication Approach in Humans Using a Novel and Stimulatory Intensification Therapy. R. J. Pomerantz, M. Otero, G. Nunnari, A. Malin, C. Coates, C. Dascenzo, J. DeSimone, T. Babinchak, H. Zhang, G. Dornadula, D. Culnan, J. Sullivan, Y. Xu, J. Stern , W. Cavert, A. Haase, and J. Kulkosky.
408-W. A Comparison of AZT/3TC vs 3TC/d4T and ddI/d4T in Combination with Efavirenz as First Line Therapy: Efficacy and Safety Results after 48 Weeks. M. R. Domula, J. C. Wasmuth, A. Jütte, G. Fätkenheuer, M. Oette, A. Theisen, C. Höhn, H. Knechten, B. Pfeil, S. Fenske, A. Rieke, and J. K. Rockstroh.
409-W. Once-Daily vs Twice-Daily Kaletra (Lopinavir/Ritonavir) in Antiretroviral-Naive HIV+ Patients: 48-Week Follow-Up. J. J. Eron, B. Bernstein, M. King, L. Manning, R. Bertz, G. Beall, F. Carpio-Cedraro, J. Feinberg, H. Horowitz, D. Wheeler, H. Kessler, D. Mildvan, P. Ruane, B. Yangco, C. Renz, S. Mayer, and E. Sun.
410-W. CHARM: A Phase III Open-Label, Randomized, Multi-Center Study to Evaluate the Efficacy and Tolerability of Adding Nevirapine (NVP) and/or Hydroxyurea (HU) to a Triple Nucleoside-Based Antiretroviral Drug Regimen in Treatment-Naive HIV-1-Infected Subjects. M. Beniowski, R. Wood, G. Gray, A. Horban, R. Schmidt, A. Lazzarin, A. Lafeuillade, D. Paes, H. Carlier, D. Blanckenberg, E. van Weert, R. van Leeuwen, and J. Lange for the CHARM Trial Study Team.
413-W. Tenofovir DF: A 48-Week Final Analysis from a Phase III Randomized, Double Blind Placebo Controlled Study in Antiretroviral Experienced Patients. K. Squires, G. Pierone, D. Berger, C. Steinhart, N. Bellos, S. L. Becker, S. S. Chen, M. D. Miller, D. F. Coakley, and A. Cheng for the Study 907 Team.
415-W. The Viread Expanded Access Program (EAP): Safety and Efficacy of Tenofovir Disoproxil Fumarate (TDF) in Antiretroviral Treatment (ART)-Experienced Patients. S. Follansbee, J. Reynes, M. Nelson, B. Clotet, A. Lazzarin, A. Adam, S. Van Doren, R. Buffels, S. Barriere, L. Zagury, I.

Miranski, and J. Rooney.

416-W. Safety Profile of Tenofovir DF in Antiretroviral-Experienced Patients from Randomized, Double-Blind, Placebo-Controlled Clinical Trials. A. Cheng, S. Barriere, D. F. Coakley, S. S. Chen, M. Wulfsohn, and J. J. Toole.

421-W. Virological and Immunological Benefit of a Salvage Therapy that Includes Kaletra plus Fortovase Preceded or not by Antiretroviral Therapy Interruption (TI) in Advanced HIV-Infected Patients (6-Month-Follow-up). L. Ruiz, E. Ribera, A. Bonjoch, J. Martínez-Picado, M. Díaz, J. Romeu, S. Marfil, E. Negredo, J. García-Prado, C. Tural, T. Puig, G. Sirera, and B. Clotet.

429-W. Single and Multiple Dose Pharmacokinetics (PK) of Stavudine (d4T) from an Extended Release (XR) Formulation in Asymptomatic HIV-Infected Subjects. S. Kaul, A. Swaminathan, D. Behr, P. Nichola, J. Gale, and E. O'Mara.

430-W. Pharmacokinetics (PK) of Stavudine (d4T) Extended Release Formulation Compared with Stavudine Immediate Release (IR) Formulation as Part of Potent Antiretroviral Combination Therapy. S. Kaul, B. Damle, J. Gale, G. McKinely, L. Slater, A. Huang, and H. Brett-Smith.

431-W. An Assessment of Plasma Amprenavir (APV) Pharmacokinetics (PK) Following Administration of Two GW433908 (908) and Ritonavir (RTV) Regimens in Combination with Efavirenz (EFV) in Healthy Adult Subjects (APV10010). M. B. Wire, C. Ballow, S. Preston, C. Hendrix, Y. Lou, P. Piliero, and D. S. Stein.

437-W. Steady-State Indinavir (Crixivan) Pharmacokinetics in Cerebrospinal Fluid (CSF) and Plasma in Patients Receiving Low-Dose Ritonavir (Norvir), as Determined by Ultra-Intensive CSF Sampling. D. W. Haas, B. Johnson, J. Nicotera, V. L. Bailey, V. L. Harris, F. Bowles, S. Raffanti, T. Finn, J. Schranz, A. Saah, and J. Stone.

439-W. Penetration of Lopinavir into the Genital Tract of HIV-1-Infected Men. S. Sankatsing, D. Burger, J. Droste, S. Jurriaans, J. Lange, and J. Prins.

441-W. Pharmacokinetics, Efficacy, and Safety of Once-Daily Saquinavir-sgc plus Low-Dose Ritonavir (1200/100 mg) in Combination with Efavirenz in HIV-Pretreated Patients. L. F. López-Cortés, P. Viciana, R. Ruiz-Valderas, R. Contreras, and A. Alarcón.

443-W. Evaluation of Steady-State Interaction between Atazanavir (ATV) and Efavirenz (EFV). S. Preston, P. Piliero, E. O'Mara, V. Mummaneni, D. Randall, C. Morvillo, M. Geraldes, S. Agarwala, and G. Drusano.

445-W. Pharmacokinetic (PK) Effect of Rifabutin (RIF) on Atazanavir (ATV) with and without Ritonavir (RTV) in Healthy Subjects. S. Agarwala, V. Mummaneni, D. Randall, M. Geraldes, R. Stoltz, and E. O'Mara.

446-W. Pravastatin 40-mg qd Does not Alter Protease Inhibitor (PI) Exposure or Virological Efficacy over 24 Weeks Therapy. G. J. Moyle, N. E. Buss, and B. Gazzard.

447-W. Pharmacokinetics (PK) of Lower Doses of Saquinavir Soft Gel Caps (SQV) (800- and 1200-mg BID) with Itraconazole (Itra) Compared to 1400 mg SQV BID without Itra in HIV-1+ Thai Patients. P. Cardiello, T. Samor, D. Burger, R. Hoetelmans, A. Mahanontharit, K. Ruxrungtham, J. Lange, D. A. Cooper, and P. Phanuphak.

449-W. Influence of Binding to Human Plasma Proteins by Protease Inhibitors May Be Overestimated in Current IQ Models. M. P. de Béthune, D. Xie, H. Azijn, P. Wigerinck, R. Hoetelmans, and R. Pauwels.

452-W. Monitoring Intracellular Triphosphorylated Anabolites of Didanosine EC (ddI) and Stavudine (d4T): Results of a Pilot Clinical Study in HIV-Infected Patients. F. Becher, R. Landman, A. Canestri, S. Mboup, C. Toure Kane, F. Liegeois, M. Vray, C. Dalban, M. H. Prevot, G. Leleu, and H. Benech.

455-W. Virological Failure Is Associated with Decreased 3TC Triphosphate (3TCTP) and Ratio of 3TCTP/Endogenous Deoxycytidine Triphosphate in HIV-Infected Individuals in a Clinical Setting. P. Hoggard, S. Kewn, J. Lloyd, S. Sales, E. Wilkins, B. Maher, E. Meaden, L. Almond, T. Jones, D. Pillay, C. Sabin, S. Khoo, and D. Back.

461-W. Genotypic and Phenotypic Analyses of Drug Susceptibility in HIV-1 Isolates from Drug-Naive Patients in Nigeria. S. M. Agwale, C. Zeh, E. Paxinos, L. Odama, D. Pienazek, C. Wambebe, M. L. Kalish, and R. Ziermann.

491-M. Rapid Initial Decay of Latently Infected Cells Following the Re-Initiation of HAART in Chronically HIV-1-Infected Patients with Treatment Interruptions. J. Blankson, J. Siliciano, D. Finzi, T. Quinn, J. Gallant, and R. Siliciano.

493-M. Levels of Cell-Free HIV Virions Released by Latently Infected, Resting CD4+ T Cells: Implications for Ongoing Viral Replication. T. W. Chun, J. Justement, P. Pandya, S. Liu, M. McLaughlin, L. Ehler, and A. S. Fauci.

514-M. Long-Term Efficacy of Subcutaneous IL-2 Therapy in HIV Infection. Final Analysis of the ANRS 079 Randomized Trial and Long-Term Follow-up. Y. Levy, C. Durier, A. S. Lascaux, C. Capitant, C. Michon, L. Weiss, E. Oksenhendler, J. A. Gastaut, C. Goujard, C. Rouzioux, J. P. Aboulker, J. F. Delfraissy, and the ANRS 079 Study Group.

515-M. Long-Term Efficacy of Subcutaneous IL-2 Therapy in HIV Infection: Pro-Viral DNA in Patients of the ANRS 079 Trial. M. Burgard, C. Durier, C. Capitant, A. S. Lascaux, C. Michon, E. Netzer, C. Goujard, V. Foubert, J. P. Aboulker, J. F. Delfraissy, Y. Levy, and C. Rouzioux for the ANRS 079 Study Group.

517-M. Baseline Characteristics Associated with CD4+ Response after 3 Cycles of Subcutaneous (SC) Recombinant Human Interleukin-2 (IL-2). A. Labriola, E. Denning, N. Klimas, F. Gordin, U.S. Dept. of Veterans Affairs Natl. Trial Coordinating Ctr., and the ESPRIT Study Group.

525-M. Long-Term Persistence and Safety of Gene-Modified Syngeneic CD4+ T Lymphocytes in HIV-Infected Patients. A. Lu, J. Tavel, B. Herpin, V. Natarajan, R. T. Davey , J. Kovacs , J. Falloon, M. A. Polis, H. Masur, and H. C. Lane.

527-M. Interleukin-2 (IL-2) Added to HAART in Primary HIV Infection Enhances Anti-HIV Immune Responses. F. Hecht, J. Kahn, B. Martinez-Marino, M. Altfeld, L. Liu, McGrath, R. Gascon, M. Busch, B. Walker, and J. Levy.

528-M. SSITT: A Prospective Trial of Treatment Interruptions in HIV Infection. B. Hirschel, C. Fagard, A. Oxenius, H. Gunthard, and F. Garcia for the Swiss HIV Cohort Study.

529-M. Structured Treatment Interruptions (STI) in Patients Receiving HAART since Primary HIV-1 Infection (PHI): Spontaneous Control of Viremia in about One Third of Cases after the First 3 Cycles Off Therapy. J. Miró, M. Plana, G. M. Ortiz, M. J. Maleno, M. Arnedo, A. del Rio, X. Claramonte, A. Garcia, E. Lazzari, J. Joseph, T. Pumarola, D. F. Nixon, T. Gallart, and J. M. Gatell.

535-M. Effect of Associating a Cytostatic Drug + HAART and Holding the Cytostatic Drug after STI and a Definitive Interruption of HAART on HIV-1-Specific Immune Responses. M. Plana, L. Lopalco, F. García, G. M. Ortiz, M. J. Maleno, A. García, J. Arostegui, J. Miró, D. F. Nixon, C. Gil, A. Cruceta, M. Arnedo, T. Pumarola, J. Alcami, F. Lori, T. Gallart, and J. M. Gatell.

537-M. Sequential Broadening of HIV-1-Specific CTL Responses during Supervised Treatment Interruption in Treated Acute Infection. X. Yu, M. M. Addo, C. Fitzpatrick, P. Lee, D. Strick, P. Goulder, E. Rosenberg, B. Walker, and M. Altfeld.

557-T. Hypersusceptibility to Protease Inhibitors Associated with Mutated Proteases at Codons 30 and 88 in Treated Patients. V. Obry, E. Race, M. Vray, J. L. Meynard, L. Morand-Joubert, D. Descamps, F. Brun-Vezinet, and F. Clavel for the ANRS 088 NARVAL Study Team.

559-T. Quantitative Estimate of the Effect of Individual Baseline Mutations in HIV Protease on the Virologic Response to Lopinavir/Ritonavir Therapy in Heavily Antiretroviral-Experienced Patients. J. Isaacson, D. Kempf, V. Calvez, I. Cohen-Codar, D. Descamps, E. Guillevic, B. Bernstein, E. Sun, J. P. Chauvin, and R. Rode.

560-T. Influence of Genotypic Resistance on the Viral Load Response of 167 Patients on Lopinavir/r (LPV/r) including an Analysis of New Protease Inhibitor Resistant Mutations in 21 Patients Who Failed. M. Loutfy, C. Thompson, M. Trpeski, C. Kovacs, A. Rachlis, J. Goodhew, G. Rubin, K. Gough1, and S. Walmsley.

562-T. Resistance to Tipranavir is Uncommon in a Randomized Trial of Tipranavir/Ritonavir (TPV/RTV) in Multiple PI-Failure Patients (BI 1182.2). R. Schwartz, P. Kazanjian, L. Slater, B. Hathaway, M. Markowitz, D. Wheeler, M. Goldman, M. Drulak, S. McCallister, and D. Mayers.

563-T. Molecular Mechanism of I50V, I54L, and I54M Resistance to Amprenavir and Other HIV-1 Protease Inhibitors. R. Xu, W. Andrews, A. Spaltenstein, D. Danger, W. Dallas, L. Carter, M. Hanlon, L. Wright, and E. Furfine.

565-T. Longitudinal Analysis of RT and Protease Mutations among Israeli Patients Infected with HIV Subtype C. Z. Grossman, S. Maayan, D. Auerbuch, E. Sahar, I. Levi, M. Lorber, G. Gottesman, K. Rizenfeld, M. Chowers, Z. Kra-Oz, E. Mendelson, Z. Bentwich, M. Elkan, D. Engelhard, S. Polak, I. Yust, and J. M. Schapiro for Israel Multi-Ctr. AIDS Study Group.

567-T. Selection for Delavirdine (DLV) Resistance Is not Associated with Loss of Nucleoside Analogue (NRTI) Resistance Mutations in Subjects with Non-Nucleoside Analogue (NNRTI) Hypersusceptibility—Results from ACTG 359. R. Swanstrom, D. Katzenstein, N. S. Hellmann, S. A. Fiscus, L. Petch, H. Cheng, R. Haubrich, and R. Gulick.

568-T. Choice of Co-Nucleoside Analog in d4T-Treated Subjects May Influence the Pattern of Thymidine Analog Mutations (TAMs) and Multi-Nucleoside Resistance Mutations (MNRs). L. Ross, Q. Liao, K. Henry, C. Cohen, A. Hirani, R.

Fisher, M. St. Clair, and J. Hernandez.

569-T. The Presence of Nucleoside Analogue Mutations (NAMs) Is Highly Correlated with Reduced Susceptibility to all NRTIs. J. M. Whitcomb, E. Paxinos, W. Huang, M. Maranta, K. Limoli, C. Chappey, N. T. Parkin, N. S. Hellmann, and C. J. Petropoulos.

570-T. M184V Selection in Suppressed Subjects at Week 24 May Not Be Associated with Treatment Outcome (NZTA4002). J. J. Eron, D. McClernon, A. Pierce, G. Sawyerr, H. Gao, M. St. Clair, J. Tolson, G. Capuano, J. Hernandez, and J. Snidow.

571-T. In Vitro Selection of the T215Y Mutation by Stavudine (d4T) in Viruses Carrying 215D/C from Drug-Naive Persons. G. García-Lerma, H. MacInnes, S. Nidtha, D. Bennett, H. Weinstock, and W. Heneine.

573-T. Novel Mutations in HIV-1 Integrase Associated with Resistance to Diketo Acids. M. Witvrouw, V. Fikkert, B. Van Maele, C. Pannecouque, N. Neamati, T. R. Burke Jr., G. Pais, E. De Clercq, and Z. Debyser.

575-T. Evolution of Phenotypic Drug Susceptibility and Viral Replication Capacity during Virologic Failure of Combination Antiretroviral Therapy. J. D. Barbour, T. Wrin, R. M. Grant, M. R. Segal, C. J. Petropoulos, and S. G. Deeks.

576-T. A Pilot Study to Analyze HIV-1 Fitness Evolution under a Protease Inhibitor-Based Therapy Shows a Diverse Response Depending of the Basal Genotypic Context of the Virus. J. Weber, H. Valdez, H. R. Rangel, B. Chakraborty, E. Connick, K. Smith, A. Landay, D. Kuritzkes, M. Lederman, and M. Quinones-Mateu.

577-T. Impaired in Vitro Fitness of Nevirapine Resistant HIV-1 Mutants. K. Soderberg, M. Thompson, and L. Alexander.

578-T. Pausing during Initiation of HIV-1 Reverse Transcription Represents an Important Determinant for Viral Replication Fitness. X. Wei, C. Liang, M. Gstte, and M. A. Wainberg.

584-T. Meta-Analysis of Antiretroviral Drug Resistance Testing in HIV-1 Infection. D. Torre and R. Tambini.

586-T. A Randomized, Prospective Study of Phenotype (P) versus Virtual Phenotype (VirtualP) Testing for Patients Failing Antiretroviral Therapy (ART). M. J. Perez-Elias, I. Garcia-Arata, V. Muñoz, I. Santos, J. Sanz, V. Abraira, A. Moreno, J. R. Arribas, J. González, A. Antela, F. Dronda, M. Pumares, P. Martí-Belda, and S. Moreno for the Realvirfen Study Group.

587-T. CREST-A Randomised Comparison of 2 Resistance Test Platforms: Genotype and Virtual Phenotype. C. Workman, G. Hales, and P. McKenna, for the CREST Study Group.

589-T. Real vs VirtualPhenotype: 12-Month Results from the GenPherex Study. F. Mazzotta, S. Lo Caputo, C. Torti, C. Tinelli, F. Castelli, P. Pierotti, G. Angarano, L. Sighinolfi, A. Poggio, N. Gianotti, R. Maserati, M. De Gennaro, A. Vivarelli, P. DelleFoglie, and G. Carosi for the GenPherex Group.

621-W. High Rates of Clustering of Tuberculosis Strains in HIV-1-Infected Patients in Harare, Zimbabwe. P. Easterbrook, A. Gibson, S. Murad, A. Ferguson, P. Mason, A. Ndudza, L. Mbengeranwa, and F. Drobniewski.

623-W. Who Gets HIV-Associated Tuberculosis in the Era of HAART? E. Girardi, G. Antonucci, P. Vanacore, F. Palmieri, S. Pauluzzi, G. Ippolito, and the GISTA-SISMIP Group.

630-W. Long-Term Follow-Up of HIV-Infected Individuals Who Have Experienced Immune Reconstitution Following Severe Immunosuppression. S. L. Koletar, J. Wu, J. A. McCutchan, P. L. Williams, R. L. Murphy, T. Nevin, and J. S. Currier for the ACTG 362 Team.

631-W. Continued Low Rates of *Mycobacterium avium* Complex (MAC) and Bacterial Pneumonia despite Withdrawal of Azithromycin Prophylaxis among Patients with CD4 Cell Rebound. W. Burman, W. El-Sadr, J. Matts, R. Hafner, L. Crane, and F. Gordin.

633-W. Discontinuation of Maintenance Therapy against Toxoplasma Encephalitis May not Be Safe despite Sustained Response to Antiretroviral Combination Therapy. S. Bertschy, M. Opravil, A. Telenti, E. Bernasconi, V. Schiffer, P. Vernazza, M. Flepp, J. P. Chave, and H. Furrer for the Swiss HIV Cohort Study.

634-W. ACTG 393: A Study of Discontinuing Maintenance Therapy in Subjects with Disseminated *Mycobacterium avium* Complex (DMAC). J. A. Aberg, P. L. Williams, T. Liu, H. M. Lederman, C. Inderlied, F. Torriani, S. Owens, T. Nevin, and J. S. Currier.

635-W. Discontinuation of Maintenance Therapy for Cryptococcal Meningitis in Patients Treated with HAART: A Multicentre Observational Study. C. Mussini, P. Pezzotti, V. Borghi, E. Martinez, J. Mirò, J. Aberg, P. Bossi, A. Bedini, P. Cinque, A. M. Cattelan, R. Manfredi, L. M. Vaira, A. Lazzarin, A. Cossarizza, R. Esposito, and A. Antinori.

637-M. Successful Immune Recovery Is Associated with Persistent Increases in HCV RNA, Infrequent LFT Flares, and Appears Unimpaired by HCV in Co-infected Subjects. R. T. Chung, S. Evans, Y. Yang, D. Theodore, H. Valdez, R. Clark, C. Shikuma, T. Nevin, and K. E. Sherman for ACTG 383 Team.

638-M. Immune Recovery during Antiretroviral Therapy in Patients Infected with HIV-1 and Hepatitis C Virus Co-Infection: A Cohort Study. S. Moreno, A. Moreno, F. Dronda, M. J. Perez-Elias, C. Quereda, J. L. Casado, A. Antela, and M. E. Moreno.

639-M. Poorer Immunological Response to HAART in HIV+ Individuals Co-Infected with Hepatitis C Virus. C. Sabin, B. Dauer, A. N. Phillips, T. Lutz, V. Miller, A. Cozzi Lepri, and S. Staszewski.

640-M. HIV-1/HCV Co-Infection: Comparison of Cellular Immune Responses against 2 Persistent Viruses. G. Lauer, T. Nguyen, C. Day, G. Robbins, M. Lucas, P. Klenerman, R. Chung, and B. Walker.

641-M. The Nature of Hepatitis C Virus-Specific Cellular Immune Responses in HIV Co-Infected Individuals. L. Barrett, J. Gamberg, M. I. Bowmer, C. Nguyen, C. Howley, M. Gallant, and M. Grant.

643-M. Comparative Analysis of HCV RNA in Serum, Liver, and Peripheral Blood Mononuclear Cells (PBMC) in Patients with HIV Infection vs Patients with HIV and HCV Co-Infection. M. Furione, M. Gatti, F. Baldanti, G. Piccinini, R. Maserati, R. Bruno, and G. Gerna.

648-M. Presence of HCV RNA in Cervico-Vaginal Lavages Obtained from HIV-1/HCV Co-Infected Women. M. Nowicki, T. Laskus, M. Radkowski, J. Rakela, and A. Kovacs.

649-M. Hepatitis C Virus Replication in the Central Nervous System. T. Laskus, M. Radkowski, J. Wilkinson, A. Bednarska, M. Nowicki, and J. Rakela.

651-M. Multicenter, Randomized, Open-Label Study of the Safety and Efficacy of Interferon (IFN) alpha-2b plus Ribavirin (RBV) for the Treatment of Hepatitis C Virus (HCV) in HIV-Infected Persons (HRN-002). M. Sulkowski, F. Felizarta, C. Smith, R. Berggren, J. Slim, D. Shoultz, L. Ball, R. Hudnall, and D. Dieterich for the Hepatitis Resource Network Clinical Trials Group.

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